ORIGINAL ARTICLE

Adalimumab plus Methotrexate for Uveitis in Juvenile Idiopathic Arthritis

Athimalaipet V. Ramanan, F.R.C.P.C.H., F.R.C.P., Andrew D. Dick, M.B., B.S., M.D., Ashley P. Jones, Ph.D., Andrew McKay, M.Sc., Paula R. Williamson, Ph.D., Sandrine Compeyrot-Lacassagne, M.D., Ben Hardwick, M.Res., Helen Hickey, B.Sc., Dyfrig Hughes, Ph.D., Patricia Woo, F.Med.Sci., Diana Benton, M.A., Clive Edelsten, M.R.C.P., F.R.C.Ophth., and Michael W. Beresford, M.B., Ch.B., Ph.D., for the SYCAMORE Study Group*

ABSTRACT

BACKGROUND

Adalimumab, a fully human anti–tumor necrosis factor α monoclonal antibody, is effective in the treatment of juvenile idiopathic arthritis (JIA). We tested the efficacy of adalimumab in the treatment of JIA-associated uveitis.

METHODS

In this multicenter, double-blind, randomized, placebo-controlled trial, we assessed the efficacy and safety of adalimumab in children and adolescents 2 years of age or older who had active JIA-associated uveitis. Patients who were taking a stable dose of methotrexate were randomly assigned in a 2:1 ratio to receive either adalimumab (at a dose of 20 mg or 40 mg, according to body weight) or placebo, administered subcutaneously every 2 weeks. Patients continued the trial regimen until treatment failure or until 18 months had elapsed. They were followed for up to 2 years after randomization. The primary end point was the time to treatment failure, defined according to a multicomponent intraocular inflammation score that was based on the Standardization of Uveitis Nomenclature criteria.

RESULTS

The prespecified stopping criteria were met after the enrollment of 90 of 114 patients. We observed 16 treatment failures in 60 patients (27%) in the adalimumab group versus 18 treatment failures in 30 patients (60%) in the placebo group (hazard ratio, 0.25; 95% confidence interval [CI], 0.12 to 0.49; P<0.0001 [the prespecified stopping boundary]). Adverse events were reported more frequently in patients receiving adalimumab than in those receiving placebo (10.07 events per patient-year [95% CI, 9.26 to 10.89] vs. 6.51 events per patient-year [95% CI, 5.26 to 7.77]), as were serious adverse events (0.29 events per patient-year [95% CI, 0.15 to 0.43] vs. 0.19 events per patient-year [95% CI, 0.00 to 0.40]).

CONCLUSIONS

Adalimumab therapy controlled inflammation and was associated with a lower rate of treatment failure than placebo among children and adolescents with active JIA-associated uveitis who were taking a stable dose of methotrexate. Patients who received adalimumab had a much higher incidence of adverse events and serious adverse events than those who received placebo. (Funded by the NIHR Health Technology Assessment Programme and Arthritis Research UK; SYCAMORE EudraCT number, 2010-021141-41.)

From University Hospitals Bristol NHS Foundation Trust (A.V.R., A.D.D., D.B.) and the School of Clinical Sciences, University of Bristol (A.V.R., A.D.D.), Bristol, National Institute for Health Research (NIHR) Biomedical Research Centre at Moorfields Eye Hospital and University College London Institute of Ophthalmology (A.D.D., P.W.) and Great Ormond Street Hospital (S.C.-L., C.E.), London, Institute of Translational Medicine, University of Liverpool (A.P.J., A.M., P.R.W., B.H., H.H., M.W.B.), and the Department of Paediatric Rheumatology, Alder Hey Children's NHS Foundation Trust (M.W.B.), Liverpool, and Bangor University, Bangor (D.H.) — all in the United Kingdom. Address reprint requests to Dr. Ramanan at the Department of Paediatric Rheumatology, Bristol Royal Hospital for Children, Bristol BS2 8BJ, United Kingdom, or at avramanan@hotmail.com.

*A complete list of the investigators in the SYCAMORE Study Group is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2017;376:1637-46.
DOI: 10.1056/NEJMoa1614160
Copyright © 2017 Massachusetts Medical Society.

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org on March 2, 2026.
Copyright © 2017 Massachusetts Medical Society. All rights reserved, including those for text and data mining, AI training, and similar technologies.

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children. Children with JIA are at risk for inflammation of the uvea (uveitis). Uveitis develops in approximately 12 to 38% of patients with JIA within 7 years after the onset of arthritis.[1,2] Despite current screening and therapeutic options, visual impairment in both eyes may develop in up to 15% of children with JIA-associated uveitis, and they may be certified as legally blind.[3,4]

Experimental models of autoimmune uveitis have shown that tumor necrosis factor α (TNF-α) plays a pivotal role in the pathogenesis,[5] findings that have been borne out in the treatment of uveitis in adults[6-8] and in pediatric case series.[9-17] Adalimumab is a fully humanized anti–TNF-α monoclonal antibody. A multicenter, randomized, double-blind, parallel-group trial showed a significant benefit of adalimumab in children with active rheumatoid arthritis.[18] We carried out the SYCAMORE trial to assess the role of adalimumab in the treatment of methotrexate-refractory JIA-associated uveitis.

METHODS

PROTOCOL AND TRIAL POPULATION

In this multicenter, double-blind, randomized, placebo-controlled trial, the primary end point was the efficacy of adalimumab in children with active JIA-associated uveitis, as measured by various scoring systems. All the patients had been receiving a stable weekly dose of methotrexate for at least 12 weeks.

An independent ethics committee and the Medicines for Healthcare Products Regulatory Agency approved the trial protocol (available with the full text of this article at NEJM.org). Each parent or guardian provided written informed consent, and each child gave assent when appropriate. The authors vouch for the fidelity of this report and the trial to the protocol. AbbVie provided the active drug and placebo that were used in the trial. AbbVie had no part in the trial design, the collection or analysis of the data, or the preparation of the manuscript. AbbVie representatives reviewed the final draft of the manuscript. All the authors assume responsibility for the accuracy and completeness of the data and analyses. University Hospitals Bristol NHS Foundation Trust, as the sponsor of this trial, has a data-sharing agreement with AbbVie in support of regulatory purposes.

Children and adolescents 2 years of age or older who had active JIA-associated uveitis were eligible to undergo randomization. Stable methotrexate treatment meant that the dose (10 to 20 mg per square meter of body-surface area; maximum dose, 25 mg) and the method of administration remained constant. Active uveitis was defined as a sustained grade (on at least two occasions) of cellular infiltrate in the anterior chamber of 1+ (indicating 6 to 15 cells in a 1-mm^2 area of the anterior chamber of the eye under a slit-lamp biomicroscope) or higher, according to the Standardization of Uveitis Nomenclature (SUN) criteria,[19] during the 12 weeks before screening despite receipt of methotrexate and glucocorticoid (systemic or topical) therapy. The SUN cell-activity score is proportional to the approximate number of cells per 1 mm^2 in the anterior chamber of the eye under a slit-lamp biomicroscope, with a higher score indicating a greater number of cells.[19] There are no internationally agreed-on minimally important differences for this scale.

Key exclusion criteria were previous exposure to adalimumab, previous exposure to another biologic agent such that the estimated level of the drug in the patient's blood was less than that predicted by 5 half-lives of the drug, receipt of more than six topical glucocorticoid drops per eye per day, and receipt of prednisone (or the equivalent) at a dose exceeding 0.2 mg per kilogram of body weight per day. The full inclusion and exclusion criteria and information regarding the concomitant medications that were and were not permitted are described in the trial protocol.[20]

RANDOMIZATION AND TRIAL PROCEDURES

Randomization was performed with the use of a Web-based system with random permuted block sizes of 3 and 6, stratified according to trial center. At enrollment, eligible patients were assigned in a 2:1 ratio to receive adalimumab or placebo. Patients were followed for 2 years after randomization. Trial visits were scheduled at 4, 8, and 12 weeks and then every 12 weeks until 18 months or until patients stopped the trial regimen because of treatment failure, after which they were followed for another 6 months.

Ophthalmic assessment of disease activity and ocular complications were measured throughout the trial with the use of slit-lamp biomicroscopy for uveitis activity, according to the SUN criteria[19] (Table S2 in the Supplementary Appendix, avail-

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org on March 2, 2026.
Copyright © 2017 Massachusetts Medical Society. All rights reserved, including those for text and data mining, AI training, and similar technologies.

able at NEJM.org). The primary and secondary end points were assessed at each trial visit and at any unscheduled visits.

TRIAL REGIMEN

We recruited patients between October 1, 2011, and April 10, 2015. The first patient underwent randomization on October 27, 2011, and the final patient underwent randomization on March 31, 2015.

All the patients received a stable dose of weekly oral or subcutaneous methotrexate (10 to 20 mg per square meter; maximum dose, 25 mg). No dose reduction or change in the method of administration was allowed. An increase in the dose was acceptable in response to somatic growth (so that the dose per square meter at trial entry was maintained throughout the trial) but not on clinical grounds. Participants received either adalimumab (at a dose of 20 mg in patients weighing <30 kg or 40 mg in patients weighing ≥30 kg), or placebo, administered as a subcutaneous injection every 2 weeks. The volume (0.8 ml) was the same across all doses and groups. AbbVie provided the investigational medicinal product (adalimumab) and matching placebo in identical, prefilled vials.

PRIMARY END POINT

The primary end point was the time to treatment failure (as assessed by means of a multicomponent intraocular inflammation score), which was defined as at least one of the following criteria being met: a two-grade increase from baseline in the SUN cell-activity score (anterior chamber cell count) over a period of two consecutive visits; no change in the SUN cell-activity score in patients with an entry grade of 3 or higher for two consecutive readings (apart from baseline); only partial improvement (decrease of one grade) or no change from baseline, with the development of another ocular coexisting condition that was sustained over a period of two consecutive visits; the worsening of an existing (on enrollment) ocular coexisting condition after 3 months; an entry grade of 1 or 2 that was still present after 6 months of therapy and that had been sustained over a period of two consecutive visits; the use of ineligible concomitant medications (medications not listed in the prespecified acceptable criteria or those that were not allowed); or the intermittent or continuous suspension of the trial regimen for a cumulative period of more than 4 weeks. All the trial assessments were carried out by persons who did not have knowledge of the trial-group assignments.

SECONDARY END POINTS

All the secondary end points were assessed at each trial visit.[20] These end points included the use of topical and systemic glucocorticoids; a flare of uveitis defined according to SUN criteria; control, remission, and duration of inactive disease (uveitis); health-related quality of life, as assessed by means of the Childhood Health Assessment Questionnaire (CHAQ; scores range from 0 to 3, with lower scores indicating better outcomes; minimal clinically important differences, −0.188 for improvement and 0.125 for worsening)[21] and the Child Health Questionnaire (CHQ; scores range from 0 to 100, with higher scores indicating better or more positive health states; no specific minimal clinically important difference is recognized)[22]; flare of JIA; remission while taking medication and remission while not taking medication[23]; minimal JIA disease activity (defined in patients with oligoarticular JIA as a physician's global assessment of ≤2.5 on a 10-cm visual-analogue scale, with higher scores indicating more disease activity, and no swollen joints; or defined in patients with polyarticular JIA as a physician's global assessment of ≤3.4 on the 10-cm visual-analogue scale, the patient's or parent's global assessment of ≤2.1 on the 10-cm visual-analogue scale, and ≤1 swollen joint)[24]; the Juvenile Arthritis Disease Activity Score (JADAS),[25] which was defined as the linear sum of four components: a physician's global assessment on the 10-cm visual-analogue scale, the patient's or parent's global assessment on the 10-cm visual-analogue scale, an active joint count as assessed in one of three ways (with any involved joints up to a maximum of 10 [JADAS 10], with 27 joints including the cervical spine, elbows, wrists, the first to third metacarpophalangeals, proximal interphalangeals, hips, knees, and ankles [JADAS 27], or with all 71 joints [JADAS 71]); and the erythrocyte sedimentation rate (ESR), which was normalized on a scale from 0 to 10 with the use of the following formula to avoid excessive weight in the overall index: (ESR [mm/hr] − 20) ÷ 10; minimal disease activity (defined as a JADAS score of 2 in patients with oligoarticular disease or 3.8 in those with polyarticular disease); and the standard American College of Rheumatology (ACR) pediatric

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org on March 2, 2026.
Copyright © 2017 Massachusetts Medical Society. All rights reserved, including those for text and data mining, AI training, and similar technologies.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Adalimumab Group (N=60)	Placebo Group (N=30)
Affected eyes — no. (%)		
One eye	43 (72)	22 (73)
Both eyes	17 (28)	8 (27)
Weight <30 kg — no./total no. (%)	33/59 (56)	17/30 (57)
Age — yr	9.07±3.94	8.56±3.79
Female sex — no. (%)	47 (78)	23 (77)
Ophthalmologic characteristics		
No. of eyes assessed	77	38
LogMAR score†	0.04±0.15	0.07±0.12
Anterior chamber cell count — no. (%)‡		
1+	52 (68)	24 (63)
2+	18 (23)	11 (29)
3+	6 (8)	3 (8)
4+	1 (1)	0
Flare score — no. (%)‡		
0	18 (23)	12 (32)
1+	49 (64)	23 (61)
2+	10 (13)	3 (8)
Intraocular pressure — mm Hg	14.76±3.85	14.11±4.27
Vitreous haze grade — no. (%)§		
0	65 (84)	32 (84)
0.5+	8 (10)	4 (11)
1+	3 (4)	2 (5)
2+	1 (1)	0
No. of topical glucocorticoid drops per eye per day	2.31±1.44	2.25±1.54
Ophthalmic complications — no. (%)		
Central band keratopathy	2 (3)	0
Synechia	18 (23)	6 (16)
Iris bombé	0	0
Membrane formation	2 (3)	0
Neovascularization	0	0
Rheumatologic characteristics		
Type of JIA — no. (%)¶		
Extended oligoarthritis	14 (23)	7 (23)
Persistent oligoarthritis	36 (60)	17 (57)
Rheumatoid factor–negative polyarthritis	8 (13)	4 (13)
Rheumatoid factor–positive polyarthritis	1 (2)	1 (3)
Psoriatic arthritis	1 (2)	1 (3)
Time since JIA diagnosis — yr	5.58±3.69	4.81 ±3.19
Physician's global assessment of disease activity‖	0.76±1.48	0.83±1.09
Rheumatoid factor — no./total no. (%)**	1/47 (2)	3/23 (13)
Antinuclear antibody — no./total no. (%)**	33/57 (58)	15/25 (60)

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org on March 2, 2026.
Copyright © 2017 Massachusetts Medical Society. All rights reserved, including those for text and data mining, AI training, and similar technologies.

Table 1. (Continued.)

Characteristic	Adalimumab Group (N = 60)	Placebo Group (N = 30)
Median active-joint count (interquartile range)	0 (0–0)	0 (0–2)
Median swollen-joint count (interquartile range)	0 (0–0)	0 (0–2)

* Plus–minus values are means ±SD.
† Scores for the log of the minimum angle of resolution (logMAR) are on a scale from 0.00 to 2.00, with higher values indicating poorer vision.
‡ The anterior chamber cell count and flare score were assessed according to the Standardization of Uveitis Nomenclature criteria.[19] Scores range from 0 to 4+, with higher scores indicating poorer vision. Grade definitions are provide in Table S2 in the Supplementary Appendix.
§ Vitreous haze grade was assessed on a scale from 0 to 4+, with higher grades indicating poorer vision.[19]
¶ The type of juvenile idiopathic arthritis (JIA) was classified according to the International League of Associations for Rheumatology criteria.[28]
‖ The physician's global assessment of disease activity was assessed on a 10-cm visual-analogue scale, with higher grades indicating more disease activity.
** Data on rheumatoid factor and antinuclear antibody were not available in some patients because repeat blood testing for the purpose of data-set completion was not warranted on the basis of clinical needs.

core outcome set variables.[26] ACR responses of ACR 30, ACR 50, ACR 70, ACR 90, and ACR 100 are defined as 30%, 50%, 70%, 90% and 100% improvement, respectively, in a minimum of three variables in the core set, with worsening of one variable by no more than 30%, as defined in the ACR criteria. The secondary end points and the post hoc analyses are provided in Table S8 in the Supplementary Appendix.

SAFETY

All the participants who received at least one dose of adalimumab or placebo were included in the safety analyses. Adverse events were recorded at each visit and reported from the receipt of the first dose of the trial regimen. Adverse events are reported regardless of severity or perceived association with the trial intervention. Data on serious adverse events were collected from the time of informed consent. Adverse events were tabulated with the use of *Medical Dictionary for Regulatory Activities*, version 18.0, system organ class and preferred terms.

STATISTICAL ANALYSIS

We originally designed the trial with 90% power to detect a 50% relative difference in the rate of treatment failure (estimated at 60% with placebo vs. 30% with adalimumab) at a two-sided 5% significance level. In view of substantial challenges in the early phases of recruitment, the independent data and safety monitoring committee and the trial steering committee, with approval from the trial funders, advised the adoption of a protocol amendment that reduced the power to 80%, required the recruitment of 114 patients (76 patients in the adalimumab group and 38 in the placebo group), and included a 5% inflation for missing data for the primary end point.

In an intention-to-treat analysis of the primary end point, we used the log-rank test to compare the two trial groups and Kaplan–Meier plots to show the distribution of time to treatment failure. Hazard ratios and 95% confidence intervals were estimated after fitting a Cox proportional-hazards model with the assumption of proportional hazards checked by means of the addition of a time-dependent treatment-effect variable to the model. A two-sided P value of less than 0.0001 was used for the Haybittle–Peto stopping boundary for the interim analysis, and a two-sided P value of less than 0.05 was considered to indicate statistical significance for the final analysis.[27] Prespecified sensitivity analyses tested the effects of missing data, participants who stopped their intervention early, and those who had been incorrectly identified as having treatment failure. The statistical analysis plan (see the protocol) includes the full details of the sensitivity analyses. Analyses were performed with the use of SAS software, version 9.3 (SAS Institute).

TRIAL OVERSIGHT AND TRIAL STOPPING

After the second interim analysis, the data and safety monitoring committee noted on March 11, 2015, that the adalimumab group had evidence of a significantly lower risk of treatment

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org on March 2, 2026.
Copyright © 2017 Massachusetts Medical Society. All rights reserved, including those for text and data mining, AI training, and similar technologies.

failure than the placebo group. On the basis of formal stopping boundaries,[27] the data and safety monitoring committee recommended that recruitment to the trial should cease, that all participants should be subsequently made aware of their trial-group assignment, that participants in the placebo group should cease taking the trial regimen and enter trial follow-up, and that participants receiving adalimumab should continue per the trial protocol. After consultation with the data and safety monitoring committee, the trial steering committee, and the co-chief investigators (the first and last authors), a decision was made to implement this recommendation, with the support of the trial team (whose members had remained unaware of the trial-group assignments throughout) and with the agreement of the trial sponsor and funders.

Patients were called in for a final assessment of response by investigators who were unaware of the trial-group assignments. Patients in the adalimumab group were asked to continue per the protocol for the duration of the trial in an open-label follow-up until the completion of their 18-month treatment, the occurrence of an adverse event that was attributed to the drug and precluded continued treatment, or treatment failure. All the patients who had received placebo stopped taking the trial regimen and completed the 6-month follow-up phase of the trial. Open-label extension of the trial continues.

RESULTS

PATIENTS

Of 332 patients who underwent screening at 14 sites in the United Kingdom, 242 did not undergo randomization because they did not meet the inclusion criteria. A total of 60 participants were randomly assigned to receive adalimumab and 30 to receive placebo (Table 1, and Fig. S1 in the Supplementary Appendix). Data for the primary end point were available for all the participants who underwent randomization.

Nine patients (15%) in the adalimumab group and seven (23%) in the placebo group discontinued the trial intervention for reasons other than treatment failure (Fig. S1 in the Supplementary Appendix). Seven of these patients in the adalimumab group and six of those in the placebo group agreed to subsequent follow-up.

TREATMENT FAILURE

The addition of adalimumab to methotrexate significantly delayed the time to treatment failure, as compared with placebo (hazard ratio, 0.25; 95% confidence interval [CI], 0.12 to 0.49; P<0.0001 by the log-rank test [the prespecified stopping boundary]) (Fig. 1A). During the 18-month trial period, the median time to treatment failure was not reached in the adalimumab group and was 24.1 weeks (95% CI, 12.4 to 81.0) in the placebo group (Fig. 1A). Treatment failure occurred in a significantly lower percentage of patients in the adalimumab group than in the placebo group (16 patients [27%] vs. 18 [60%]; relative risk, 0.40; 95% CI, 0.22 to 0.73; P = 0.002) (Tables S3 and S4 in the Supplementary Appendix). Nine sensitivity analyses confirmed the conclusion found in the primary analysis (Table S5 in the Supplementary Appendix).

SAFETY AND ADVERSE EVENTS

Summary data of the adverse events are listed in Table 2, and serious adverse events are listed in Table 3. A total of 588 adverse events, including minor infections and respiratory disorders, were reported in 53 patients (88%) in the adalimumab group, and 103 adverse events were reported in 25 patients (83%) in the placebo group. The rate of serious adverse events was 0.29 events per patient-year (95% CI, 0.15 to 0.43) in the adalimumab group, as compared with 0.19 events per patient-year (95% CI, 0.00 to 0.40) in the placebo group; the corresponding rates of adverse events per patient-year were 10.07 (95% CI, 9.26 to 10.89) and 6.51 (95% CI, 5.26 to 7.77). Full listings of all the adverse events are provided in Tables S6 and S7 in the Supplementary Appendix.

SECONDARY END POINTS

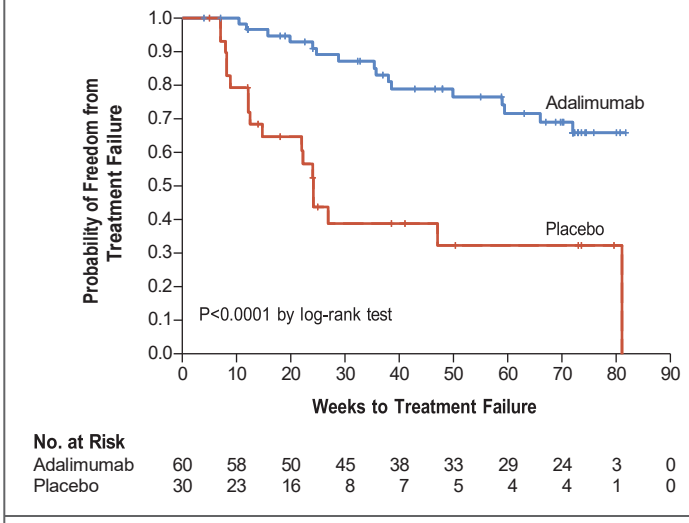
A full summary of the analyses of the secondary end points is provided in Table S8 in the Supplementary Appendix. At randomization, six participants (five in the adalimumab group and one in the placebo group) were taking systemic glucocorticoids (permitted dose, <0.20 mg per kilogram per day; median dose, 0.14 mg per kilogram per day). Three of the participants in the adalimumab group stopped taking systemic glucocorticoids (median duration of treatment, 18.1 weeks). The patient in the placebo group stopped taking systemic glucocorticoids after 5.6 weeks.

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org on March 2, 2026.
Copyright © 2017 Massachusetts Medical Society. All rights reserved, including those for text and data mining, AI training, and similar technologies.

Of 63 participants who were taking two or more drops of topical glucocorticoids per day at randomization, a significantly greater percentage of patients in the adalimumab group than in the placebo group had a reduction to less than two drops (23 of 45 patients [51%] vs. 3 of 18 [17%]; hazard ratio for reduction, 3.72; 95% CI, 1.09 to 12.71; P = 0.04) (Fig. 1B). Of 74 participants who were taking one or more drops at randomization, a significantly greater percentage of patients had a reduction to zero drops in the adalimumab group than in the placebo group (23 of 49 patients [47%] vs. 4 of 25 [16%]; hazard ratio, 3.58; 95% CI, 1.24 to 10.32; P = 0.02) (Fig. S2 in the Supplementary Appendix).

Patients in the adalimumab group had a significantly longer mean (±SE) duration of sustained inactive disease (zero cells) than did those in the placebo group (179.3±16.9 days vs. 14.5±23.9 days; estimated treatment effect, 164.8 days; 95% CI, 104.4 to 225.2; P<0.0001 [the prespecified stopping boundary]). Patients in the adalimumab group took the trial regimen for twice as long as those in the placebo group (mean [±SD] duration, 315.9±173.8 days vs. 151.6±150.3 days).

Arthritis flare occurred in no patients in the adalimumab group during the trial period, as compared with three patients (10%) in the placebo group (relative risk, 0.07; 95% CI, 0.00 to 1.36; P = 0.03). Because most of the children entered the trial with minimal arthritis (Table 1), the ACR 30, ACR 50, ACR 70, ACR 90, and ACR 100 values and the JADAS 10, 27, and 71 values were only minimally affected (Tables S11 and S12 in the Supplementary Appendix). There was no significant difference between the two trial groups with regard to health-related quality of life, as assessed by means of the CHQ and CHAQ, across time (Tables S13 and S14 in the Supplementary Appendix).



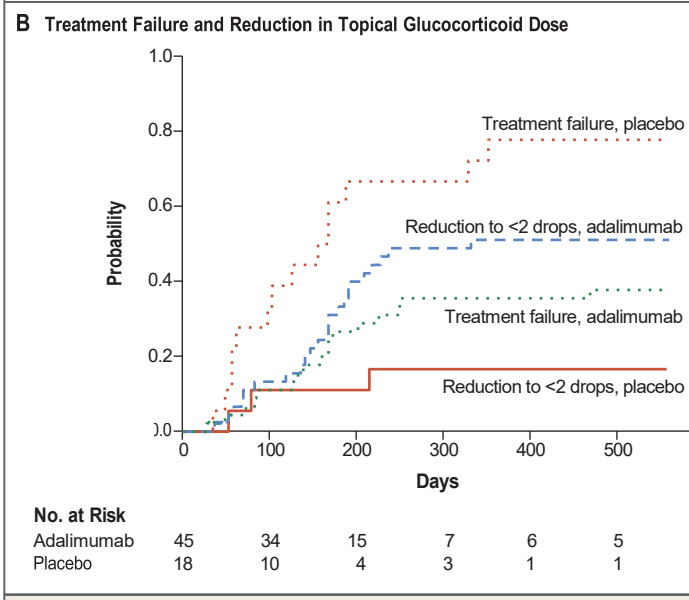


Figure 1. Treatment Failure and Reduction in Topical Glucocorticoid Dose over Time.

In Panel A, the hazard ratio for treatment failure with adalimumab versus placebo was 0.25 (95% CI, 0.12 to 0.49; P<0.0001). Tick marks indicate censored data. In Panel B, the hazard ratio for the dose reduction was 3.72 (95% CI, 1.09 to 12.71; P = 0.04).

POST HOC ANALYSES

An exploratory analysis of the time to treatment response showed a difference between the adalimumab group and the placebo group in favor of adalimumab (hazard ratio, 3.15; 95% CI, 1.42 to 7.00; P = 0.003 by the log-rank test) (Fig. S3 in the Supplementary Appendix). Another exploratory analysis showed a difference in favor of adalimumab in the percentage of patients with a response at 3 months and at 6 months (P = 0.004 for the comparison at each time point). A total of 34 patients (57%) in the adalimumab group and 5 (17%) in the placebo group were classified as having had a response (Table S15 in the Supplementary Appendix).

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org on March 2, 2026.
Copyright © 2017 Massachusetts Medical Society. All rights reserved, including those for text and data mining, AI training, and similar technologies.

Table 2. Adverse Events Reported in at Least 5% of the Patients in the Adalimumab Group.

Event	Adalimumab Group (N=60)	Placebo Group (N=30)
	number (percent)	
Blood or lymphatic system disorder: lymphadenopathy	3 (5)	0
Eye disorder: eye pain	4 (7)	0
Gastrointestinal disorder		
Abdominal pain	3 (5)	0
Diarrhea	8 (13)	1 (3)
Nausea	5 (8)	2 (7)
Vomiting	18 (30)	5 (17)
General disorder or injection-site condition		
Injection-site erythema	3 (5)	1 (3)
Injection-site mass	3 (5)	0
Injection-site pain	5 (8)	2 (7)
Injection-site pruritus	3 (5)	0
Injection-site reaction	7 (12)	0
Injection-site swelling	4 (7)	1 (3)
Pyrexia	12 (20)	2 (7)
Infection or infestation		
Ear infection	6 (10)	2 (7)
Impetigo	3 (5)	1 (3)
Lower respiratory tract infection	8 (13)	2 (7)
Nasopharyngitis	15 (25)	7 (23)
Oral herpes	3 (5)	1 (3)
Paronychia	3 (5)	1 (3)
Pharyngitis	4 (7)	0
Tonsillitis	12 (20)	0
Upper respiratory tract infection	4 (7)	1 (3)
Urinary tract infection	9 (15)	3 (10)
Varicella infection	3 (5)	0
Viral infection	13 (22)	1 (3)
Injury, poisoning, or procedural complication: fall	3 (5)	0
Investigation		
Alanine aminotransferase increased	4 (7)	1 (3)
Aspartate aminotransferase increased	3 (5)	1 (3)
Intraocular pressure increased	4 (7)	0
Musculoskeletal or connective-tissue disorder: arthralgia	12 (20)	2 (7)
Neoplasms benign, malignant, or unspecified, including cysts and polyps: skin papilloma	5 (8)	0
Nervous system disorder: headache	12 (20)	4 (13)
Respiratory, thoracic, or mediastinal disorder		
Cough	22 (37)	3 (10)
Epistaxis	3 (5)	0
Oropharyngeal pain	16 (27)	2 (7)
Skin or subcutaneous-tissue disorder: rash	3 (5)	1 (3)

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org on March 2, 2026.
Copyright © 2017 Massachusetts Medical Society. All rights reserved, including those for text and data mining, AI training, and similar technologies.

Table 3. Serious Adverse Events, According to Trial Group.

Event	Adalimumab Group (N = 60)		Placebo Group (N = 30)		All Patients (N = 90)	
	no. of events	*no. of patients (%)*	*no. of events*	*no. of patients (%)*	*no. of events*	*no. of patients (%)*
Any serious adverse event	17	13 (22)	3	2 (7)	20	15 (17)
Eye disorder*	1	1 (2)	3	2 (7)	4	3 (3)
Gastrointestinal disorder	2	2 (3)	0	0	2	2 (2)
Infection or infestation	10	8 (13)	0	0	10	8 (9)
Nervous system disorder	1	1 (2)	0	0	1	1 (1)
Respiratory, thoracic, or mediastinal disorder	1	1 (2)	0	0	1	1 (1)
Surgical or medical procedure	2	2 (3)	0	0	2	2 (2)

* One event in the adalimumab group and two events in the placebo group were a flare of uveitis that resulted in hospitalization and treatment. One event in the placebo group was worsening of vision with a flare of uveitis and macular edema.

DISCUSSION

In this randomized, placebo-controlled trial involving patients with JIA-associated uveitis, treatment with adalimumab significantly delayed the time to treatment failure, as compared with methotrexate alone (hazard ratio, 0.25; 95% CI, 0.12 to 0.49; P<0.0001 [the prespecified stopping boundary]). A significantly greater proportion of patients in the adalimumab group than in the placebo group had a reduction in their topical glucocorticoid dose (hazard ratio for reduction, 3.72; 95% CI, 1.09 to 12.71; P = 0.04). A significantly greater number of patients in the adalimumab group than in the placebo group discontinued topical glucocorticoids (hazard ratio, 3.58; 95% CI, 1.24 to 10.32; P = 0.02).

However, there were many more adverse events and more severe adverse events in the adalimumab group than in the placebo group. The most common adverse events in the adalimumab group were minor infections, respiratory disorders, and gastrointestinal disorders. The rate of adverse events per patient-year was higher in the adalimumab group than in the placebo group (10.07 vs. 6.51 events per patient-year). The number of serious adverse events was also higher in the adalimumab group than in the placebo group. The follow-up period during the course of the trial was not long enough for us to detect events such as cancers and demyelinating diseases. The sample size precludes commentary regarding rarer events.

Limitations of the trial include the use of the anterior chamber cell count (SUN criteria) as a component of the primary end point. Although internationally recognized, the SUN criteria have not been validated for use in children. All the participating clinicians were instructed in the assessment of SUN criteria.

In conclusion, adalimumab in combination with methotrexate was an effective therapy in children and adolescents with JIA-associated uveitis. However, the drug was associated with a higher incidence of adverse and serious adverse events than was placebo plus methotrexate.

Supported by grants from the National Institute for Health Research Health Technology Assessment Programme (09/51/01) and Arthritis Research UK (19612).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the staff of the National Institute for Health Research Clinical Research Network Children for assistance in the setup and delivery of this trial; the members of the trial steering committee (Dr. Ian Bruce [chair], Dr. Carlos Pavesio, and Mr. Matthew Sydes) and the independent data and safety monitoring committee (Dr. John Sparrow [chair], Dr. Steff Lewis, Dr. Justine Smith, and Dr. Nico Wulffraat); Dr. Janine Grey for serving as an independent member of the trial steering committee before having to leave her role; the staff of all participating centers; the multidisciplinary teams assisting with the trial; and all the children, adolescents, and families who took part in this trial. University Hospitals Bristol NHS Foundation Trust, as the sponsor of this trial, has a data-sharing agreement with AbbVie in support of regulatory purposes.

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org on March 2, 2026.
Copyright © 2017 Massachusetts Medical Society. All rights reserved, including those for text and data mining, AI training, and similar technologies.

REFERENCES

1. Kotaniemi K, Kautiainen H, Karma A, Aho K. Occurrence of uveitis in recently diagnosed juvenile chronic arthritis: a prospective study. Ophthalmology 2001; 108:2071-5.
2. Saurenmann RK, Levin AV, Feldman BM, et al. Prevalence, risk factors, and outcome of uveitis in juvenile idiopathic arthritis: a long-term followup study. Arthritis Rheum 2007;56:647-57.
3. Wolf MD, Lichter PR, Ragsdale CG. Prognostic factors in the uveitis of juvenile rheumatoid arthritis. Ophthalmology 1987;94:1242-8.
4. de Boer J, Wulffraat N, Rothova A. Visual loss in uveitis of childhood. Br J Ophthalmol 2003;87:879-84.
5. Dick AD, Forrester JV, Liversidge J, Cope AP. The role of tumour necrosis factor (TNF-alpha) in experimental autoimmune uveoretinitis (EAU). Prog Retin Eye Res 2004;23:617-37.
6. Imrie FR, Dick AD. Biologics in the treatment of uveitis. Curr Opin Ophthalmol 2007;18:481-6.
7. Levy-Clarke G, Jabs DA, Read RW, Rosenbaum JT, Vitale A, Van Gelder RN. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. Ophthalmology 2014; 121(3):785-96.e3.
8. Cordero-Coma M, Yilmaz T, Onal S. Systematic review of anti-tumor necrosis factor-alpha therapy for treatment of immune-mediated uveitis. Ocul Immunol Inflamm 2013;21:19-27.
9. Biester S, Deuter C, Michels H, et al. Adalimumab in the therapy of uveitis in childhood. Br J Ophthalmol 2007;91:319-24.
10. Foeldvari I, Nielsen S, Kümmerle-Deschner J, et al. Tumor necrosis factor-alpha blocker in treatment of juvenile idiopathic arthritis-associated uveitis refractory to second-line agents: results of a multinational survey. J Rheumatol 2007; 34:1146-50.
11. Gallagher M, Quinones K, Cervantes-Castañeda RA, Yilmaz T, Foster CS. Biological response modifier therapy for refractory childhood uveitis. Br J Ophthalmol 2007;91:1341-4.
12. Saurenmann RK, Levin AV, Rose JB, et al. Tumour necrosis factor alpha inhibitors in the treatment of childhood uveitis. Rheumatology (Oxford) 2006;45:982-9.
13. Sharma SM, Ramanan AV, Riley P, Dick AD. Use of infliximab in juvenile onset rheumatological disease-associated refractory uveitis: efficacy in joint and ocular disease. Ann Rheum Dis 2007;66: 840-1.
14. Tynjälä P, Kotaniemi K, Lindahl P, et al. Adalimumab in juvenile idiopathic arthritis-associated chronic anterior uveitis. Rheumatology (Oxford) 2008;47:339-44.
15. Simonini G, Druce K, Cimaz R, Macfarlane GJ, Jones GT. Current evidence of anti-tumor necrosis factor α treatment efficacy in childhood chronic uveitis: a systematic review and meta-analysis approach of individual drugs. Arthritis Care Res (Hoboken) 2014;66:1073-84.
16. Sen ES, Sharma S, Hinchcliffe A, Dick AD, Ramanan AV. Use of adalimumab in refractory non-infectious childhood chronic uveitis: efficacy in ocular disease — a case cohort interventional study. Rheumatology (Oxford) 2012;51:2199-203.
17. Sen ES, Dick AD, Ramanan AV. Uveitis associated with juvenile idiopathic arthritis. Nat Rev Rheumatol 2015;11: 338-48.
18. Lovell DJ, Ruperto N, Goodman S, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med 2008;359:810-20.
19. Jabs DA, Nussenblatt RB, Rosenbaum JT, Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data: results of the First International Workshop. Am J Ophthalmol 2005; 140:509-16.
20. Ramanan AV, Dick AD, Benton D, et al. A randomised controlled trial of the clinical effectiveness, safety and cost-effectiveness of adalimumab in combination with methotrexate for the treatment of juvenile idiopathic arthritis associated uveitis (SYCAMORE Trial). Trials 2014;15:14.
21. Nugent J, Ruperto N, Grainger J, et al. The British version of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ). Clin Exp Rheumatol 2001;19:Suppl 23: S163-S167.
22. Oliveira S, Ravelli A, Pistorio A, et al. Proxy-reported health-related quality of life of patients with juvenile idiopathic arthritis: the Pediatric Rheumatology International Trials Organization multinational quality of life cohort study. Arthritis Rheum 2007;57:35-43.
23. Wallace CA, Ruperto N, Giannini E, Childhood Arthritis and Rheumatology Research Alliance, Pediatric Rheumatology International Trials Organization, Pediatric Rheumatology Collaborative Study Group. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. J Rheumatol 2004;31: 2290-4.
24. Magni-Manzoni S, Ruperto N, Pistorio A, et al. Development and validation of a preliminary definition of minimal disease activity in patients with juvenile idiopathic arthritis. Arthritis Rheum 2008;59: 1120-7.
25. Consolaro A, Ruperto N, Bazso A, et al. Development and validation of a composite disease activity score for juvenile idiopathic arthritis. Arthritis Rheum 2009; 61:658-66.
26. Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum 1997;40: 1202-9.
27. Pocock SJ. Current controversies in data monitoring for clinical trials. Clin Trials 2006;3:513-21.
28. Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004; 31:390-2.

Copyright © 2017 Massachusetts Medical Society.

RECEIVE IMMEDIATE NOTIFICATION WHEN AN ARTICLE IS PUBLISHED ONLINE FIRST

To be notified by e-mail when *Journal* articles are published Online First, sign up at NEJM.org.

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org on March 2, 2026.
Copyright © 2017 Massachusetts Medical Society. All rights reserved, including those for text and data mining, AI training, and similar technologies.

RHEUMATOLOGY

Rheumatology 2013;52:825–831
doi:10.1093/rheumatology/kes186
Advance Access publication 9 August 2012

Concise report

Current evidence of methotrexate efficacy in childhood chronic uveitis: a systematic review and meta-analysis approach

Gabriele Simonini[1], Priyamvada Paudyal[2], Gareth T. Jones[2], Rolando Cimaz[1] and Gary J. Macfarlane[2]

Abstract

Objective. To summarize evidence regarding the effectiveness of MTX in the treatment of childhood autoimmune chronic uveitis (ACU).

Methods. A systematic search of articles between January 1990 and June 2011 was conducted using EMBASE, Ovid MEDLINE, Evidence-Based Medicine Reviews—ACP Journal Club, the Cochrane Library and EBM Reviews. Studies investigating the efficacy of MTX as a single immunosuppressant medication in the treatment of ACU refractory to therapy with topical treatment and/or systemic treatment in children (416 years) were eligible for inclusion. The primary outcome measure was the improvement of intraocular inflammation, expressed as Tyndall, as defined by the Standardization of Uveitis Nomenclature working group criteria. The effect measure for each study was the proportion of people classified as responders. We determined a combined estimate of the proportion of children in the eligible studies responding to MTX.

Results. The initial search identified 246 articles of which 52 were potentially eligible. Nine eligible articles, all retrospective chart reviews, remained in the analysis. The number of children in studies ranged from 3 to 25, and the dose of MTX varied from 7.5 to 30 mg/m^2. Altogether, 95 of 135 children responded to MTX. The pooled analysis suggested that MTX has a favourable effect in the improvement of intraocular inflammation: the proportion of responding subjects was 0.73 (95% CI 0.66, 0.81).

Conclusion. Although randomized controlled trials are needed, the available evidence supports the use of MTX in the treatment of childhood ACU: approximately three-quarters of patients on MTX can expect improvement in intraocular inflammation.

Key words: methotrexate, autoimmune chronic uveitis, childhood, refractory uveitis.

Introduction

Non-infectious uveitis in childhood, with an incidence and prevalence estimated at 5 and 30 per 100 000, respectively, is a serious disease, with the potential for significant long-term complications and eventually blindness. Although frequently associated with an underlying systemic disease, e.g. JIA, Behc¸ et's disease, sarcoidosis or tubulointerstitial nephritis, a significant number of cases are idiopathic. In case of refractory uveitis, early and aggressive immune-modulatory treatment, even in children, seems a reasonable approach to control inflammation, to achieve a CS-sparing effect and to decrease the risk of sight-threatening ocular damage [1]. However, there is much less experience and fewer cumulative data in treating children with uveitis or other inflammatory ocular diseases [2], and a lack of randomized controlled trials (RCTs) means that treatment with immunosuppressive drugs is supported only at evidence level III: expert opinion, clinical experience or descriptive studies [3]. MTX, a folate analogue inhibiting the enzyme

[1]Rheumatology Unit-Department of Paediatrics, University of Florence, Firenze, Italy and [2]Musculoskeletal Research Programme-Epidemiology Group, Institute of Applied Health Sciences, University of Aberdeen, UK.

Submitted 17 January 2012; revised version accepted 30 May 2012.

Correspondence to: Gabriele Simonini, Rheumatology Unit-Department of Pediatrics, University of Florence, Anna Meyer's Children Hospital, viale Pieraccini 24, Firenze 50139, Italy.
E-mail: gabriele.simonini@unifi.it

Downloaded from http://rheumatology.oxfordjournals.org/ at National Dong Hwa University Library on March 28, 2014

© The Author 2012. Published by Oxford University Press on behalf of the British Society for Rheumatology. All rights reserved. For Permissions, please email: journals.permissions@oup.com

dihydrofolate reductase, is the most frequently used immunosuppressive in the paediatric uveitis population, but the lack of evidence from RCTs limits our understanding of effectiveness, the optimal time to start therapy and optimal duration [2, 3]. Due to its common use as steroid-sparing treatment in children, the purpose of this review is to summarize the best available evidence to date regarding the effectiveness of MTX in childhood autoimmune chronic uveitis (ACU).

Methods

Eligibility criteria

The following criteria were used to select eligible studies: (i) patients had vision-threatening non-infectious autoimmune uveitis; (ii) autoimmune uveitis was refractory to therapy with topical and/or systemic treatment, thus showing a chronic disease course with regard to steroid therapy according to the Standardization of Uveitis Nomenclature (SUN) criteria definition, that is persistent uveitis characterized by relapse within 3 months after discontinuation of therapy; (iii) patients had disease onset at or before 16 years of age; (iv) patients received MTX as single immunosuppressant medication for the treatment of uveitis; (v) outcome measures to assess the effectiveness of MTX were collected according to the SUN criteria [4]. Intraocular inflammation was considered active or uncontrolled if the inflammatory activity was grade 51+ at any examination. Uveitis was defined as improved, and MTX as successful, when its activity decreased by two steps in the level of inflammation (anterior chamber cells and/or vitreous haze) or decreased to grade 0 [4]. For studies not completely adherent to the SUN criteria and those performed before 2005, where possible, we retrospectively applied the SUN activity terminology with regard to reported activity grading and only an activity grade of 0 was considered as improved; (vi) studies were published in English. Exclusion criteria were as follows: (i) the concomitant use of other immunosuppressant agents in addition to MTX; (ii) starting time of MTX administration after 16 years of age; and (iii) lack of applicability/adherence to the SUN working group criteria definition of improvement in uveitis activity.

Outcome measures

The main outcome measure used to assess the effect of MTX was the improvement of intraocular inflammation as Tyndall (anterior chamber cells), according to the definition of improvement of the SUN working group criteria [4]. As secondary outcomes, tapering and/or stopping systemic steroid administration, improvement in visual acuity post MTX treatment according to the SUN working group criteria, discontinuation of MTX, time to remission (the duration of MTX treatment needed to achieve remission-inactive disease), time on remission on therapy (the duration of on-going/persistent remission, while MTX treatment continued) and time on remission off therapy (the period with on-going/persistent remission after discontinuing MTX treatment), and safety of administered drug were considered.

Information sources

Publications were retrieved using a computerized search of the following databases: EMBASE, Ovid MEDLINE, Evidence-Based Medicine (EBM) Reviews—ACP Journal Club, EBM Reviews—Cochrane Central Register of Controlled Trials, EBM Reviews—Cochrane Database of Systematic Reviews and EBM Reviews—Database of Abstracts of Reviews of effects. Publications between January 1990 and June 2011 were included.

Search strategy

Databases were searched with the key words chronic uveitis or chronic iridocyclitis or recurrent uveitis or refractory uveitis or non-infectious uveitis or autoimmune uveitis or inflamma$ ocul$ or inflamma$ eye and were crossed with Metotrexate or Methotrexate or MTX. Of note, we did not include children, age or age limits in the search as MeSH terms because we may have been able to extract, if possible, a subcohort of children from studies including both children and adults. No limitation with regard to the type of the study was entered. This strategy excluded records related to infectious and/or suppurative uveitis.

Study selection

Two reviewers (G.S., P.P.) independently screened the retrieved titles and abstracts and excluded duplicates and those obviously irrelevant. If the information in the abstracts was insufficient to make a decision, full papers were retrieved. Full papers of the selected articles were examined to determine whether they satisfied the criteria (G.S.) and then confirmed by a second reviewer (P.P.). The references of all eligible articles including reviews, expert opinion papers and systematic reviews were manually searched for potentially eligible publications. During consensus meetings (G.S., P.P., G.J., G.M.), disagreements of selections were resolved. In addition, we contacted authors of studies to determine whether data on an eligible subgroup were available.

Data extraction and items

Data were extracted by a single reviewer (G.S.) using a standard form, and checked by a second reviewer (P.P.). The data items extracted were as follows: study design, study start/end dates, length of follow-up, aim of the study, characteristics of participants (number of children, gender, age and associated conditions), dose of MTX and all outcome measures.

Statistical analysis

A meta-analysis was conducted to determine a combined estimate of the proportion of children in the eligible studies responding to MTX. The effect measure for each study was the proportion of participants classified as responders on MTX, with respect to intraocular inflammation [p(i)], where i refers to study i. If not provided in the

Downloaded from http://rheumatology.oxfordjournals.org/ at National Dong Hwa University Library on March 28, 2014

original manuscript, we calculated a 95% CI for the observed proportion. We tested for heterogeneity between the effect estimates from studies by conducting Cochrane's ^{2} test, which has k — 1 degrees of freedom, where k is the number of studies. In combining estimates, each study estimate was given a weight as the inverse of the proportion variance {i.e. n(i)/(p(i)[1 — p(i)] for study i}, where n(i) is the number of persons in study i. The combined estimate (p) and its standard error were then calculated in order to provide a 95% CI for this combined estimate of the proportion of patients improving.

Results

A total of 246 articles were identified by searches of databases, and, from these, 194 were excluded by examination of their titles and abstracts. Excluded studies were mainly studies not reporting paediatric cases, duplicates, studies on diseases other than autoimmune non-infectious uveitis, studies on overall mortality among patients receiving immunosuppressive treatment and studies on drugs other than MTX. Full text of the remaining 52 studies and 20 additional papers obtained by screening of their references were scrutinized. From the selection process, a total of nine relevant articles were deemed eligible. The other 63 potential eligible papers were excluded because they were reviews and/or expert opinion papers, they had no information regarding MTX efficacy as single immunosuppressive therapy, it was not possible to extract data on children from an overall study population and this was not available from authors, they did not include data on the principal outcome and/or were non-adherent to SUN criteria.

Table 1 summarizes data items from each eligible paper. All of the included studies were retrospective chart reviews, with a median follow-up time of 22.5 months (range 1-96). The number of children in these studies ranged from 3 to 28, providing a total of 135 children. It was not possible to extract detailed childhood descriptive data from some of the included studies: regarding gender from three studies [6, 9, 11] and age at uveitis onset from one [11]. Twenty-three subjects were male, 46 were female, and the median age of uveitis onset was 8 years (range 1.8-16). Chronic uveitis was associated with JIA (n = 121), early-onset sarcoidosis (n = 5) and tubulointerstitial nephritis (n = 3); the remaining were idiopathic. Six of the nine studies, with a total of 119 patients, were exclusively in JIA patients. Four studies reported a MTX dose between 7.5 and 30 mg/m^2, weekly, with 15 mg/m^2 the most commonly used dose. Four studies did not report the dose per m^2 of body surface and the MTX dose varied from 7.5 to 40 mg/week (median dose/week 12.5 mg); in one study MTX was administered at a dose of 0.5-1 mg/kg, weekly [13].

All included studies reported our main outcome measure: the improvement of intraocular inflammation as Tyndall (anterior chamber cells), according to the definition of improvement of the SUN working group criteria. Altogether, 95 children out 135 included responded to the treatment. The pooled analysis suggested that MTX has a favourable effect in the improvement of intraocular inflammation: 0.73 (95% CI 0.67, 0.81) was the combined estimate of the proportion of subjects improving on MTX (Fig. 1), and there was no evidence of heterogeneity across studies (P = 0.5). In a subanalysis including only those studies exclusively on JIA the estimate was very similar (0.74, 95% CI 0.67, 0.82).

Not all of the secondary outcome variables were present in each study and often were reported in diverse ways; thus we were not able to perform effect size analyses on these. All eligible papers, except Samson *et al.* [11], which did not report separate childhood data, had information regarding MTX discontinuation: MTX was discontinued in 35 (32.7%) out of 107 children, due to persistent remission in 21 (19.6%), lack of efficacy in 7 (6.5%) and adverse events in the remaining 7. Time to remission on MTX was described in 5 [5-7, 9, 12] out of 9 eligible papers: 45 (73.8%) out of 61 children obtained remission over a median time of 3.5 months (range 1-12). In addition, Foeldvari *et al.* [7] along with Weiss *et al.* [13] reported that 25/29 children remained on remission on MTX for a median time of 10.6 months (range 3-27). However, Heiligenhaus *et al.* [6] reported that remission as per SUN criteria was not obtained in any of the patients during a follow-up period of 27.6 months, and Foeldvari showed that, after MTX discontinuation, 2 of 6 children experienced uveitis flares 3 and 8 months later [7]. During MTX administration, tapering and/or stopping systemic steroid administration was possible in 22 of 23 children, but data were available from only four papers [5, 6, 8, 12]. Data regarding visual outcome have been reported in three articles [6, 8, 10]: 11 of 13 children (84.6%) showed improvement or stable visual acuity post MTX treatment. We could not extract information from Heiligenhaus study [6] because some of their patients (7 of 35) received MTX along with other immunemodulatory drugs. Among 107 MTX exposed children (data regarding children were not available from Samson *et al.*'s study [11]), 21 (19.6%) experienced adverse events due to MTX administration: 10 children had gastrointestinal discomfort, mostly nausea, 6 showed elevation of liver enzymes, reversible in 3, the remaining 5 children presented both nausea and increased liver function tests.

Discussion

We have estimated that the overall probability of improvement of intraocular inflammation in children affected by refractory ACU treated with MTX is 73%. The estimates of response were similar across studies, in particular when we considered those studies (6 of 9) that included only patients with JIA. However, several caveats have to be discussed before drawing firm conclusions from our systematic review. We recognize RCTs as the gold standard in assessing drug effectiveness; thus because none are available we acknowledge the generally poor quality of evidence. The majority of eligible studies only included patients with JIA, along with other diseases. However, the small number of the available studies meant we

Downloaded from http://rheumatology.oxfordjournals.org/ at National Dong Hwa University Library on March 28, 2014

TABLE 1 Main outcome measure and secondary outcomes entered for each of nine eligible studies

Reference, country	Follow-up	*n* (male/female)	Age, years	Disease	Dose of MTX	Results/outcomes	Adverse events
Kalinina Ayuso *et al.* (2011) [5], The Netherlands	3.1 years	22 (7/15)	8 (±4.0)	JIA	10-15 mg/m^2	Uveitis activity: Improved activity in 18 (82%) patients. Discontinuation of MTX: One patient due to gastrointestinal side effects. One patient due to elevated liver enzymes. Thirteen patients due to persistent remission. Steroid intake: Three of four patients on steroid stopped the intake within 2 months after the MTX treatment. Time for remission on MTX: Fifteen patients achieved remission within 1 year (median = 0.5). Time on remission on MTX: 1.5 years (1 month-3 years)	Eleven patients: Gastrointestinal complaints in 7 Elevated liver enzyme in 2 Combination of both in 2
Heiligenhaus *et al.* (2007) [6], Germany	27.6 (11-89) months	35 (15/20)	4.1 (1-7) onset arthritis; 4.8 (2-10) onset uveitis	JIA	15 mg/m^2	Uveitis activity: Improved activity in 25 (71%) patients. Mean time for uveitis flares up after the treatment: 10.3 (3-25) months. Discontinuation of MTX: One patient due to nausea. Three patients due to lack of efficacy. Time for improvement on MTX: 3.75 (2-11) months. Time on remission without MTX: None achieved remission. Steroid intake: All eight patients on steroid stopped the intake after MTX treatment. Visual acuity: Information available on 66 eyes out of 70 eyes; 91% stable and/or improved. Uveitis complications: No new complication occurred in 20. Progression was observed in 15 others.	Increased liver enzyme, 2 patients, nausea, 1 patient
Foeldvari and Wierk (2005) [7], Germany	2.2 years	25 (11/14)	7.9 (1.25-15.7) onset arthritis; 8 (1.8-9) onset uveitis	JIA	15.6 (10-25) mg/m^2	Uveitis activity: Improved activity in 21 (84%) patients. Discontinuation of MTX: Six patients due to persistent remission for 12 months. One patient discontinued due to MTX adverse events. Time for remission on MTX: 4.5 (1-12) months. Time on remission on MTX: 10.3 months (3-27).	One patient

(continued)

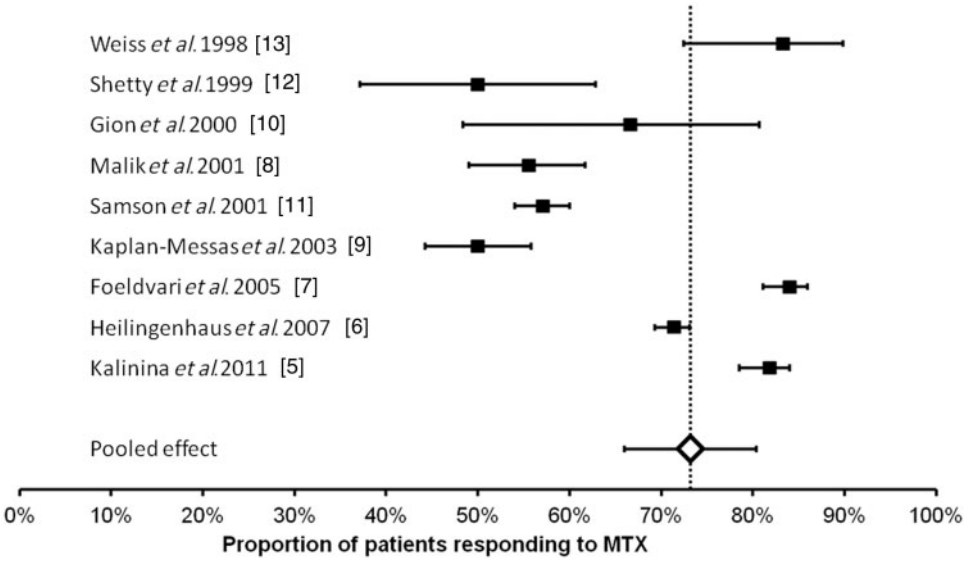
Downloaded from http://rheumatology.oxfordjournals.org/ at National Dong Hwa University Library on March 28, 2014

TABLE 1 Continued

Reference, country	Follow-up	*n* (male/female)	Age, years	Disease	Dose of MTX	Results/outcomes	Adverse events
Malik and Pavesio (2005) [8], UK	22.5 (4-40) months	9 (2/7)	11.9 (7-16)	Six patients with idiopathic uveitis and three with Sarcoidosis	23.8 (17.5-30) mg/m^2	Uveitis activity: Improved activity in 5 (55%) patients. Discontinuation of MTX: None. Steroid intake: All the seven children, taking steroid reduced intake after MTX treatment. Initial dose 18 (10-40) mg/die, final dose 2.85 (5-7.5) mg/die. Visual acuity: Improved or stable in all patients.	Nausea, 2 patients
Kaplan-Messas *et al.* (2003) [9], Israel	21.5 months (±12.6)	10	3-16	JIA	10-15 mg/week	Uveitis activity: Improved activity in 5 (50%) patients. Discontinuation of MTX: Three patients due to side effects. Two patients due to lack of efficacy. Two patients due to persistent remission after 20.9 (±9.2) months. Time for remission: 2.4 (±0.8) months.	Nausea/vomiting, elevated liver enzymes, 3 patients
Gion *et al.* (2000) [10], USA	19.6 months (6-34)	3 (2/1)	13 (13-15)	TINU	7.5-12.5 mg/week	Uveitis activity: Improved activity in 2 (67%) patients. Discontinuation of MTX: One patient-due to lack of efficacy. Steroid intake: Discontinued in the two patients in whom activity improved. Visual acuity: Among patients who improved in activity: one stable. one improved.	Abdominal pain, 1 patient
Samson *et al.* (2001) [11], USA	16.4 months (1-96)	21	-	JIA	12.3 (7.5-40) mg/week	Uveitis activity: Improved activity in 12 (59%) patients.	-
Shetty *et al.* (1999) [12], USA	28.8 months	4 (1/3)	10.5	2 JIA 2 Sarcoidosis	7.5-12.5 mg/week	Uveitis activity: Improved activity in two patients. Discontinuation of MTX: None. Steroid intake: Reduced intake in all patients. One patient stopped steroid within 30 months of MTX and three reduced the dose up to 0.15 mg/die in 20 months.	No adverse events
Weiss *et al.* (1998) [13], USA	10 months (6-12)	6 (-/6)	7 (4-14)	JIA	0.5-1 mg/kg/week	Uveitis activity: Improved activity in five patients. Discontinuation of MTX: One patient due to lack of efficacy. Time for remission: 3.5 (2.5-4) months (for four patients). Time on remission on MTX: 11 (8-12) months available for four patients.	Reversible liver toxicity, 2 patients

Downloaded from http://rheumatology.oxfordjournals.org/ at National Dong Hwa University Library on March 28, 2014

FIG. 1 Proportion of children with refractory ACU responding to MTX in each study and the overall effect size showed by the pooled analysis, 95% CI are shown.



could not consider results separately according to the underlying disease. We did not include studies when it was not possible extract information on eligible children from those studies (e.g. a study of Behc¸ et's disease [14]). This affected several large studies on this topic—e.g. Yu *et al.* [15]. We contacted authors to determine whether information was specifically available on children to allow the study to be included, but this did not result in any additional study being eligible. The main outcome measure used in this systematic review might be considered another limitation: the definition of improvement of the SUN working group criteria [4] is not assessed in childhood, and therefore not validated for childhood use. However, it is otherwise the only standardized measure available for assessing differences in uveitis inflammation, and thus to date, the only item able to compare different studies, across different decades and different childhood diseases. The different steroid use, as systemic administration rather than eye drop, significantly changed over the considered time period, might be an additional potential caveat.

There are no clear recommendations for MTX use in childhood, even though it is largely used in chronic uveitis, mostly when associated with JIA [2, 3, 16-20]. The results of this review could be helpful for clinicians in judging the utility of this treatment and its effect size on visual prognosis, as well in making a therapeutic decision based on current available evidence. Our findings support the clinical use of MTX for refractory ACU in children. However, it needs to be considered in the context that all the current evidence is from retrospective chart reviews. The results of this meta-analysis should prompt the conduct of RCTs on this topic, involving paediatric rheumatologists, ophthalmologists and pharmaceutical companies, to provide a higher quality evidence base.

Rheumatology key messages

- There are few cumulative data on treating children with chronic uveitis.
- MTX seems an effective therapy for childhood non-infectious uveitis associated with JIA and possibly other conditions.
- Randomized clinical trials in childhood ACU treatment seem mandatory.

Disclosure statement: G.T.J. has received grants/research support from Pfizer Inc, NY, USA. All other authors have declared no conflicts of interest.

References

1 Cunningham ET. Uveitis in children. Ocul Immunol Inflamm 2000;8:251-61.

2 Agle LMA, Vazquez-Cobian LB, Lehman TJA. Clinical trials in pediatric uveitis. Curr Rheum Rep 2003;5:477-81.

3 Simonini G, Cantarini L, Bresci C *et al*. Current therapeutic approaches to autoimmune chronic uveitis in children. Autoimmun Rev 2010;9:674-83.

4 Jabs DA, Nussemblatt RB, Rosembaum JT. Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop. Am J Ophthalmol 2005;140:509-16.

5 Kalinina Ayuso V, van de Winkel EL, Rothova A, de Boer JH. Relapse rate of uveitis post-methotrexate

Downloaded from http://rheumatology.oxfordjournals.org/ at National Dong Hwa University Library on March 28, 2014

treatment in juvenile idiopathic arthritis. Am J Ophthalmol 2011;151:217-22.

6 Heiligenhaus A, Mingels A, Heinz C, Ganser G. Methotrexate for uveitis associated with juvenile idiopathic arthritis: value and requirement for additional anti-inflammatory medication. Eur J Ophthalmol 2007;17:743-8.

7 Foeldvari I, Wierk A. Methotrexate is an effective treatment for chronic uveitis associated with juvenile idiopathic arthritis. J Rheumatol 2005;32:362-5.

8 Malik AR, Pavesio C. The use of low dose methotrexate in children with chronic anterior and intermediate uveitis. Br J Ophthalmol 2005;89:806-8.

9 Kaplan-Messas A, Barkana Y, Avni I, Neumann R. Methotrexate as a first-line corticosteroid-sparing therapy in a cohort of uveitis and scleritis. Ocul Immunol Inflamm 2003;11:131-9.

10 Gion N, Stavrou P, Foster CS. Immunomodulatory therapy for chronic tubulointerstitial nephritis-associated uveitis. Am J Ophthalmol 2000;129:764-8.

11 Samson CM, Waheed N, Baltatzis S, Foster CS. Methotrexate therapy for chronic noninfectious uveitis: analysis of a case series of 160 patients. Ophthalmology 2001;108:1134-9.

12 Shetty AK, Zganjar BE, Ellis GS Jr, Ludwig IH, Gedalia A. Low-dose methotrexate in the treatment of severe juvenile rheumatoid arthritis and sarcoid iritis. J Pediatr Ophthalmol Strabismus 1999;36:125-8.

13 Weiss AH, Wallace CA, Sherry DD. Methotrexate for resistant chronic uveitis in children with juvenile rheumatoid arthritis. J Pediatr 1998;133:266-8.

14 Zakka FR, Chang PY, Giuliari GP, Foster CS. Current trend in the management of ocular symptoms in Adamantiades-Bec¸ het's disease. Clin Opthalmol 2009;3:567-9.

15 Yu ENY, Meniconi ME, Tufail F, Baltatzis S, Foster CS. Outocomes of treatment with immunomodulatory therapy in patients with corticosteroid-resistant juvenile idiopathic arthritis-associated chronic iridocyclitis. Ocul Immunol Inflam 2005;13:353-60.

16 Lyon F, Gale RP, Lightman S. Recent developments in the treatment of uveitis: an update. Expert Opin Investig Drugs 2009;18:609-16.

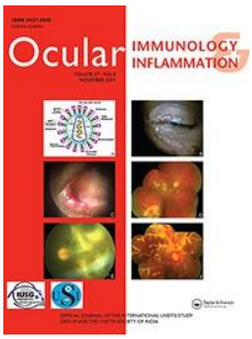
17 Jabs DA, Rosenbaum JT, Foster CS *et al*. Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. Am J Ophthalmol 2000;130:492-513.

18 Zierhut M, Doycheva D, Biester S *et al*. Therapy of uveitis in children. Int Ophthalmol Clin 2008;48:131-52.

19 Holzinger D, Frosch M. New treatment approaches in juvenile idiopathic arthritis. Int J Adv Rheumatol 2009;7:1-7.

20 Sharma SM, Dick AD, Ramanan AV. Non-infectious pediatric uveitis: an update on immunomodulatory management. Paediatr Drugs 2009;11:229-41.

Downloaded from http://rheumatology.oxfordjournals.org/ at National Dong Hwa University Library on March 28, 2014



Ocular Immunology and Inflammation

ISSN: 0927-3948 (Print) 1744-5078 (Online) Journal homepage: www.tandfonline.com/journals/ioii20

Efficacy of High-Dose Methotrexate in Pediatric Non-Infectious Uveitis

Wietse G. Wieringa, Wineke Armbrust, G. Elizabeth Legger & Leonoor I. Los

To cite this article: Wietse G. Wieringa, Wineke Armbrust, G. Elizabeth Legger & Leonoor I. Los (2019) Efficacy of High-Dose Methotrexate in Pediatric Non-Infectious Uveitis, Ocular Immunology and Inflammation, 27:8, 1305-1313, DOI: 10.1080/09273948.2018.1529800

To link to this article: https://doi.org/10.1080/09273948.2018.1529800

© 2019 The Author(s). Published with license by Taylor & Francis Group, LLC.

Published online: 22 Oct 2018.

Submit your article to this journal

Article views: 3651

View related articles

View Crossmark data

Citing articles: 7 View citing articles

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=ioii20

Ocular Immunology & Inflammation, 2019; 27(8): 1305–1313
© 2019 The Author(s). Published with license by Taylor & Francis Group, LLC.
ISSN: 0927-3948 print / 1744-5078 online
DOI: 10.1080/09273948.2018.1529800

OPEN ACCESS Check for updates

ORIGINAL ARTICLE

Efficacy of High-Dose Methotrexate in Pediatric Non-Infectious Uveitis

Wietse G. Wieringa, BSc, MPA[1], Wineke Armbrust, MD, PhD[2], G. Elizabeth Legger, MD[2], and Leonoor I. Los, MD, PhD[1,3]

[1]*Department of Ophthalmology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands,* [2]*Department of Children's Rheumatology and Immunology, Beatrix Children's Hospital, Groningen, the Netherlands, and* [3]*W.J. Kolff Institute, Graduate School of Medical Sciences, University of Groningen, Groningen, the Netherlands*

ABSTRACT

Purpose: To analyze the efficacy of high dose (≥ 15mg/m2/week) methotrexate (MTX) versus low dose (<15mg/m2/week) MTX in relation to time to remission on medication.

Methods: Retrospective observational cohort study of pediatric patients with auto-immune uveitis with or without underlying systemic disease treated with MTX at the University Medical Center Groningen (the Netherlands) between 1990 and 2014. Primary outcome was time to remission on medication, which was defined as an observable inactive disease in the affected eye for longer than 3 months without the use of systemic corticosteroids.

Results: A total of 42 patients were included. Mean age at uveitis diagnosis was 6.5 years (range 1.7 – 14.4), and 22 (52.4%) patients were male. Bilateral disease was found in 33 patients. Most patients (*n*=25) had anterior uveitis. JIA was the underlying systemic disease in 21 patients. Overall, 28 (66.7%) patients reached remission on medication in (median) 22.5 months (IQR 10.4- 45). Time to remission on medication in the low dose group (median 35.2, IQR 20.5 – 72.1 months) was significantly longer than in the high dose group (median 16.6, IQR 7.8 – 22.5 months) (p= 0.01). No statistically significant differences in ocular complications, steroid-sparing effect, cumulative dosage and side effects of MTX were found between the high and low dose groups.

Conclusion: In this retrospective study on pediatric auto-immune uveitis, high dose MTX was associated with a shorter time to remission on medication as compared to low dose MTX, while side effects were comparable in both groups.

KEYWORDS: Pediatric auto-immune uveitis, high dose methotrexate, efficacy, side effects

INTRODUCTION

Uveitis is an inflammatory disorder of the eye, involving the uveal tract. It is classified as anterior, intermediate, posterior or panuveitis, depending on the part of the eye affected by the inflammatory process. Uveitis can be associated with a systemic auto-immune disease, can be caused by an infection, and it can occur as an isolated ocular condition. In the developed countries, 87–89% of the pediatric uveitis cases are non-infectious and the majority (41.5%) are related to juvenile idiopathic arthritis (JIA).[1]

Pediatric uveitis is a potentially blinding disorder and accounts for 3.2–15.2% of all cases of legal blindness in the affected eye(s) in the United States.[2,3] Many children with uveitis do not report any symptoms. [4] This may lead to a delay in

Received 9 July 2018; revised 17 September 2018; accepted 25 September 2018

Correspondence: Wietse G. Wieringa, Bsc, MPA, Department of Ophthalmology, University Medical Center Groningen, Hanzeplein 1, 9700 RB Groningen, The Netherlands. E-mail: w.wieringa@umcg.nl

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way.

19

diagnosis and treatment, resulting in complications such as band keratopathy, posterior synechiae, cataract, glaucoma and amblyopia, which give a guarded prognosis.[5] Early detection and aggressive treatment of uveitis can prevent visual loss and ocular complications. [6]

The first line of treatment are local corticosteroids. If these are insufficient, local injections with corticosteroids can be considered. Systemic prednisone is started in case of severe uveitis or in case of failure of the local therapy. In case of chronic uveitis, steroid sparing immunosuppressive therapy may be indicated. Because of its long track record and good safety profile, methotrexate (MTX) is the steroid sparing immunosuppressive agent of first choice in almost all cases of non-infectious pediatric uveitis. [7]

MTX is an efficacious drug, since remission on medication is reached in about 70% of pediatric non-infectious uveitis cases. [8] However, MTX also has side-effects such as gastro-intestinal discomfort (nausea and vomiting), which are frequently reported, and the less common hepatic toxicity and bone marrow suppression. [9,10] Also, anticipatory nausea and needle phobia in case of subcutaneous administration of MTX are common.

In pediatric uveitis patients, evidence regarding optimal dosage of MTX is scarce. [8,11] Frequently used medication regimens start with low-dose MTX, with increasing doses at 2–6 monthly intervals in case of insufficient effectiveness. In the treatment of JIA there is evidence on the effectiveness of higher starting doses and faster dose-escalation schemes. [11–13] Therefore, it would be relevant to evaluate whether such schemes would also be more efficient in the treatment of pediatric uveitis.

Optimizing the treatment of pediatric uveitis patients would be relevant because vision threatening complications are directly related to uveitis activity. [6,14] Shortening the time to remission on medication will probably reduce or postpone long-term ocular complications and may improve visual prognosis. Also, it seems likely that a higher steroid sparing effect will be achieved with less side effects and complications of systemic corticosteroids. The present retrospective study aims primarily to evaluate the effectiveness of high-dose (≥15 mg/m^2/week) and that of low-dose MTX (<15 mg/m^2/week) in relation to time to remission on medication. Secondarily, the steroid sparing effect, cumulative dosage of MTX, side effects of MTX treatment, ocular complications and visual acuity are evaluated.

PATIENTS AND METHODS

We performed a retrospective observational cohort study on pediatric patients treated with MTX for uveitis between 1990 and 2014 at the University Medical Center of Groningen, The Netherlands. This study reflects the daily practice in a tertiary center. The Medical Ethical Committee of the University Medical Center of Groningen ruled that approval was not required for this study. Patients were identified from the digital uveitis database of the University Medical Center of Groningen. All patients who were younger than 18 years of age at the start of their uveitis and who were treated with MTX for longer than 6 months were included. MTX treatment was classified as high (≥15 mg/m^2/week, maximum of 25 mg/week/sc) or low (<15 mg/m^2/week) dose, based on the MTX dose given before remission on medication was reached or medication was switched. Based on this classification, patients were divided into a high (≥15 mg/m2/week) or low (<15 mg/m2/week) -dose group. Before 2007, most patients received low-dose MTX, and hereafter most patients were treated with high-dose MTX. This reflects evolving treatment strategies. Data collection was done from the pediatric and ophthalmological medical records. The diagnosis of uveitis was made by an ophthalmologist specialized in uveitis and dedicated to this patient group. During the follow up period two other ophthalmologists were occasionally involved in the ophthalmological care for these patients. Classification of uveitis was done according to the Standardization of Uveitis Nomenclature (SUN) criteria [15] and was based on the available information in the ophthalmological medical record. Children were evaluated for the presence of an underlying systemic disease by a pediatric rheumatologist. When JIA was diagnosed, it was classified according to the ILAR (International League of the Association for Rheumatology) criteria. [16]

General Descriptives

For each patient the following descriptives were recorded: age, gender, ethnicity, date of first diagnosis of uveitis (further referred to as: uveitis onset), type of uveitis, laterality, date of onset of arthritis, diagnosis and subtype of underlying systemic disease, weight and length (at several time points during follow-up), anti-nuclear antibody (ANA) serologic status, HLA B27 status and ophthalmological findings at presentation. Prognostic signs for a worse outcome (young age, male gender, severity of uveitis at presentation, vitreous involvement and oligo arthritis) were recorded. [5]

Uveitis Diagnosis and Classification

Uveitis was diagnosed when cells could be observed in the anterior chamber (AC) or in the vitreous. Activity of AC inflammation (cells) evaluated by standard slit-

lamp examination was recorded according to the recommendations of the SUN working group.[15] Cells in vitreous humor were scored as being present or not. The diagnosis of posterior and panuveitis was made by fundoscopy and in some cases fluorescein angiography (FA) was performed.

Treatment

MTX dosage and route of administration at the start was recorded as mg/m^2/week/orally or subcutaneously. Indications (uveitis, arthritis or both) and date for MTX dosage changes were documented. The MTX dosage was related to body surface area (BSA) at the moments of dosage change. Body surface area was calculated by the Mosteller formula [BSA (m^2) = (Height(cm) × Weight (kg)/3600)^{½}].[17] Measurements of length and weight were performed at the start of the treatment and during follow up. Length and weight values were plotted routinely in the growth curves corrected for age, sex and race. When a value was missing the growth line was plotted between the two existing values. Cumulative dosages of MTX were calculated by multiplying the time (weeks) to remission on medication by the dose in mg/m^2 of MTX. Route of administration (oral or subcutaneous) and – in case the route of administration was switched – the indications for switch were noted. Side effects and indications to stop MTX were recorded. Initially, liver enzyme testing is done after four weeks, and thereafter every 3 months. In case of elevated liver enzymes, testing is more frequently performed. The steroid sparing effect of MTX was evaluated by calculating/counting the number of weeks in which patients were treated with oral corticosteroids in a dosage of more than 0.5 mg/kg/day.

In case of cataract or glaucoma surgery (Baerveldt glaucoma implant), patients were given intravenous corticosteroids during surgery followed by a tapering dosage of oral corticosteroids in the period thereafter. In case of glaucoma surgery MTX was stopped for 2 months prior to surgery and re-introduced after the Baerveldt implant was functional. During this period, patients were treated with oral corticosteroids.

Remission on Medication

Remission on medication was defined as an observable inactive disease in the affected eye for longer than 3 months without the use of systemic corticosteroids or local steroid injections (subtenon or subconjunctival). During this period local steroid medication such as eye drops or ointment were allowed in a maintenance dosage of less than 4 drops per eye daily. With this treatment regimen, sufficient compliance-adherence was expected and it was regarded as being compatible with daily activities.[18] Patients were advised to use the eye drops during mealtimes and – when necessary – before sleeping. A relapse was defined as a recurrence of the uveitis after a quiet episode described in the patient file. The total follow up time, time to remission on medication, time between dose adjustments and time to cataract and glaucoma surgery were documented.

Visual Acuity

The decimal equivalent of the Snellen visual acuity (VA) of the affected eyes was recorded at presentation, 6, 12 and 24 months and at last follow-up. Snellen VA was converted to logarithm of the minimum angle of resolution units (LogMAR) VA for calculations.

Ocular Complications

The following ocular complications were scored per eye; band keratopathy, posterior synechiae, cataract and amblyopia. Ocular hypertension was defined as an intra-ocular pressure above 21 mmHg without treatment.[15] Glaucoma was defined as glaucomatous changes to the optic nerve or visual field.[15] Surgery for medically uncontrollable intra-ocular pressure was separately scored.

Statistics

Statistical analysis was performed by SPSS® software version 22 (SPSS, Inc., Chicago, IL) .A $P < 0.05$ was considered statistically significant. Descriptive statistics were used to present mean and standard deviation (SD) in normally distributed data or median and range if data were abnormally distributed. For the differences between the nominal data in the high and low-dose groups we used the Chi-square test. In case of non-normally distributed linked samples, the Wilcoxon test for paired samples and the Mann-Whitney U test for independent samples were used. Analysis of VA at presentation compared to that at 6, 12 and 24 months and at the end of follow up was done by the independent samples T-test. A Kaplan-Meier survival analysis with a log rank test was used to analyze survival curves and to compare the two treatment groups. Finally, a multiple regression model was used to assess the weight and influence of treatment groups, age, gender, underlying disease and anatomic location of the uveitis on the time to remission on medication.

RESULTS

Patient, ocular and disease characteristics at uveitis onset are summarized in Table 1. A total of 44 (22 male)

© 2019 the Author(s). Published with license by Taylor & Francis Group, LLC

TABLE 1. Patient characteristics.

	Total	low	high	Difference high/low
Number of patients	42	25	17	
Mean age at onset uveitis (yrs, SD)	6.5 (± 3.4)	7.6 (± 3.5)	5.0 (± 2.7)	P 0.01¥
Median follow up (years, range)	5.6 (0.9 – 19.2)	6.9 (1.4 – 15.4)	4.0 (0.9 – 19.2)	P 0.02¥
Male/female	22/20	13/12	9/8	P 0.95§
Anatomic location uveitis				P 0.64§
Anterior uveitis	25	15	10	
Intermediate uveitis	7	4	3	
Posterior uveitis	2	2	0	
Pan uveitis	8	4	4	
Bilateral disease	33	20	13	P 0.55§
Prognostic poor at presentation*	34	18	16	P 0.11§
Ethnicitiy				P 0.53
Caucasian	32/42	19	13	
Other	10/42	6	4	
Underlying systemic disease	21/42	11	10	P 0.35§
Cogan's syndrome	1/42	0	1	
JIA	21/42	12	9	P 0.55§
Mean age at onset JIA (yrs, SD)	4.1 (±2.2)	4.4 (±2.2)	3.5 (±2.1)	P 0.38¥
Systemic	1	1	0	
Oligo articular persistent	10	4	6	
Oligo articular extended	5	4	1	
Poly articular RF-positive	1	1	0	
Poly articular RF-negative	4	2	2	
Lab characteristics				
ANA positive	23/42	15	8	P 0.53§
HLA-B27 positive	2/14	0	2	P 0.16§

* One or more of the following characteristics present: young age (< 6 years), male gender, severity of uveitis at presentation, signs of vitreous involvement, oligo arthritis

¥ Mann-Whitney test

§ Chi-square test.

JIA = juvenile idiopathic arthritis, ANA = anti-nuclear antibody

TABLE 2. Remission on medication, cumulative MTX dose and steroid use.

	Total	Low	High	Difference high/low
Patients (%) reaching remission on medication	28/42 (66.7%)	15/25 (60%)	13/17 (76.5%)	P 0.27§
Time to remission on medication (months, IQR)	Median 22.5 (10.4 – 45.0)	Median 35.2 (20.5 – 72.1)	Median 16.6 (7.8 – 22.5)	P 0.01*
Median cumulative dose MTX ¶ (mg/m^2, IQR) (n = 28)	Median 1329.3 (604–2172.3)	Median 1597.4 (693–2871.2) (n = 15)	Median 1213.1 (538.9–1934.3) (n = 13)	P 0.29*
Patients with remission on oral administration	9/28 (32.1%)	8/9 (88.9%)	1/9 (11.1%)	P 0.06§
Time to remission on oral administration (months, IQR)	Median 20.5 (6.3 – 41) (n = 9)	Median 24.4 (n = 8) (8.4 – 44.5)	2.5 (n = 1)	P 0.12*
Cumulative dose MTX¶ (mg/m2, IQR) (n = 9)	Median 693 (320.3 – 1484.6)	Median 821.2 (396.6 – 1567.7) (n = 8)	282.1 (n = 1)	P 0.25*
Patients with remission on subcutaneous administration	19/28 (67.9%)	7/19 (36.8%)	12/19 (63.2%)	P 0.01§
Time to remission (months, IQR) on sc administration	Median 23.5 (12.5 – 50.4)	Median 62.6 (35.1 – 118.1)	Median 17.2 (8.6 – 23)	P 0.001*
Cumulative dose MTX¶ (mg/m^2 IQR) (n = 19)	Median 1597.3 (956.6 – 2875.5)	Median 2871.2 (1597.3 −9606.1) (n = 7)	Median 1276.6 (650.4 −2065.7) (n = 12)	P 0.05*
Steroid use‡ (weeks, IQR) (n = 26) ¥	Median 17.2 (11.9 – 26.8)	Median 18.3 (10 – 29.2) (n = 13)	Median 16 (11.9 – 22.6) (n = 13)	P 0.70*

§ Chi-square test

*Mann-Whitney test

¶ Total dosage of MTX until remission on medication

‡ Number of weeks on >0.5 mg/kg daily

¥ Two patients in the low-dose group both with mild JIA related uveitis were not treated with systemic corticosteroids

IQR = inter quartile range. Sc = subcutaneous administration

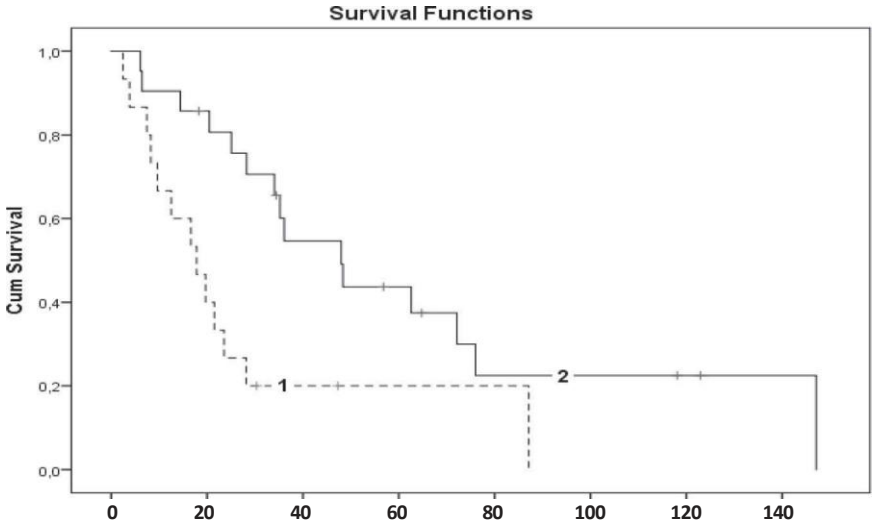


FIGURE 1. Kaplan-Meier curves showing the time to and chance of remission on medication. Cum = cumulative. 1 = High dose (>15 mg/m²/week) methotrexate. 2 = Low dose (<15 mg/m²/week) methotrexate. The difference between the groups is statistically significant (P = 0.007, Log Rank test). HD = High dose, LD = Low dose

patients were primarily identified, two of whom (both female, Caucasian JIA- patients with longstanding bilateral anterior uveitis) were excluded because of incomplete data. In four patients with JIA-uveitis active arthritis (next to the uveitis) was the indication to start MXT. The 17 patients in the high-dose group were significantly younger (mean 5.0 ± 2.7 years) than the 25 patients in the low-dose group (mean 7.6 ± 3.5 years, P = 0.01). The follow up time was statistically significantly shorter in the high-dose group (median 4.0 years, range 0.9–19.2) as compared to the low-dose group (median 6.9 years, range 1.4–15.4, P = 0.02).

No differences were found between the high and low-dose groups regarding severity of the uveitis at presentation and the need for ocular surgery for cataract or medically uncontrollable intra ocular pressure during follow-up (Table 1).

The median starting dose and median maximum dose were both significantly lower in the low-dose group. The median starting dose in the low-dose group was 10.4 (min 5.7 – max 14.8) mg/m²/week and in the high-dose group 17.9 (min 11.8 – max 24.6) mg/m²/week (P < 0.001). The median maximum dose in the low-dose group was 13.4 (min 10.9 – max 14.9) mg/m²/week and in the high-dose group it was 20.7 (min 16.7 – max 25.3) mg/m²/week (P < 0.001). The time to maximum dose of MTX was -although not statistically significant -shorter in the high-dose group. The median time to maximum dose in the low-dose group was 20.9 (min 2.1 – max 120.1) months versus median 9.1 (min 4.6 – max 21.7, P = 0.10) in the high-dose group.

A total of 13 patients (76.6%) treated with high-dose MTX reached remission on medication after a median of 16.6 months (inter quartile range (IQR); 7.8–22.5). In the low-dose group 15 (60%) patients reached remission on medication in a median of 35.2 months (IQR; 20.5–72.1). The difference in time to remission on medication was statistically significant (P = 0.01) (Table 2, Figure 1).

Patients (n = 12) treated with high-dose subcutaneous MTX had a statistically significantly shorter time to remission on medication (median 17.2 months) than patients (n = 7) who reached remission on medication on low-dose subcutaneous MTX (median 62.6 months; p = 0.001; Table 2). Of the 9 patients who reached remission on medication on oral MTX, 1

TABLE 3. MTX-related side effects.

	Total n = 41*	Low n = 24*	High n = 17	P value§ High vs Low
Patients	25/41	14/24	11/17	P 0.74
Nausea	13/41	7/24	6/17	P 0.43
Needle phobia	7/41	3/24	4/17	P 0.33
Elevated liver enzymes¶	9/41	5/24	4/17	P 0.78
Combination	4/41	1/24	3/17	P 0.14

*1 missing in the low-dose group

§ Chi-square test

¶ Alanine aminotransferase (ALT) above 45 U/L and aspartate aminotransferase (AST) above 40 U/L

© 2019 the Author(s). Published with license by Taylor & Francis Group, LLC

TABLE 4. Ocular complications*.

	Eyes	Low dose	High dose	Difference¶ high/low
Band keratopathy	18/75	10/51	8/24	P 0.22
Posterior synechiae	34/75	23/51	11/24	P 0.49
Cataract	38/75	23/51	15/24	P 0.42
Cataract extraction	31/75	23/51	8/24	P 0.56
Baerveldt glaucoma implant	30/75	20/51	10/24	P 0.84
Amblyopia	12/75	7/51	5/24	P 0.26

*Affected eyes at any moment during follow up.
¶ Chi-square test between high and low dose

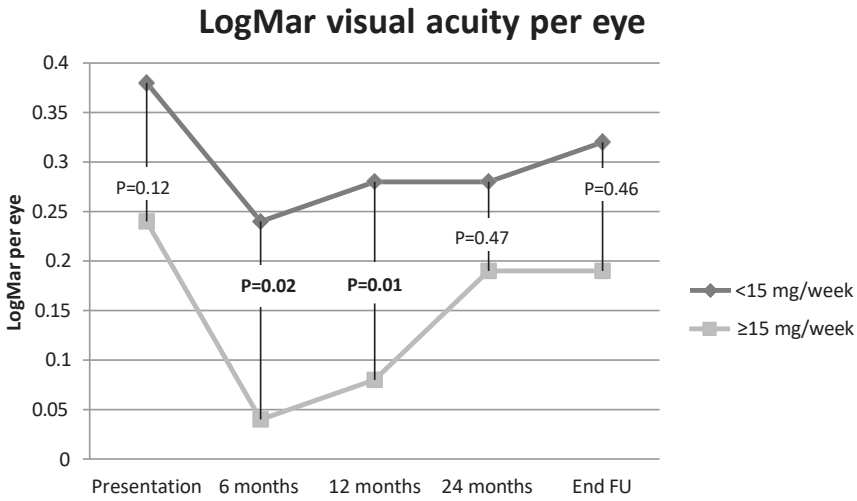


FIGURE 2. Visual acuity in the high MTX dose group is better at all time points (lower LogMAR visual acuity corresponds to higher Snellen visual acuity) and the difference is statistically significant at 6 and 12 months.
*FU=follow up; §=Independent Samples T-Test

was treated with high-dose and 8 with low-dose MTX. By using a multivariate linear regression model time to remission on medication was analyzed. Within this model; age, gender, anatomic location of the uveitis, presence of juvenile idiopathic arthritis and the two treatment groups were taken into account. With this model (R^2 = 0.4, P = 0.05, B = 68.6 (CI 24.8 – 112.4)) we found that treatment with a higher dose MTX was associated with a statistically significantly shorter time to remission on medication (P 0.008) (Table 4).

The cumulative dose of MTX, in the 28 patients reaching remission on medication, was lower in the high-dose group as compared to the low-dose group, but this difference was not statistically significant (Table 2). MTX related side effects were reported by 25 out of 41 patients (Table 3). No statistically significant differences regarding side effects were found between the high- and low-dose groups.

On average, patients used more than 0.5 mg/kg/day of oral corticosteroids for 17.2 weeks (Table 2); no statistically significant differences in steroid use were seen between the two groups (Table 2). The high-dose group had a better visual acuity at presentation (Figure 2), but this difference was not statistically significant. At 6 and 12 months, visual acuity in the high-dose group was significantly higher than in the low-dose group. At later time points, this difference was no longer statistically significant (Figure 2).

DISCUSSION

This study of 42 pediatric patients with non-infectious uveitis shows that patients who were treated with a high dose of MTX (≥15 mg/m^2/week, maximum of 25 mg/week/sc) reached remission on medication sooner compared to patients who were treated with a low dose of MTX (<15 mg/m^2/week). The data also indicate that an MTX dose of ≥15 mg/m^2/week administered by subcutaneous injection is the most effective in establishing rapid remission on medication. With regard to visual acuity measurements at 6 and 12 months the data suggests a favorable outcome in the high-dose group. High- and low-dose groups were comparable with regard to severity of uveitis, incidence of ocular complications and surgery, steroid

sparing capacity of MTX, cumulative dose of MTX and side effects.

In our study, we found an overall success rate of 67% of MTX in the treatment of uveitis, which is similar to the effectiveness of 70% described in the literature. [8] More patients reached disease remission on subcutaneously administered MTX when compared to oral administration. Time to disease remission on medication did not significantly differ between patients on oral and subcutaneous administration. Patients treated with high-dose MTX had a significantly shorter time to remission on medication than the patients treated with low-dose MTX. A shorter time to remission on medication may be favorable for the prognosis of an inflammatory disease as was shown for rheumatoid arthritis (RA) in several studies. [19–22] By analogy, it would be plausible to assume that achieving early remission on medication will help to prevent or delay secondary complications of uveitis and to preserve visual function. [14,23]

Our retrospective study did not find statistically significant differences in the prevalence of ocular complications at any time point between high and low-dose groups, including complications already present at presentation. Therefore and because high-dose MTX was mainly given from 2007 onwards, we assume that MTX dose was mainly based on evolving treatment strategies and not primarily on the severity or complications of the uveitis. We did find a statistically significantly better visual acuity in the high-dose group at 6 and 12 months, which is suggestive of a better outcome favorable for the daily functioning and development of a child. However, there may be some inclusion bias, since the high-dose group had a better, though not statistically significantly better, visual acuity at presentation.

A faster remission reached by a predefined quick dose escalation scheme is probably more rewarding and motivating for a patient than a slow escalation scheme based on dose adjustments because of persisting disease activity. Also, the frequently reported MTX intolerance after longer use of MTX, might be prevented if remission on medication is sooner reached.-[24,25] Finally, MTX failure will be apparent after a shorter time interval when a faster dose escalation scheme is used, thus enabling an earlier switch in therapy. Our high-dose group is comparable to the intermediate MTX dose group of Ruperto et al. [12] who evaluated the effectiveness and side effects of MTX in JIA. They found a better effect of an intermediate (15 mg/m^2/week) MTX dose as compared to a low MTX dose (10 mg/m^2/week). In addition, they observed that increasing the MTX dose to 30 mg/m^2/week (with a maximum of 40 mg/week by intra muscular or subcutaneous administration) was not associated with any therapeutic benefit and resulted in more adverse events.[12] In line with that study, our maximum MTX dose is 25 mg/week by subcutaneous administration. Our findings indicating a positive effect of higher MTX dosages in pediatric non-infectious uveitis are in line with the results of a systematic review[8] that showed that the proportion of children responding to MTX is the highest in the studies with an MTX dosage of ≥15 mg/m^2/week.[26–29]

No significant differences were found in steroid sparing effect, cumulative MTX dosage until remission on medication and side effects of MTX between our two study groups. The first is possibly explained by our reluctance to use systemic steroids in children, since they were mainly given in case of severe uveitis at presentation and peri-operatively. The second reflects that remission on medication is reached sooner in the high-dose group as compared to the low-dose group. And the latter may be explained by the lower cumulative MTX dosage in the high-dose group.

The results of the current study are limited by the fact that the study is retrospective, the numbers of patients are small and there is a large variability in follow up time. The better outcome in the high-dose group is possibly influenced by positive developments in treatment options and improved screening programs for JIA uveitis. The reporting of side-effects is influenced in an uncertain way because of the retrospective study design and variability in follow up time. All patients were included from a tertiary center and two patients had to be excluded because of missing data, therefore this study does not represent the total spectrum of pediatric non-infectious uveitis. Also, personal experience or preferences of ophthalmologists and pediatric rheumatologist may have influenced the choice of treatment. The strengths of this study are the systematic way in which data were collected, its adherence to the SUN classification system and guidelines for publications and the dose adjustment for body surface area.

Based on our findings, we would recommend an MTX starting dose of ≥15 mg/m^2/week with a maximum of 25 mg/week by subcutaneous administration in the treatment of pediatric non-infectious uveitis. After reaching remission on medication a lower (10–15 mg) – possibly oral – maintenance dosage can be considered to maintain remission. Earlier publications about the efficacy of low-dose MTX in rheumatoid arthritis are supporting this.[30–33] Because of the lower and varying bioavailability of oral MTX when compared to subcutaneous administration[34–36] the effect of switching from subcutaneous to oral administration is difficult to predict. Ayuso et al.[29] described a higher relapse rate after withdrawal of MTX in pediatric non-infectious uveitis. Their results indicate that the period of inactivity before withdrawal should be preferably longer than 2 years.[29] They do not describe a dose reduction after remission on medication is reached. By sharing our treatment experiences and advising on steps to optimize treatment regimens, we hope to make a

© 2019 the Author(s). Published with license by Taylor & Francis Group, LLC

contribution to the improvement of care for children with non-infectious uveitis.

In conclusion, children with non-infectious uveitis can benefit from early treatment with high-dose MTX (≥15 mg/m^2/week, maximum 25 mg/week/sc) preferably by subcutaneous administration. Such a strategy may lead to a shorter time to remission on medication, a higher rate of remission on MTX and similar rates of side effects as in low-dose MTX treatment strategies. Future studies, most preferably randomized controlled trials, are needed to confirm these findings.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

FUNDING

The authors have no financial supports or other benefits from commercial sources for the work reported on in the manuscript. Also the authors have no financial interests or a potential conflict of interest with regard to the manuscript and the results presented.

REFERENCES

1. Mehta PJ, Alexander JL, Sen HN. Pediatric uveitis: new and future treatments. *Curr Opin Ophthalmol*. 2013;24(5):453–462. doi:10.1097/ICU.0b013e3283641ede.
2. Sauberan DP. Pediatric uveitis. *Int Ophthalmol Clin*. 2010;50(4):73–85. doi:10.1097/IIO.0b013e3181f0f2b5.
3. de Boer J, Wulffraat N, Rothova A. Visual loss in uveitis of childhood. *Br J Ophthalmol*. 2003;87:879–884.
4. Wentworth BA, Freitas-Neto CA, Foster CS. Management of pediatric uveitis. *F1000Prime Rep*. 2014;6:41. eCollection 2014. doi:10.12703/P6-41.
5. Rosenberg KD, Feuer WJ, Davis JL. Ocular complications of pediatric uveitis. *Ophthalmology*. 2004;111(12):2299–2306. doi:10.1016/j.ophtha.2004.06.014.
6. Gregory AC 2nd, Kempen JH, Daniel E, et al. Risk factors for loss of visual acuity among patients with uveitis associated with juvenile idiopathic arthritis: the systemic immunosuppressive therapy for eye diseases study. *Ophthalmology*. 2013;120(1):186–192. doi:10.1016/j.ophtha.2012.07.052.
7. Wong VG. Methotrexate treatment of uveal disease. *Am J Med Sci*. 1966;251:239–241.
8. Simonini G, Paudyal P, Jones GT, Cimaz R, Macfarlane GJ. Current evidence of methotrexate efficacy in childhood chronic uveitis: a systematic review and meta-analysis approach. *Rheumatology (Oxford)*. 2013;52(5):825–831. doi:10.1093/rheumatology/kes186.
9. Visser K. van der Heijde D. Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: a systematic review of the literature. *Ann Rheum Dis*. 2009;68(7):1094–1099. doi:10.1136/ard.2008.092668.
10. Chan ES, Cronstein BN. Methotrexate–how does it really work? *Nat Rev Rheumatol*. 2010;6(3):175–178. doi:10.1038/nrrheum.2010.5.
11. Hashkes PJ, Becker ML, Cabral DA, et al. Methotrexate: new uses for an old drug. *J Pediatr*. 2014;164(2):231–236. doi:10.1016/j.jpeds.2013.10.029.
12. Ruperto N, Murray KJ, Gerloni V, et al. A randomized trial of parenteral methotrexate comparing an intermediate dose with a higher dose in children with juvenile idiopathic arthritis who failed to respond to standard doses of methotrexate. *Arthritis Rheum*. 2004;50(7):2191–2201. doi:10.1002/art.20288.
13. Visser K, Katchamart W, Loza E, et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E initiative. *Ann Rheum Dis*. 2009;68(7):1086–1093. doi:10.1136/ard.2008.094474.
14. Smith JA, Mackensen F, Sen HN, et al. Epidemiology and course of disease in childhood uveitis. *Ophthalmology*. 2009;116(8):1544–51, 1551.e1. doi:10.1016/j.ophtha.2009.05.002.
15. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. results of the first international workshop. *Am J Ophthalmol*. 2005;140:509–516.
16. Petty RE, Southwood TR, Manners P, et al. International league of associations for rheumatology classification of juvenile idiopathic arthritis: second revision, edmonton, 2001. *J Rheumatol*. 2004;31:390–392.
17. El Edelbi R, Lindemalm S, Eksborg S. Estimation of body surface area in various childhood ages–validation of the mosteller formula. *Acta Paediatr*. 2012;101(5):540–544. doi:10.1111/j.1651-2227.2011.02580.x.
18. Sharma SM1, Ad D, Ramanan AV. Non-infectious pediatric uveitis: an update on immunomodulatory management. *Paediatr Drugs*. 2009;11:229–241.
19. van Nies JA, Tsonaka R, Gaujoux-Viala C, Fautrel B, van der Helm-van Mil AH. Evaluating relationships between symptom duration and persistence of rheumatoid arthritis: does a window of opportunity exist? Results on the Leiden early arthritis clinic and ESPOIR cohorts. *Ann Rheum Dis*. 2015;74(5):806–812. doi:10.1136/annrheumdis-2014-206047.
20. van Nies JA, Krabben A, Schoones JW, Huizinga TW, Kloppenburg M, van der Helm-van Mil AH. What is the evidence for the presence of a therapeutic window of opportunity in rheumatoid arthritis? A systematic literature review. *Ann Rheum Dis*. 2014;73(5):861–870. doi:10.1136/annrheumdis-2012-203130.
21. Wallace CA, Giannini EH, Spalding SJ, et al. Trial of early aggressive therapy in polyarticular juvenile idiopathic arthritis. *Arthritis Rheum*. 2012;64(6):2012–2021. doi:10.1002/art.34343.
22. Magnani A, Pistorio A, Magni-Manzoni S, et al. Achievement of a state of inactive disease at least once in the first 5 years predicts better outcome of patients with polyarticular juvenile idiopathic arthritis. *J Rheumatol*. 2009;36:628–634. doi:10.3899/jrheum.080560.
23. Wolf MD, Lichter PR, Ragsdale CG. Prognostic factors in the uveitis of juvenile rheumatoid arthritis. *Ophthalmology*. 1987;94:1242–1248.
24. van Dijkhuizen EH, Wulffraat NM. Prediction of methotrexate efficacy and adverse events in patients with juvenile idiopathic arthritis: A systematic literature review. *Pediatr Rheumatol Online J*. 2014;12:51–0096-12–51. eCollection 2014. doi:10.1186/1546-0096-12-51.

25. van Dijkhuizen EH, Bulatovic Calasan M, Pluijm SM, et al. Prediction of methotrexate intolerance in juvenile idiopathic arthritis: a prospective, observational cohort study. *Pediatr Rheumatol Online J*. 2015;13:5–015-0002–3. eCollection 2015. doi:10.1186/s12969-015-0002-3.
26. Malik AR, Pavesio C. The use of low dose methotrexate in children with chronic anterior and intermediate uveitis. *Br J Ophthalmol*. 2005;89(7):806–808. doi:10.1136/bjo.2004.054239.
27. Foeldvari I, Wierk A. Methotrexate is an effective treatment for chronic uveitis associated with juvenile idiopathic arthritis. *J Rheumatol*. 2005;32:362–365.
28. Heiligenhaus A, Mingels A, Heinz C, Ganser G. Methotrexate for uveitis associated with juvenile idiopathic arthritis: value and requirement for additional anti-inflammatory medication. *Eur J Ophthalmol*. 2007;17:743–748.
29. Kalinina Ayuso V, van de Winkel EL, Rothova A, de Boer JH. Relapse rate of uveitis post-methotrexate treatment in juvenile idiopathic arthritis. *Am J Ophthalmol*. 2011;151 (2):217–222. doi:10.1016/j.ajo.2010.08.021.
30. Hoffmeister RT. Methotrexate in rheumatoid arthritis (abstract). *Arthritis Rheumatol*. 1972;15:114.
31. Hoffmeister RT. Methotrexate therapy in rheumatoid arthritis: 15 years' experience. *Am J Med*. 1983;(75):69–73. doi:10.1016/0002-9343(83)90477-1.
32. Willkens RF, Watson MA, Paxson CS. Low dose pulse methotrexate therapy in rheumatoid arthritis. *J Rheumatol*. 1980;7:501–505.
33. Willkens RF, Watson MA. Methotrexate: a perspective of its use in the treatment of rheumatic diseases. *J Lab Clin Med*. 1982;100:314–321.
34. Tuková J, Chládek J, Nemcová D, Chládková J, Dolezalová P. Methotrexate bioavailability after oral and subcutaneous dministration in children with juvenile idiopathic arthritis. *Clin Exp Rheumatol*. Nov-Dec 2009;27(6):1047–1053.
35. Braun J. Optimal administration and dosage of methotrexate. *Clin Exp Rheumatol*. 2010 Sep-Oct;28(5Suppl 61):S46–51. Epub 2010 Oct 28.
36. Bello AE, Perkins EL, Jay R, Efthimiou P. Recommendations for optimizing methotrexate treatment for patients with rheumatoid arthritis. *Open Access Rheumatol*. 2017 Mar 31;9:67–79. doi:10.2147/OARRR.S131668.

© 2019 the Author(s). Published with license by Taylor & Francis Group, LLC

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Arthritis Care Res (Hoboken). Author manuscript; available in PMC 2020 April 01.

Published in final edited form as:

Arthritis Care Res (Hoboken). 2019 April ; 71(4): 482–491. doi:10.1002/acr.23610.

Childhood Arthritis and Rheumatology Research Alliance consensus treatment plans for juvenile idiopathic arthritis-associated and idiopathic chronic anterior uveitis

Sheila T. Angeles-Han, MD, MSc[*,1], **Mindy S. Lo, MD, PhD**[*,2], **Lauren A. Henderson, MD, MMSc**[2], **Melissa A. Lerman, MD, PhD, MSCE**[3], **Leslie Abramson, MD**[4], **Ashley M. Cooper, MD**[5], **Miriam F. Parsa, MD**[6], **Lawrence S. Zemel, MD**[7], **Tova Ronis, MDCM**[8], **Timothy Beukelman, MD, MSCE**[9], **Erika Cox, BS**[10], **H. Nida Sen, MD, MHS**[11], **Gary N. Holland, MD**[12], **Hermine I. Brunner, MD, MSc**[1], **Andrew Lasky, MD**[13], **C. Egla Rabinovich, MD, MPH**[14], and **on behalf of the Juvenile Idiopathic Arthritis Disease-Specific and Uveitis Subcommittee of Childhood Arthritis Rheumatology and Research Alliance**

[1]Division of Rheumatology, Cincinnati Children's Hospital Medical Center and Department of Pediatrics, University of Cincinnati, Cincinnati, OH [2]Division of Immunology, Boston Children's Hospital and Department of Pediatrics, Harvard Medical School, Boston, MA [3]The Children's Hospital of Philadelphia, Philadelphia, PA [4]Vermont Children's Hospital at University of Vermont Medical Center, Burlington, VT [5]Children's Mercy-Kansas City, Kansas City, MO [6]UCLA, Los Angeles, CA [7]Connecticut Children's Medical Center, Hartford CT [8]Children's National Health System, Washington, DC [9]University of Alabama at Birmingham, Birmingham, AL [10]Parent Partner, Camas, WA [11]National Eye Institute, National Institutes of Health, Bethesda, Maryland [12]UCLA Stein Eye Institute and David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA [13]Randall Children's Hospital at Legacy Emmanuel, Portland, OR [14]Duke University Medical Center, Durham, NC

Abstract

Objective—Systemic immunosuppressive treatment of pediatric chronic anterior uveitis (CAU), both juvenile idiopathic arthritis (JIA)-associated and idiopathic varies, making it difficult to identify best treatments. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) developed consensus treatment plans (CTPs) for CAU for the purpose of reducing practice variability and allowing future comparison of treatments by comparative effectiveness analysis techniques.

Methods—A core group of pediatric rheumatologists, ophthalmologists with uveitis expertise, and a lay advisor comprised the CARRA uveitis workgroup who performed literature review on pharmacologic treatments, held teleconferences, and developed a case-based survey administered

Address for reprints and corresponding author: C. Egla Rabinovich, MD, Box 3212 DUMC, Durham NC 27710; Phone: 919-684-6627; Fax: 919-684-6616; egla.rabinovich@duke.edu.

*Drs. Angeles-Han and Lo contributed equally to this work

DR. SHEILA T ANGELES-HAN (Orcid ID : 0000-0002-9552-6464)

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

to the CARRA membership to delineate treatment practices. We utilized 3 face-to-face consensus meetings using nominal group technique to develop CTPs.

Results—The survey identified areas of treatment practice variability. We developed 2 CTPs for the treatment of CAU, case definitions, and monitoring parameters. The first CTP is directed at children naïve to steroid-sparing medication, and the second at children initiating biologic therapy with options for methotrexate, adalimumab and infliximab. We defined a core dataset and outcome measures with data collection at 3 and 6 months after therapy initiation. The CARRA membership voted acceptance of the CTPs with a >95% (N = 233) approval.

Conclusion—Using consensus methodology, two standardized CTPs were developed for systemic immunosuppressive treatment of CAU. These CTPs are not meant as treatment guidelines, but are designed for further pragmatic research within the CARRA research network. Use of these CTPs in a prospective comparison effectiveness study should improve outcomes by identifying best practice options.

Pediatric chronic anterior uveitis (CAU) is an inflammatory ocular disease that can lead to vision loss and ocular complications in up to 60% of affected children (1–15). Idiopathic uveitis, i.e. without associated systemic illness, constitutes approximately 50% of pediatric CAU (1, 2, 16–19). Juvenile idiopathic arthritis (JIA) is the most common systemic disease associated with pediatric CAU, wherein 10-15% of these children will develop CAU (20, 21). Early detection and appropriate timely treatment may prevent sight-threatening complications such as cataracts, glaucoma, and synechiae (22).

There are presently no widely accepted approaches to the treatment of CAU. There are few pediatric randomized controlled trials, except for adalimumab in JIA-associated uveitis (JIA-U) (23, 24). Topical steroids are typical initial therapy, but prolonged use can lead to complications such as cataracts and increased intraocular pressure. Inadequate response to, and/or toxic effects from steroids necessitate the addition of steroid-sparing immunosuppressive therapy. However, evidence for specific agents is lacking.

Best practice guidelines for management of pediatric CAU have been developed by multiple groups but are not widely adopted in North America (25–27). Examination of JIA-associated patients enrolled in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry, a large registry of North American pediatric rheumatology patients, demonstrated that a broad range of biologic and non-biologic medications are prescribed (28). Additionally, the lack of pediatric standardized outcome measures for CAU limits the comparison of treatment strategies. Management is further complicated by the need for close collaboration between ophthalmologists and rheumatologists, with disease assessment by ophthalmologists, while steroid sparing systemic treatment typically prescribed by rheumatologists.

Through CARRA, we developed standardized treatment approaches, i.e. consensus treatment plans (CTPs), for children with typical JIA-associated and idiopathic CAU. These CTPs are meant for use in pragmatic research within the CARRA network, and not intended as standard treatment guidelines. We chose to include idiopathic CAU as systemic treatment approaches are the same as JIA-U, ocular complications similar, and this is an underserved

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

population for research. In addition, the antinuclear antibody (ANA) + CAU may represent a forme fruste of JIA. These CTPs were developed through a robust consensus process and represent current clinical practice of North American pediatric rheumatologists, with expert input from ophthalmologists specializing in uveitis care. These CTPs, as with other CTPs developed by CARRA, differ from expert guidelines in that they are treatment strategies developed by consensus methods amongst CARRA members with the primary goal of streamlining care and reducing practice variability (29). Ultimately, formal implementation of these CTPs in the treatment of patients enrolled in the CARRA registry will facilitate comparative effectiveness studies of different treatment approaches (29–33). We developed two CTPs with multiple treatment options intended for common CAU scenarios: 1) initiation of MTX therapy, and 2) initiation of biologic therapy.

II. Materials and methods

Core Workgroup

A core workgroup of 10 board-certified pediatric rheumatologists with special interest in CAU, two ophthalmologists with expertise in uveitis, and a parent of a child with JIA-U was formed. Tasks of the workgroup included: 1) defining a target population, 2) identifying similarities and disparities among treatment approaches, 3) reviewing the literature on comparative efficacies of treatment approaches, and 4) achieving consensus on criteria to assess inflammation and treatment response. To identify relevant literature on uveitis treatment strategies, we performed a search of the PubMed database using the terms “juvenile arthritis”, “uveitis”, “treatment”, “subcutaneous”, “oral”, “dose”, “methotrexate”, “TNF inhibitor”, “etanercept”, “adalimumab”, and “infliximab” through April 1, 2014, and updated in July 2016.

Besides face-to-face meetings, workgroup interactions occurred via teleconferences, surveys and email discussions between April 2012 and June 2016 (Figure 1).

Delphi Survey

To better understand existing practice patterns in the treatment of CAU by the pediatric rheumatology community, we administered an anonymous web-based survey to CARRA voting members who actively treat children with CAU (trainees ineligible). We presented clinical scenarios to identify common approaches for selection of: 1) an initial steroid-sparing agent in CAU, 2) a second-choice steroid-sparing agent in the event of initial treatment failure in patients with and without complications from CAU, and 3) a second-choice steroid-sparing agent in the event of intolerance to initial therapy (Supplementary Appendix).

Consensus Meetings

The first face-to-face meeting of the workgroup was held in April 2014. One ophthalmologist participated via conference call (NS). A syllabus consisting of a summary of the pre-consensus survey, prior phone discussions, literature review, and existing guidelines was presented. Two CTPs were drafted for two scenarios of uncontrolled CAU: 1)

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

initiation of MTX in children naïve to steroid-sparing agents, and 2) initiation of biologic therapy in children with inadequate response or intolerant to MTX.

Modified nominal group technique (NGT) was used to seek consensus (defined as ≥75% agreement) on the two draft CTPs (30–33). The NGT discussion was facilitated by an experienced moderator (HB), and responses were tabulated by a non-voting CARRA member (LH).These post-consensus CTPs were further refined by the uveitis workgroup during follow-up calls, and via NGT in face-to-face discussion in April 2015. An ophthalmologist (GNH) specializing in uveitis was present for these discussions.

The CTP strategies on the use of MTX and TNFi for CAU were presented to the CARRA JIA research committee in April 2016. Approval was obtained after members reviewed patient characteristics, data collection items, collection time points, primary and secondary outcomes, and the final CTP strategies. Consensus was based on show of hands or anonymous formal voting when needed. It is important to note that the number of voting members varied at each session, hence the variance in our numbers.

We disseminated final CTPs to the CARRA-wide membership as an anonymous online survey to confirm willingness to use at least one of the treatment plans to support comparative effectiveness research.

III. Results

Delphi Survey Results

Our case-based survey was sent to all CARRA members (Supplementary Appendix). We received 129 responses (50% response rate). Five respondents indicated that they did not provide care for children with uveitis and were excluded from analysis.

For a child with CAU not controlled by topical corticosteroids, MTX was most frequently selected as the initial systemic drug. Respondents could select more than one response; half of the respondents (N = 60/120, 50%) selected oral dosing as the initial mode of administration, while subcutaneous dosing was selected more frequently (79/120, 66%). Therapy with a TNFi, with or without concomitant use of MTX, was less frequently selected (1-6%).

For patients with continued uncontrolled uveitis despite MTX, most (114/120, 95%) would add, instead of substitute, a systemic immunosuppressive agent. Adalimumab (73/117, 62%) was favored over infliximab (40/117, 34%). In contrast, infliximab (63/120, 53%) was favored over adalimumab (52/120, 43%) in a child with uncontrolled uveitis and uveitis-related complications despite MTX.

In the case of MTX intolerance requiring drug discontinuation in a child with inactive uveitis, adalimumab was the most frequently selected alternative (66/112, 59%) followed by mycophenolate mofetil (29/112, 26%) and infliximab (13/112, 11%). Less frequently selected systemic therapies included abatacept (2/112, 2%), azathioprine (1/112, 1%), and etanercept (1/112, 1%).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Key questions considered important to address through a CTP were: 1) timing of and criteria for initiation of a systemic agent, 2) selection of first-line and second-line therapies, and 3) criteria for assessing response to therapy.

Face-to-face Consensus Meetings

Based on the practice variability noted in the preconsensus survey, the workgroup agreed to develop CTPs that would determine: 1) the preferred form of MTX administration and 2) preferred biologic therapy for CAU. Accordingly, we developed two CTPs for children with uncontrolled CAU: one for initiation of MTX in patients who have failed topical steroids, and one for initiation of TNF inhibitor (TNFi) therapy. Consensus on these CTPs was achieved by the JIA research committee at the 2016 CARRA annual meeting (27/28, 96%; 25/25, 100%).

Target Population

Table 1 defines the patient population targeted for these CTPs. There was consensus among the uveitis workgroup at the 2014 meeting and the CARRA JIA research committee in 2016 that these CTPs are appropriate for CAU that is: 1) idiopathic, or 2) JIA-associated, the most common categories of pediatric non-infectious uveitis. Although enrolling two distinct patient populations may introduce heterogeneity in the observed response to therapy, both are treated similarly, and a diagnosis of JIA does not influence outcomes (21). Two distinct target populations emerged from the consensus discussions, each with their own CTPs. The first CTP is for children naïve to steroid-sparing therapy and compares oral versus subcutaneous MTX administration. The second CTP is for a heterogeneous population of children initiating a TNFi: 1) failed MTX, 2) intolerant of MTX, and 3) naïve to MTX but with need for urgent treatment as determined by the clinician (e.g., patients presenting with acute uveitis and ocular complications from either uveitis or steroid therapy). This CTP compares adalimumab weekly, adalimumab every other week, and infliximab. Based on expert opinion, the more severely affected eye will dictate treatment in bilateral disease.

Both CTPs are suitable for the treatment of children who fulfill any of the following criteria: 1) ongoing uveitis activity despite the use of topical steroids, 2) worsening uveitis activity while on topical steroids, 3) recurrent uncontrolled disease (≥1+ anterior chamber (AC) cells) with taper of topical steroids to twice daily or less, 4) development of new ocular complications attributable to either inflammation or treatment during topical steroid therapy, and 5) intolerant or unable to adhere to therapy with topical corticosteroid drops. Examples of complications include increased intraocular pressure, hypotony, cataracts, posterior synechiae, band keratopathy, and cystoid macular edema. While twice-daily topical steroids is not preferred for long term management, based on expert opinion, it is acceptable, as this dose is accepted by the ophthalmology community for patients who do not have corticosteroid-induced ocular hypertension(34). There was consensus that these CTPs could also be applied to children on systemic steroids or with a history of unsuccessful subtenon steroid injections.

Experts agreed that the CTPs were not designed for the treatment of children with other uveitis categories, i.e. intermediate and posterior uveitis, symptomatic acute unilateral

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

anterior uveitis (AAU), uveitis attributable to other inflammatory conditions (e.g., sarcoidosis, Behcet's disease), the presence of ocular co-morbidities that could affect interpretation of outcomes, and contraindications to therapy (Table 1). There was ≥80% consensus on all points. The CTPs were restricted to CAU because it is most common in children along with the lack of generally accepted criteria to assess disease activity in intermediate, posterior, or panuveitic uveitis. Patients with previous exposure to a biologic agent within 3 months prior to enrollment are also not appropriate for these CTPs.

Categorization of Uveitis Disease Activity

Consensus was achieved to adopt the Standardization of Uveitis Nomenclature (SUN) Working Group methods of reporting clinical data (Table 2) (35). These include a grading scheme for AC cells and flare, uveitis activity, ocular complications, and outcomes. There was consensus that the course of uveitis can be categorized as: 1) inactive, 2) worsened, 3) improved or 4) controlled based on the degree of AC cells (35).

There was consensus to define adequately controlled CAU as follows: 1) not on systemic steroids; 2) no more than 0.5+ AC cells; 3) on topical steroids ≤2 drops/day; and 4) no new ocular complications for at least 3 months. We agreed with consensus that although 0.5+ AC cells is considered "active" by SUN criteria, we would not necessarily escalate therapy based on the presence of 0.5+ cells. For the purposes of these CTPs, the presence of AC cells ≥1+ (6-15 cells/hpf) constitutes uncontrolled uveitis.

MTX Therapy Consensus Treatment Plan

Patients with CAU as defined, naive to steroid-sparing therapy, are appropriate for the MTX CTP. Although the majority of the uveitis workgroup agreed that subcutaneous MTX has higher bioavailability and is preferred, data for superior efficacy of subcutaneous administration is lacking. In addition, a survey of pediatric rheumatologists indicated both routes are used equally (28). Therefore, both oral and subcutaneous MTX are treatment options. Dosing for MTX is 0.5-1 mg/kg/week, with a maximum of 30 mg per week; doses closer to 1 mg/kg/week are preferred (Fig. 2).

Consensus was reached that 3 months of treatment is necessary before assessing MTX efficacy. After 3 months, patients who failed MTX are recommended to change to the TNFi CTP. For children on oral MTX, an alternative is to enter the subcutaneous MTX arm. In addition, JIA patients who develop new uveitis while on MTX for arthritis would be considered to have failed MTX; the TNFi CTP should be considered.

TNFi Consensus Treatment Plan

Patients who fail MTX should be considered for the TNFi CTP using monoclonal antibody TNFi. For patients who are not intolerant of MTX, TNFi should be added to, rather than replace, MTX. The TNFi CTP can also be considered for MTX-naïve patients with uncontrolled (≥1+ AC cells) uveitis and severe disease (e.g. ocular structural complications due to uveitis, or complications of topical steroid therapy on presentation). MTX should be started simultaneously, utilizing either the subcutaneous or oral MTX options from the MTX CTP. Consensus was achieved at the 2015 meeting that we would not specifically define

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

"severe disease" at this time, but that the TNFi CTP should be considered at the provider's discretion. Although inclusion of patients who are MTX naïve and failed MTX may confound analysis of outcomes, we should be able to correct for this in analysis, and do not want to limit therapy in children in whom the clinician has determined that TNFi initiation is necessary.

There was unanimous agreement that etanercept has no role in the treatment of pediatric uveitis, and that there is insufficient data to recommend either adalimumab or infliximab as the preferred agent. Selection is left open to the treating provider, acknowledging that there may be individual factors influencing this decision, such as patient preference for medication route, insurance coverage, and compliance concerns.

The TNFi CTP includes three treatment options: 1) adalimumab SQ injections weekly, 2) adalimumab SQ injections every other week, and 3) infliximab infusions every 4 weeks after loading. Dosing for adalimumab parallels those for polyarticular JIA: 10 mg for patients 10 kg to <15 kg; 20 mg for patients 15 kg to <30 kg; 40 mg for patients ≥30 kg (Fig. 3). The workgroup agreed that adalimumab dose can be escalated 8 weeks after initiation if uveitis remains uncontrolled (≥1+ AC) or if unable to begin tapering steroids after 4 weeks due to persistent CAU. Dose escalation through either doubling the every-other-week dose (if on 10 or 20 mg), or increasing the frequency to weekly, are equally acceptable.

Dosing for infliximab starts at 6-10 mg/kg (Fig. 3). A loading regimen is recommended, giving infusions at 0, and 2 weeks, followed by every 4 weeks thereafter. Dose escalation is permitted based on exam after 8 weeks, up to a maximum dose of 20 mg/kg. MTX dose can be lowered while on a TNFi.

The CARRA JIA research committee agreed with infliximab dosing range of 6-10 mg/kg (27/28, 96%), and both a weekly and every other week adalimumab dosing arm (27/28, 96%).

Core Documentation for Children with CAU

We defined the data collection items, time points and outcome measures for data collection through consensus discussions at the 2015 meeting (10/13, 77%), and obtained approval by the JIA committee (26/26, 100%). Data will be collected at enrollment, 3 months and 6 months. An eye exam should occur within 6 weeks after starting therapy but will not be considered a separate study visit. All eye exam records in between study visits should be reviewed. Data points include demographics, uveitis clinical data (duration, age at uveitis onset, JIA-associated or idiopathic uveitis, anatomical location, laterality, AC cells by SUN criteria, visual acuity, ocular complications, ocular surgeries), reason not adherent to topical steroids if applicable, current and maximum daily steroid use (topical and systemic), start and stop dates of medications, and patient reported outcome measures (PROs) (Table 3). PROs will include the Patient-Reported Outcome Measurement Information System (PROMIS) global health scale, and the Effects of Youngsters' Eyesight on Quality of Life (EYE-Q) (36, 37). Adverse effects of therapy, such as leukopenia and hepatorenal toxicity from MTX, will be recorded. Monitoring toxicity of medications schedule is deferred to the

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

prescribing physician. Definitions of disease activity, recurrence, flare, and complications will be based on SUN criteria (35) (Table 2). Ophthalmology exam results will be included.

Interpretation of Patient Response

Primary outcome is defined as improvement or worsening of AC cells at 6 months as defined by SUN criteria. Secondary outcome measures include proportion with inflammation <1+ cells, visual acuity, eye complications, eye surgeries, PROs, adverse events, and corticosteroid use. It is the goal of most uveitis specialists to reduce AC cells to below a threshold of 1+ cells.

Treatment Failure is defined as ongoing uncontrolled uveitis, development of damage/eye complications, or intolerance/non-adherence to treatment. Another CTP treatment arm can be considered for patients who fail initial treatment. If treatment changes for arthritis but not uveitis, or if the patient chooses not to continue in the CTP, this will be captured by the CTP.

Methotrexate Intolerance

Suggestions for management of MTX intolerance were considered beyond the scope of these CTPs. The workgroup emphasizes that MTX intolerance can often be managed through the use of anti-emetics, folic acid and/or leucovorin and dose adjustment, but children experiencing MTX intolerance can also be considered for the TNFi CTP.

Systemic Steroids

The workgroup acknowledged that provision and dosing of systemic and topical corticosteroids are typically made by the treating ophthalmologist, rather than the rheumatologist. Therefore, this CTP does not include corticosteroid recommendations. However, based on expert opinion, systemic steroids should be avoided in the treatment of CAU. Systemic steroids should be used only as a temporizing measure while awaiting efficacy of steroid-sparing therapy, and steroid taper should begin no longer than 2 weeks after initiation of a steroid-sparing agent. This was unanimously agreed upon by the CARRA JIA committee (27/27, 100%).

Ophthalmology Screening

Although the AAP has guidelines for ophthalmology screening of JIA children, no guidelines exist for children with a history of CAU. Expert consensus was reached that children with uncontrolled uveitis should be monitored at least every 2-6 weeks (27/28, 96%).

Third-line Therapy

There are insufficient data to recommend treatment of uveitis refractory to MTX and TNFi. Although consensus was not achieved, members considered one or more of these medications: mycophenolate mofetil (13/18, 72%), abatacept (10/18, 56%), cyclosporine (7/18, 39%), tocilizumab (6/18, 33%), golimumab (1/18, 5%) azathioprine (1/18, 5%), leflunomide (1/18, 5%), and rituximab (1/18, 5%). These preferences may change as experience with these agents grows.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Post-consensus survey

The workgroup sought approval from the CARRA-wide membership through an online survey. Response rate was 81% (N = 247/306); among these, 10% (24/247) reported that they did not manage uveitis, and their responses were excluded. Consensus was achieved on the target population (216/223, 97%) and on the criteria for application of the TNFi CTP (215/223, 97%). Ninety-seven percent (215/233) reported willingness to use at least one arm of the methotrexate CTP and 99% (220/233) at least one arm of the TNFi CTP. There was broad consensus on the data collection measures outlined above.

IV. Discussion

Informed by the available medical evidence, expert consensus was achieved among pediatric rheumatologists and ophthalmologists participating in CARRA on treatment strategies for children with CAU. Hence, these CTPs may provide general guidance for the management of typical pediatric CAU, but are not meant as treatment guidelines. Rather, as with CTPs developed for other rheumatologic conditions, these CTPs are primarily intended to facilitate future comparative effectiveness research within the CARRA network (29).

Two CTPs were developed for use in patients enrolled in the CARRA registry. One for MTX in children without prior exposure to DMARDs, and the other for TNFi in children who failed MTX, are MTX intolerant, or in need of urgent treatment as determined by the clinician. These CTPs may not be relevant for cases that do not fit the most common scenarios described here. Active uveitis may be associated with active arthritis; these plans are intended to be used in situations where uveitis is guiding the choice of therapy.

In general, MTX is the first line agent for children with uveitis in need of systemic immunosuppression. In complicated or refractory disease, infliximab and adalimumab are equally preferred, and little data supports superiority of either TNFi (38–43). Small studies suggest that adalimumab may be as effective or superior to infliximab in achieving remission, but there were differences in the dose and frequency given (41, 44–46). Doses of infliximab greater than 7.5 mg/kg and as high as 20mg/kg/dose every 4 weeks may be necessary for recalcitrant disease (42, 47–49).

Our CTPs are intended to help standardize treatment approaches while also allowing future comparison of different treatment strategies in observational comparative effectiveness studies. Accordingly, our CTPs provide options that allow for comparatively higher dose regimens of TNFi and are intended for children with both JIA-associated and idiopathic CAU.

In addition to standardization of care, there is also a need for standardized outcome measures. The SUN criteria can be used for measuring treatment response. Heiligenhaus et. al. proposed outcome measures specific for children with JIA-U (50). We propose an expanded group of outcome measures through these CTPs (Table 3).

Regular monitoring by an ophthalmologist experienced in uveitis is crucial. Although guidelines for children with JIA exist, none exist for children with idiopathic uveitis, as this

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

typically falls within the treating ophthalmologist's purview. We suggest that children with uncontrolled uveitis or undergoing therapy changes be monitored at least every 2-6 weeks. In addition, if access to a uveitis specialist is available, all children should be evaluated at least once. We emphasize the importance of close communication between pediatric rheumatologists and ophthalmologists to ensure best visual outcomes. This can be done through shared medical records, combined subspecialty clinics, and/or standardized communication forms.

These CTPs address two important issues in CAU treatment. First, the preferred route of MTX administration is unknown. Subcutaneous administration has higher bioavailability and may have fewer gastrointestinal side effects (51, 52). Since the route of administration will be based on provider's and patient's preference, we may be able to optimize route through the conduct of observational studies of patients treated with these CTPs. This CTP will also enable comparative study of adalimumab and infliximab.

A limitation is the inability to recommend a tapering schedule for topical steroids, as this is purveyed by ophthalmologists. Collaboration between subspecialties is crucial. As with any analysis of JIA-U therapy, treatment may be guided by arthritis. This would be captured in data collection and not be used for comparison. Since data on treatment using other TNFi are lacking, they were not included in this CTP.

With implementation of these CTPs utilizing the CARRA registry in comparative effectiveness research, we can address factors associated with treatment success, including preferred duration of therapy, and the risk of relapse after medication discontinuation (49, 53, 54).

V. Conclusion

There is significant variability in current treatment strategies of CAU. We outline a consensus-based strategy to standardize the initial care of children with JIA-associated and idiopathic CAU. Standardizing care will enable comparative effectiveness studies and future clinical trials, identification of preferred treatment, and ultimately optimize visual outcomes for children with CAU.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors wish to thank Carol Wallace, Karyl Barron, Yukiko Kimura, Daniel Kingsbury, Anjali Patwardhan, Jennifer Weiss, and Jay Mehta.

Grant support: Supported by the NIH/National Institute of Arthritis and Musculoskeletal and Skin Diseases (grant 1RC1-AR-058605-01), the Childhood Arthritis and Rheumatology Research Alliance (CARRA), the Arthritis Foundation, the Waisie Foundation, and Friends of CARRA.

Other financial support: Dr. Angeles-Han is supported by Award Number K23EY021760 from the National Eye Institute, the Rheumatology Research Foundation, and the CCHMC Research Innovation and Pilot Fund. Dr. Sen is supported by the NEI Intramural Research Program. The Effects of Youngsters' Eyesight on Quality of Life (EYE-

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Q) has a license through Emory University and was developed by Dr. Angeles-Han. No royalties have been received by any authors.

References

1. Kump LI, Cervantes-Castaneda RA, Androudi SN, Foster CS. Analysis of pediatric uveitis cases at a tertiary referral center. Ophthalmology. 2005; 112(7):1287–92. [PubMed: 15921752]
2. Rosenberg KD, Feuer WJ, Davis JL. Ocular complications of pediatric uveitis. Ophthalmology. 2004; 111(12):2299–306. [PubMed: 15582090]
3. Kanski JJ. Juvenile arthritis and uveitis. Survey of ophthalmology. 1990; 34(4):253–67. [PubMed: 2188388]
4. Kotaniemi K, Kautiainen H, Karma A, Aho K. Occurrence of uveitis in recently diagnosed juvenile chronic arthritis: a prospective study. Ophthalmology. 2001; 108(11):2071–5. [PubMed: 11713082]
5. Sabri K, Saurenmann RK, Silverman ED, Levin AV. Course, complications, and outcome of juvenile arthritis-related uveitis. J Aapos. 2008; 12(6):539–45. [PubMed: 18789737]
6. BenEzra D, Cohen E, Behar-Cohen F. Uveitis and juvenile idiopathic arthritis: A cohort study. Clin Ophthalmol. 2007; 1(4):513–8. [PubMed: 19668530]
7. Dana MR, Merayo-Lloves J, Schaumberg DA, Foster CS. Visual outcomes prognosticators in juvenile rheumatoid arthritis-associated uveitis. Ophthalmology. 1997; 104(2):236–44. [PubMed: 9052627]
8. Angeles-Han ST, McCracken C, Yeh S, Jenkins K, Stryker D, Rouster-Stevens K, et al. Characteristics of a cohort of children with Juvenile Idiopathic Arthritis and JIA-associated Uveitis. Pediatric rheumatology online journal. 2015; 13:19. [PubMed: 26031738]
9. Angeles-Han ST, Pelajo CF, Vogler LB, Rouster-Stevens K, Kennedy C, Ponder L, et al. Risk markers of juvenile idiopathic arthritis-associated uveitis in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry. J Rheumatol. 2013; 40(12):2088–96. [PubMed: 24187099]
10. Paroli MP, Speranza S, Marino M, Pirraglia MP, Pivetti-Pezzi P. Prognosis of juvenile rheumatoid arthritis-associated uveitis. European journal of ophthalmology. 2003; 13(7):616–21. [PubMed: 14552595]
11. Heiligenhaus A, Niewerth M, Ganser G, Heinz C, Minden K, German Uveitis in Childhood Study G. Prevalence and complications of uveitis in juvenile idiopathic arthritis in a population-based nation-wide study in Germany: suggested modification of the current screening guidelines. Rheumatology (Oxford). 2007; 46(6):1015–9. [PubMed: 17403710]
12. Thorne JE, Woreta F, Kedhar SR, Dunn JP, Jabs DA. Juvenile idiopathic arthritis-associated uveitis: incidence of ocular complications and visual acuity loss. American journal of ophthalmology. 2007; 143(5):840–6. [PubMed: 17362866]
13. Chen CS, Roberton D, Hammerton ME. Juvenile arthritis-associated uveitis: visual outcomes and prognosis. Can J Ophthalmol. 2004; 39(6):614–20. [PubMed: 15559647]
14. Bolt IB, Cannizzaro E, Seger R, Saurenmann RK. Risk factors and longterm outcome of juvenile idiopathic arthritis-associated uveitis in Switzerland. J Rheumatol. 2008; 35(4):703–6. [PubMed: 18278829]
15. Saurenmann RK, Levin AV, Feldman BM, Rose JB, Laxer RM, Schneider R, et al. Prevalence, risk factors, and outcome of uveitis in juvenile idiopathic arthritis: a long-term followup study. Arthritis and rheumatism. 2007; 56(2):647–57. [PubMed: 17265500]
16. Thorne JE, Suhler E, Skup M, Tari S, Macaulay D, Chao J, et al. Prevalence of Noninfectious Uveitis in the United States: A Claims-Based Analysis. JAMA Ophthalmol. 2016; 134(11):1237–45. [PubMed: 27608193]
17. Ferrara M, Eggenschwiler L, Stephenson A, Montieth A, Nakhoul N, Araujo-Miranda R, et al. The Challenge of Pediatric Uveitis: Tertiary Referral Center Experience in the United States. Ocular immunology and inflammation. 2018:1–8.
18. Stoffel PB, Sauvain MJ, von Vigier RO, Beretta-Piccoli BC, Ramelli GP, Bianchetti MG. Non-infectious causes of uveitis in 70 Swiss children. Acta Paediatr. 2000; 89(8):955–8. [PubMed: 10976838]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

19. BenEzra D, Cohen E, Maftzir G. Uveitis in children and adolescents. Br J Ophthalmol. 2005; 89(4):444–8. [PubMed: 15774921]
20. Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet. 2007; 369(9563):767–78. [PubMed: 17336654]
21. Holland GN, Denove CS, Yu F. Chronic anterior uveitis in children: clinical characteristics and complications. American journal of ophthalmology. 2009; 147(4):667–78 e5. [PubMed: 19195641]
22. Edelsten C, Lee V, Bentley CR, Kanski JJ, Graham EM. An evaluation of baseline risk factors predicting severity in juvenile idiopathic arthritis associated uveitis and other chronic anterior uveitis in early childhood. The British journal of ophthalmology. 2002; 86(1):51–6. [PubMed: 11801504]
23. Quartier P, Despert V, Poignant S, Elie C, Kone-Paut I, Belot A, et al. THU0235 Adjuvite: A Double-Blind, Randomized, Placebo-Controlled Trial of Adalimumab in Juvenile Idiopathic Arthritis Associated Uveitis. Annals of the rheumatic diseases. 2016; 75(Suppl 2):273.
24. Ramanan AV, Dick AD, Jones AP, McKay A, Williamson PR, Compeyrot-Lacassagne S, et al. Adalimumab plus Methotrexate for Uveitis in Juvenile Idiopathic Arthritis. N Engl J Med. 2017; 376(17):1637–46. [PubMed: 28445659]
25. Bou R, Adan A, Borras F, Bravo B, Calvo I, De Inocencio J, et al. Clinical management algorithm of uveitis associated with juvenile idiopathic arthritis: interdisciplinary panel consensus. Rheumatology international. 2015
26. Levy-Clarke G, Jabs DA, Read RW, Rosenbaum JT, Vitale A, Van Gelder RN. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. Ophthalmology. 2014; 121(3):785–96 e3. [PubMed: 24359625]
27. Heiligenhaus A, Michels H, Schumacher C, Kopp I, Neudorf U, Niehues T, et al. Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis. Rheumatology international. 2012; 32(5):1121–33. [PubMed: 22083610]
28. Henderson LA, Zurakowski D, Angeles-Han ST, Lasky A, Rabinovich CE, Lo MS, et al. Medication use in juvenile uveitis patients enrolled in the Childhood Arthritis and Rheumatology Research Alliance Registry. Pediatric rheumatology online journal. 2016; 14(1):9. [PubMed: 26879972]
29. Ringold S, Nigrovic PA, Feldman BM, Tomlinson GA, von Scheven E, Wallace CA, et al. The Childhood Arthritis & Rheumatology Research Alliance Consensus Treatment Plans: Towards Comparative Effectiveness in the Pediatric Rheumatic Diseases. Arthritis Rheumatol. 2018
30. DeWitt EM, Kimura Y, Beukelman T, Nigrovic PA, Onel K, Prahalad S, et al. Consensus treatment plans for new-onset systemic juvenile idiopathic arthritis. Arthritis care & research. 2012; 64(7): 1001–10. [PubMed: 22290637]
31. Mina R, von Scheven E, Ardoin SP, Eberhard BA, Punaro M, Ilowite N, et al. Consensus treatment plans for induction therapy of newly diagnosed proliferative lupus nephritis in juvenile systemic lupus erythematosus. Arthritis care & research. 2012; 64(3):375–83. [PubMed: 22162255]
32. Li SC, Torok KS, Pope E, Dedeoglu F, Hong S, Jacobe HT, et al. Development of consensus treatment plans for juvenile localized scleroderma: a roadmap toward comparative effectiveness studies in juvenile localized scleroderma. Arthritis care & research. 2012; 64(8):1175–85. [PubMed: 22505322]
33. Ringold S, Weiss PF, Colbert RA, DeWitt EM, Lee T, Onel K, et al. Childhood arthritis and rheumatology research alliance consensus treatment plans for new-onset polyarticular juvenile idiopathic arthritis. Arthritis care & research. 2014; 66(7):1063–72. [PubMed: 24339215]
34. Thorne JE, Woreta FA, Dunn JP, Jabs DA. Risk of cataract development among children with juvenile idiopathic arthritis-related uveitis treated with topical corticosteroids. Ophthalmology. 2010; 117(7):1436–41. [PubMed: 20363502]
35. Jabs DA, Nussenblatt RB, Rosenbaum JT, Standardization of Uveitis Nomenclature Working G. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005; 140(3):509–16. [PubMed: 16196117]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

36. Angeles-Han ST, Yeh S, McCracken C, Jenkins K, Stryker D, Myoung E, et al. Using the Effects of Youngsters' Eyesight on Quality of Life Questionnaire to Measure Visual Outcomes in Children With Uveitis. Arthritis care & research. 2015; 67(11):1513–20. [PubMed: 26037544]
37. Irwin DE, Gross HE, Stucky BD, Thissen D, DeWitt EM, Lai JS, et al. Development of six PROMIS pediatrics proxy-report item banks. Health Qual Life Outcomes. 2012; 10:22. [PubMed: 22357192]
38. Garcia-De-Vicuna C, Diaz-Llopis M, Salom D, Bou R, Diaz-Cascajosa J, Cordero-Coma M, et al. Usefulness of adalimumab in the treatment of refractory uveitis associated with juvenile idiopathic arthritis. Mediators of inflammation. 2013; 2013:560632. [PubMed: 24489444]
39. Tynjala P, Kotaniemi K, Lindahl P, Latva K, Aalto K, Honkanen V, et al. Adalimumab in juvenile idiopathic arthritis-associated chronic anterior uveitis. Rheumatology (Oxford). 2008; 47(3):339–44. [PubMed: 18238789]
40. Vazquez-Cobian LB, Flynn T, Lehman TJ. Adalimumab therapy for childhood uveitis. The Journal of pediatrics. 2006; 149(4):572–5. [PubMed: 17011337]
41. Simonini G, Taddio A, Cattalini M, Caputo R, de Libero C, Parentin F, et al. Superior efficacy of Adalimumab in treating childhood refractory chronic uveitis when used as first biologic modifier drug: Adalimumab as starting anti-TNF-alpha therapy in childhood chronic uveitis. Pediatric rheumatology online journal. 2013; 11:16. [PubMed: 23587261]
42. Ardoin SP, Kredich D, Rabinovich E, Schanberg LE, Jaffe GJ. Infliximab to treat chronic noninfectious uveitis in children: retrospective case series with long-term follow-up. American journal of ophthalmology. 2007; 144(6):844–9. [PubMed: 17953940]
43. Saurenmann RK, Levin AV, Rose JB, Parker S, Rabinovitch T, Tyrrell PN, et al. Tumour necrosis factor alpha inhibitors in the treatment of childhood uveitis. Rheumatology (Oxford). 2006; 45(8): 982–9. [PubMed: 16461435]
44. Simonini G, Taddio A, Cattalini M, Caputo R, De Libero C, Naviglio S, et al. Prevention of flare recurrences in childhood-refractory chronic uveitis: an open-label comparative study of adalimumab versus infliximab. Arthritis care & research. 2011; 63(4):612–8. [PubMed: 21452272]
45. Doycheva D, Zierhut M, Blumenstock G, Stuebiger N, Januschowski K, Voykov B, et al. Immunomodulatory therapy with tumour necrosis factor alpha inhibitors in children with antinuclear antibody-associated chronic anterior uveitis: long-term results. The British journal of ophthalmology. 2014; 98(4):523–8. [PubMed: 24457365]
46. Zannin ME, Birolo C, Gerloni VM, Miserocchi E, Pontikaki I, Paroli MP, et al. Safety and efficacy of infliximab and adalimumab for refractory uveitis in juvenile idiopathic arthritis: 1-year followup data from the Italian Registry. J Rheumatol. 2013; 40(1):74–9. [PubMed: 23118110]
47. Kahn P, Weiss M, Imundo LF, Levy DM. Favorable response to high-dose infliximab for refractory childhood uveitis. Ophthalmology. 2006; 113(5):860–4 e2. [PubMed: 16545455]
48. Richards JC, Tay-Kearney ML, Murray K, Manners P. Infliximab for juvenile idiopathic arthritis-associated uveitis. Clinical & experimental ophthalmology. 2005; 33(5):461–8. [PubMed: 16181269]
49. Lerman MA, Burnham JM, Chang PY, Daniel E, Foster CS, Hennessy S, et al. Response of pediatric uveitis to tumor necrosis factor-alpha inhibitors. J Rheumatol. 2013; 40(8):1394–403. [PubMed: 23818712]
50. Heiligenhaus A, Foeldvari I, Edelsten C, Smith JR, Saurenmann RK, Bodaghi B, et al. Proposed outcome measures for prospective clinical trials in juvenile idiopathic arthritis-associated uveitis: a consensus effort from the multinational interdisciplinary working group for uveitis in childhood. Arthritis care & research. 2012; 64(9):1365–72. [PubMed: 22438273]
51. Braun J, Kastner P, Flaxenberg P, Wahrisch J, Hanke P, Demary W, et al. Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. Arthritis and rheumatism. 2008; 58(1):73–81. [PubMed: 18163521]
52. Schiff MH, Jaffe JS, Freundlich B. Head-to-head, randomised, crossover study of oral versus subcutaneous methotrexate in patients with rheumatoid arthritis: drug-exposure limitations of oral methotrexate at doses >/=15 mg may be overcome with subcutaneous administration. Annals of the rheumatic diseases. 2014; 73(8):1549–51. [PubMed: 24728329]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

53. Shakoor A, Esterberg E, Acharya NR. Recurrence of uveitis after discontinuation of infliximab. Ocular immunology and inflammation. 2014; 22(2):96–101. [PubMed: 23876234]

54. Ayuso VK, van de Winkel EL, Rothova A, de Boer JH. Relapse Rate of Uveitis Post-Methotrexate Treatment in Juvenile Idiopathic Arthritis. American journal of ophthalmology. 2011; 151(2):217–22. [PubMed: 21145533]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Significance and Innovations

- Systemic immunosuppressive treatment of children with JIA-associated anterior uveitis and idiopathic chronic anterior uveitis varies significantly among pediatric rheumatologists.
- Consensus treatment plans for pediatric chronic anterior uveitis were developed by the Childhood Arthritis and Rheumatology Research Alliance to standardize systemic therapies for children with chronic anterior uveitis, and enable comparison of treatments, with the goal of ultimately improving visual outcomes.

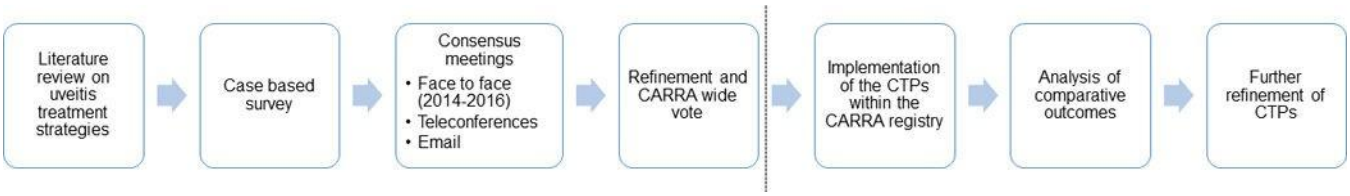


Figure 1.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

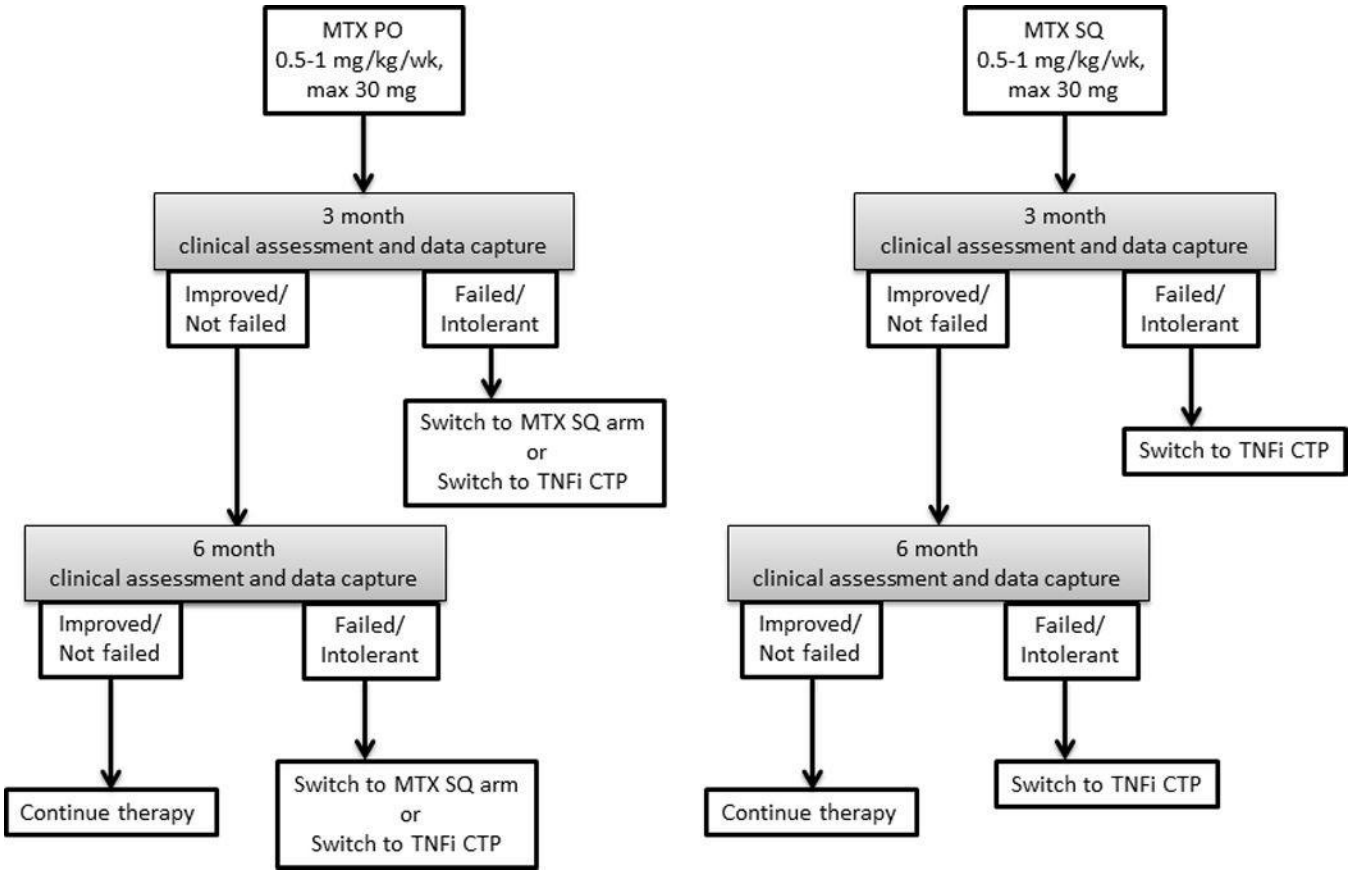


Figure 2.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

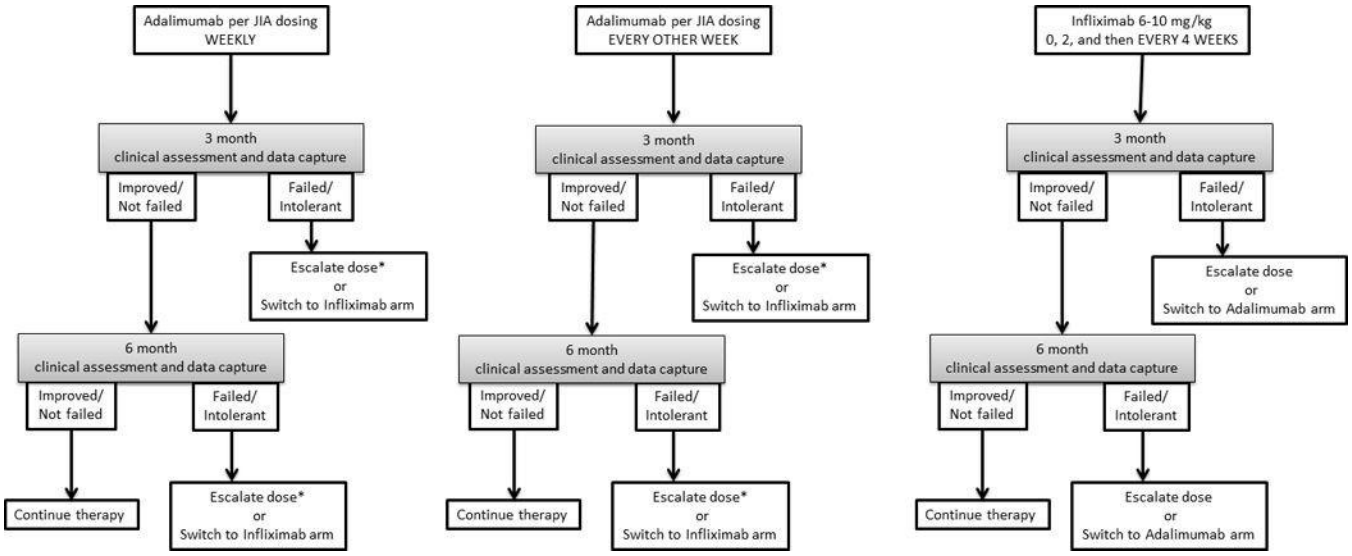


Figure 3.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1

Characteristics of patients for use of the CTPs

Patients should have:
• Anterior uveitis only: idiopathic or JIA-associated
• <18 years old at enrollment
• **Uncontrolled chronic active uveitis**, as evidenced by any of the following:
– Ongoing uveitis activity, ≥1+ (6-15 cells/hpf) despite use of topical steroids or if unable to adhere or intolerant of topical steroids.
– Worsening uveitis activity while on topical steroids
– Recurrent disease (≥1+) with taper of topical steroids to ≤BID
– Development of new ocular complications * attributable to inflammation or treatment during topical therapy
Patients should not have:
• Panuveitis, intermediate, or posterior uveitis
• Acute unilateral anterior uveitis
• Retinal vasculitis
• Active systemic infection or infectious uveitis
• Uveitis associated with systemic disease other than JIA (e.g., Behcet's disease, sarcoidosis)
• Contraindication to either methotrexate or anti-TNFα therapy
• Exposure to biologic therapy within prior 3 months
• Ocular co-morbidity not due to uveitis
• Corrected visual acuity <20/200 not due to active uveitis
• Pregnancy
• History of malignancy

* Complications include: increased intraocular pressure, hypotony, cataracts, posterior synechiae, band keratopathy, and cystoid macular edema.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2

Adapted Standardization of Uveitis Nomenclature (SUN) Definitions[22].

Grading Scheme for Anterior Chamber Cells:	
Grade	**Cells in Field***
0	0
0.5+	1-5
1+	6-15
2+	16-25
3+	26-50
4+	>50

Definitions of Disease Activity:	
Inactive	Grade 0 cells in anterior chamber
Worsening activity	Two step increase in inflammation by anterior chamber cells, or 3+ to 4+
Improved activity	Two step decrease in level of inflammation by anterior chamber cells, or decrease to 0
Remission	Inactive disease for ≥3 months after discontinuing all treatments for eye disease

* Field size is 1 mm × 1 mm slit beam

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 3

Data collection points

Data collection points at 0, 3, 6 months or end of study			
Variables		**0 mos**	**3, 6 mos and/or end of study**
Baseline	Disease duration	X	
	Age at disease onset	X	
	JIA subtype or idiopathic uveitis	X	
Uveitis	Anatomical Location	X	X
	Laterality	X	X
	Anterior chamber cells by SUN criteria	X	X
	Visual acuity	X	X
	Ocular complications	X	X
	Ocular surgeries	X	X
PROs	VAS	X	X
	Overall QOL: PROMIS global health score	X	X
	Uveitis related QOL: EYE-Q	X	X



Ocular Immunology and Inflammation

ISSN: 0927-3948 (Print) 1744-5078 (Online) Journal homepage: www.tandfonline.com/journals/ioii20

Methotrexate Experience in the Treatment of Pediatric Non-Infectious Uveitis: Is Monotherapy Enough?

Dilbade Yildiz Ekinci & Mehtap Savar Caglayan

To cite this article: Dilbade Yildiz Ekinci & Mehtap Savar Caglayan (2025) Methotrexate Experience in the Treatment of Pediatric Non-Infectious Uveitis: Is Monotherapy Enough?, Ocular Immunology and Inflammation, 33:10, 2288-2293, DOI: 10.1080/09273948.2025.2524007

To link to this article: https://doi.org/10.1080/09273948.2025.2524007

Published online: 02 Jul 2025.

Submit your article to this journal

Article views: 82

View related articles

View Crossmark data

Citing articles: 1 View citing articles

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=ioii20

OCULAR IMMUNOLOGY AND INFLAMMATION
2025, VOL. 33, NO. 10, 2288–2293
https://doi.org/10.1080/09273948.2025.2524007

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Check for updates

Methotrexate Experience in the Treatment of Pediatric Non-Infectious Uveitis: Is Monotherapy Enough?

Dilbade Yildiz Ekinci, MD and Mehtap Savar Caglayan, MD

Department of Ophthalmology, University of Healthy Science, Diyarbakir, Turkey

ABSTRACT

Purpose: This study aimed to evaluate the efficacy of methotrexate (MTX) treatment in pediatric non-infectious uveitis (NIU) cases.

Methods: Patients diagnosed with pediatric NIU and initiated on subcutaneous MTX at a dose of 10 mg/m^2/week between 2023 and 2025 were included in the study. The patients' age, age at uveitis diagnosis, anatomical localization and etiology of uveitis, baseline and final best-corrected visual acuity (BCVA), and anterior and posterior segment complications detected at the initial visit were recorded.

Results: A total of 127 eyes from 64 patients were included in the study. Of these patients, 39 were female, and 25 were male. The mean age was 9.89 ± 3.56 years (3-17 years). At the initial visit, at least one ocular complication in at least one eye was detected in 49 patients. Remission was achieved in 23 cases with MTX treatment, whereas 41 patients did not achieve remission. Among the 49 patients with at least one ocular complication, remission was achieved in 13 with MTX treatment. In contrast, among the 15 patients without any complications, remission was achieved in 10 (p = 0.005). The risk of non-responsiveness to MTX treatment was found to be 10.7 times higher in patients with at least one ocular complication at diagnosis.

Conclusion: MTX is an effective and safe treatment for pediatric NIU. However, in a significant proportion of patients, particularly those with ocular complications, MTX alone may be insufficient, necessitating the addition of other immunosuppressive agents.

ARTICLE HISTORY
Received 7 March 2025
Revised 18 May 2025
Accepted 17 June 2025

KEYWORDS
Methotrexate; monotherapy; ocular complications; pediatric non-infectious uveitis; remission

Methotrexate (MTX) is an antimetabolite agent used in the treatment of rheumatologic, dermatologic, and ophthalmologic inflammatory diseases. It exerts its anti-inflammatory effects by inhibiting a group of folate-dependent enzymes, thereby suppressing lymphocyte proliferation, reducing the release of pro-inflammatory cytokines, and attenuating the humoral response.[1–7] MTX is frequently used in ophthalmology for the treatment of non-infectious uveitis (NIU).[5,8] The drug can be administered via two different routes: oral and subcutaneous. Subcutaneous administration is known to have higher absorption and stronger efficacy compared to oral intake.[8] The therapeutic effect of MTX typically becomes apparent within approximately three months. Adverse effects may include elevated liver enzymes, myelosuppression, stomatitis, and interstitial pneumonitis. In children, nausea and vomiting are particularly significant factors that limit its use.[9–12] To mitigate these adverse effects, folic acid supplementation is prescribed to patients.[13]

There is no universally accepted treatment algorithm for pediatric uveitis. The primary treatment for acute exacerbations includes topical, local, and systemic corticosteroids. However, in cases where steroid-related complications develop, recurrence occurs after steroid tapering, or the disease remains refractory, long-term immunosuppressive therapies with proven efficacy and safety are employed. MTX is often preferred as the first-line immunosuppressive treatment in childhood uveitis.[2–5,8,14] The reported remission rates with MTX vary, with a meta-analysis indicating that ocular inflammation is controlled in 73% of cases.[5,8,9] There is no consensus on when to discontinue MTX in patients who achieve remission. It has been suggested that MTX can be discontinued after maintaining remission for at least two years, with each additional year in remission before discontinuation reducing the risk of relapse by 93%.[15] In cases where remission is not achieved with MTX alone, other conventional immunosuppressive agents may be added to the treatment regimen, and in severe cases, combination therapy with biologic agents may be considered.[14,16]

Certain uveitis subtypes are associated with poor prognostic indicators. Studies have demonstrated that patients with these risk factors tend to exhibit poor treatment responses and higher complication rates. In juvenile idiopathic arthritis-associated uveitis (JIA-U), factors such as initial uveitis severity, the presence of ocular complications at the time of diagnosis, male sex, and uveitis onset preceding arthritis have been linked to worse visual prognosis.[17,18] Additionally, polyarticular JIA, a history of systemic steroid use, and younger age at JIA onset have been identified as predictors of poor response to MTX therapy.[19] In another pediatric uveitis entity, pars planitis (PP), poor prognostic factors include early age of onset, uveitis duration exceeding three years, male sex, and macular edema.[20,21]

CONTACT Mehtap Savar Caglayan, M drmehtap85@hotmail.com Department of Ophthalmology, University of Health Science, Gazi Yasargil Training and Research Hospital

© 2025 Taylor & Francis Group, LLC

In this study, our primary objective was to evaluate the efficacy of MTX in pediatric NIU cases. Secondly, we aimed to determine whether the initial clinical findings at presentation could be utilized to predict MTX resistance.

Materials and methods

This retrospective study included pediatric NIU patients who were followed up at the Uvea Clinic of Gazi Yasargil Training and Research Hospital, Department of Ophthalmology, between 2023 and 2025.

Inclusion criteria

(1) The study included patients younger than 17 years who were under follow-up with a diagnosis of non-infectious uveitis.
(2) Patients followed for at least six months with a diagnosis of NIU.
(3) Patients who attended follow-ups regularly.
(4) Patients who received MTX as the initial immunosuppressive treatment.

Exclusion criteria

(1) Patients who declined participation in the study.
(2) Patients who discontinued treatment.
(3) Patients with irregular follow-ups.
(4) Patients who had received any prior immunosuppressive therapy.

Ethical approval was obtained before initiating the study (ethical approval number: 2025/318), and the study was conducted in accordance with the principles of the Helsinki Declaration. Patient data were retrospectively analyzed from an electronic database. Recorded variables included age, age at diagnosis, sex, mean follow-up duration, prior diagnosis at another center, anatomical localization and etiology of uveitis, presence and type of ocular complications at initial presentation and new ocular complication developing during follow-up period (glaucoma, cataract, synechiae, band keratopathy, macular edema, papillitis, retinal complications), achievement of remission with MTX monotherapy, necessity of additional medication, timing of additional medication initiation, need for ocular surgery and best-corrected visual acuity (BCVA) at the initial and final visits.

Patients were categorized into two groups based on remission status with MTX monotherapy. Group 1 included patients who achieved remission with MTX monotherapy, while group 2 consisted of those who did not achieve remission and required additional treatment. The groups were compared in terms of age, age at diagnosis, sex, presence of at least one ocular complication at diagnosis, type of complication, anatomical localization and etiology of uveitis, and initial and final BCVA values.

Additionally, the impact of sex (female/male), age at disease onset (<8 years vs. ≥8 years), prior diagnosis at another center (yes/no), and presence of at least one ocular complication (yes/no) on MTX treatment response was analyzed.

All patients underwent an etiological investigation at the time of uveitis diagnosis. Systemic symptoms, previously diagnosed systemic diseases, and prior treatments were reviewed. Infectious causes were excluded. Anterior chamber reaction and vitritis were assessed according to the Standardization of Uveitis Nomenclature (SUN) Working Group recommendations.[22] Uveitis classification was recorded based on the International Uveitis Working Group classification.[23]

All patients with anterior uveitis were initially treated with topical steroids and cycloplegic agents. Systemic corticosteroid therapy (1 mg/kg/day) was initiated for patients with severe inflammation and complications. Patients presenting with ocular complications, severe inflammation regardless of etiology, or a diagnosis of juvenile idiopathic arthritis-associated uveitis (JIA-U) were started on subcutaneous MTX at a dose of 10 mg/m^2/week along with steroid therapy. The primary reason for immediate MTX initiation in patients with glaucoma or cataract was to prevent the need for repeated steroid treatments.

During follow-up, MTX was initiated in patients without complications if uveitis flared when systemic steroid dosage was reduced to ≤5 mg/day or topical steroid dosage was reduced to ≤ 2 drops/day, or if frequent recurrences occurred after achieving remission or discontinuing steroid therapy, leading to decreased visual acuity.

All patients received folic acid supplementation for two days after each weekly MTX dose to mitigate side effects. Routine laboratory evaluations, including complete blood count, liver function tests, and renal function tests, were performed at one month and every three months thereafter.

Recurrence and remission were assessed based on periods when the patient was not receiving topical or systemic steroids. Recurrence was defined as anterior chamber reaction > 1+, or the development of vitritis, papillitis, or macular edema after a minimum of three months of inactivity. Remission was defined as an anterior chamber reaction < 0.5+, with no evidence of vitritis, papillitis, or macular edema, and absence of vascular leakage and disc staining in fundus fluorescein angiography in patients followed with intermediate and panuveitis.

Insufficient response to MTX treatment was defined as frequent uveitis recurrences, the development of new complications, or worsening of existing complications at least three months after initiating MTX. The time of additional treatment initiation in MTX-resistant cases was recorded in months.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA, version 24.0). Categorical variables were expressed as frequency and percentage, while numerical variables were presented as mean ± standard deviation (SD) (minimum–maximum).

The chi-square test and Fisher's exact test were used to compare categorical variables. The Wilcoxon signed-rank test was used for paired numerical variables, while the Mann-Whitney U test was applied for independent numerical variables.

Binary logistic regression analysis was conducted to identify risk factors for methotrexate resistance. The suitability of the

regression model was assessed using the Hosmer-Lemeshow test. If the p-value of the Hosmer-Lemeshow test was < 0.05, the regression model was considered statistically appropriate. The odds ratio (OR) was calculated with a 95% confidence interval (95% CI). A p-value of < 0.05 was considered statistically significant.

Results

A total of 127 eyes from 64 patients were included in the study. Demographic and clinical characteristics of the patients are summarized in Table 1. Prior to admission to our clinic, 47 patients (73.4%) had already been diagnosed with uveitis, whereas 17 patients (27%) received their initial diagnosis at our center. At the first visit, 49 patients (76.5%) had at least one ocular complication in at least one eye (Table 1). During the follow-up period, 8 eyes of 8 patients experienced a new ocular complication (3 eyes had cataracts and 3 eyes had synechiae, 1 eye had glaucoma, and 1 eye had retinoschisis). These patients had at least one ocular complication at the first visit. Additionally, 2 patients underwent cataract surgery, 1 patient underwent corneal debridement for band keratopathy and 1 patient received intravitreal bevacizumab injection due to macular neovascularization. The mean baseline best-corrected visual acuity (BCVA), according to the Snellen chart, was 0.80 ± 0.25, which increased to 0.93 ± 0.17 at the final visit, showing a statistically significant improvement ($p < 0.001$).

Table 1. Demographic and clinical characteristics of the patients.

Variable	Values (n)
Age (years)	9.89 ± 3.56
Age at diagnosis (years)	7.62 ± 3.25
Gender (F/M)	39/25
Follow-up period (months)	17.88 ± 6.3
Anatomical localization	
Anterior uveitis	32
Intermediate uveitis	14
Panuveitis	18
Etiology of uveitis	
JIA	26
PP	14
IP	10
VKH	7
IAU	6
TINU	1

N: number of patients; F/M: Female/Male; JIA: Juvenile idiopathic arthritis; PP: Pars planitis; IP: Idiopathic panuveitis, VKH: Vogt-Koyanagi-Harada; IAU: Idiopathic anterior uveitis; TINU: Tubulointerstitial nephritis and uveitis.

Remission was achieved with MTX alone in 23 patients (35.9%) which is defined group 1, and 41 patients (64.1%) required the addition of a biological agent, which is defined group 2. Demographic and clinical characterestic of Groups 1 and 2 are summarized in Table 2.

The mean time from initiation of methotrexate (MTX) to remission was 5.7 ± 2.9 months in the idiopathic panuveitis group, 7.3 ± 5.7 months in the JIA-U group, 6.8 ± 4.4 months in the Vogt-Koyanagi-Harada group, 8.2 ± 5.1 months in the PP group, and 5.3 ± 3.0 months in the idiopathic anterior uveitis group. There was only one patient in the tubulointerstitial nephritis and uveitis (TINU) group, with a time to remission of 12 months. Due to the unequal distribution of patients across groups, statistical comparison was not feasible. However, the longest time to remission was observed in the PP group. The mean time to initiation of biological therapy was 7.66 ± 4.38 months. In male patients, the mean time to biological treatment initiation was 6.7 ± 3.7 months, whereas in female patients, it was 8.57 ± 4.8 months ($p = 0.157$). The remission rate was significantly higher in female patients ($p = 0.033$). Among the 39 female patients, 18 (46.1%) achieved remission with MTX alone, whereas remission was observed in only 5 (20%) of the 25 male patients.

No significant differences were observed between the groups regarding the types of ocular complications ($p > 0.05$ for all comparisons, Table 3). However, a significant difference was found between the groups regarding the presence of at least one ocular complication in at least one eye ($p = 0.005$). Among the 49 patients with at least one ocular complication, 13 (26.5%) achieved remission with MTX. Among the 15 patients without any ocular complications, 10 (66.6%) achieved remission with MTX.

Binary logistic regression analysis identified the presence of ocular complications at the time of diagnosis as the only significant predictor (risk factor) for MTX resistance (Table 4, $p = 0.007$). The risk of MTX treatment failure was found to be 10.7 times higher in patients with at least one ocular complication at the time of diagnosis. Gender, age at

Table 2. Comparison of demographic and clinical variables between groups.

Variable	Group 1 (n:23)	Group 2 (n:41)	P
Age (years)	10.39 ± 4.0	9.61 ± 3.30	0.617*
Age at diagnosis (years)	8.47 ± 3.75	7.14 ± 2.8	0.198*
Follow-up period (months)	16.39 ± 6.9	18.71 ± 5.9	0.210*
Initial BCVA	0.82 ± 0.28	0.81 ± 0.20	0.367*
Final BCVA	0.96 ± 0.11	0.96 ± 0.11	0.862*
Gender (F/M)	18/5	21/20	0.033&
Ocular Complications (Present/Absent)	13/10	36/5	0.005&
Previous Diagnosis (Present/Absent)	15/8	32/9	0.265&
Anatomical Localization			
Anterior uveitis	13	19	0.709&
Intermediate uveitis	4	10	
Panuveitis	6	12	

*Mann-Whitney U test, &Chi-square test, n: Number of cases, Group 1: Remission with MTX, Group 2: No remission with MTX.

Table 3. Comparison of ocular complication rates between groups.

Ocular Complications	Group 1 (n: 23)	Group 2 (n: 41)	P
Glaucoma			
Present	0	2	
Absent	23	39	0.532*
Cataract			
Present	2	9	
Absent	21	32	0.301*
Posterior Synechia			
Present	8	21	
Absent	15	20	0.205&
Band Keratopathy			
Present	2	11	
Absent	21	30	0.111*
Papillitis			
Present	8	13	
Absent	15	28	0.802&
Macular Edema			
Present	1	3	
Absent	22	38	1.00*
Retinal Complications			
Present	1	3	
Absent	22	38	1.00*

*Fisher's exact test, &Chi-square test, n: Number of cases, Group 1: Remission with MTX, Group 2: No remission with MTX.

Table 4. Evaluation of risk factors for MTX treatment resistance.

Variable	P*	OR	95% CI
Age at diagnosis	0.306	1.93	0.548–6.795
Gender	0.209	0.43	0.118–1.595
Previous Diagnosis	0.607	1.46	0.345–6.181
Ocular Complications	**0.007**	**10.75**	**1.892–60.744**

*Binary Logistic Regression; OR: Odds Ratio.

diagnosis, and prior uveitis diagnosis before admission were not significantly associated with MTX resistance.

Discussion

Methotrexate is the first-line immunomodulatory agent used in childhood NIU apart from steroids. Its efficacy and safety have been well-established, particularly in JIA-U, and it is widely used in other uveitic entities as well.[4,5,8,18,19] Although MTX provides a high rate of remission in NIU treatment, side effects such as nausea, vomiting, and hepatotoxicity limit its use.[9,10,12,14,15,24] However, considering the risk of permanent vision loss due to complications, the difficulty of managing these complications in children compared to adults, and the inability to use systemic steroids for prolonged periods, MTX emerges as the most cost-effective agent for achieving remission and preventing vision loss.

Anterior uveitis is the most frequently affected anatomical localization in pediatric patients.[14,25–27] The etiology varies depending on geographical region, race, and genetic diversity. While a significant portion of childhood uveitis cases are idiopathic, JIA-U is the most common form in Europe and the United States.[26–28] A multicenter study conducted in Turkey (BUST Study) reported that anterior uveitis was the most common anatomical form, while pars planitis was the most frequently identified etiology.[25] In our study, which included 64 patients followed between 2023 and 2025, half of the patients had anterior uveitis. Unlike the BUST study conducted in Turkey, the most common etiology in our study was JIA-U, similar to findings in Europe and the United States of America (U.S.) This difference may be attributed to the single-center nature of our study and the relatively small patient population.

Some pediatric uveitis patients may be asymptomatic, while others may be too young to recognize vision loss, leading to delayed initial presentation. If these patients are not treated in a timely and effective manner, they may develop severe ocular complications.[27,29] Ferrara et al. reported that 78.3% of patients in the U.S. presented with complications, and the vast majority required systemic treatment.[29] A study from Greece found that the most common complication in anterior and panuveitis cases was synechiae, while macular and disc edema were the most frequent complications in intermediate uveitis cases.[30] In an Indian study evaluating 104 pediatric cases, cataract was detected in 24% of patients at the initial visit, band keratopathy in 18.2%, and glaucoma in 6.2%. This study highlighted that while cataract was the most severe initial complication, maculopathy was the leading cause of blindness.[31] Rosenberg et al. found that 34% of pediatric uveitis patients had at least one complication at initial presentation, and this rate increased to 86.3% after three years. The most common initial complication was posterior synechiae.[32] The same study reported that anterior and intermediate uveitis were frequently associated with band keratopathy, while intermediate uveitis was linked to macular edema. Complications were least common in anterior uveitis and most frequent in panuveitis. JIA-U was associated with an increased risk of band keratopathy, cataract, and synechiae, while pars planitis had a higher risk of macular edema. Additionally, both JIA-U and pars planitis patients had an elevated risk of glaucoma compared to other uveitic conditions.[32] In our study, 76.5% of our patients had at least one ocular complication at the time of their first application. posterior synechiae was the most commonly observed complication at initial presentation, consistent with previous studies.

At the end of the follow-up period, 35.9% of our patients achieved remission with MTX alone. The remission rate was higher in female patients compared to males. Studies have shown that the prognosis is generally worse in male patients with JIA-U and pars planitis.[21,33,34] Rosenberg et al. also reported that male patients had lower MTX remission rates and required biological therapy more frequently, although the difference was not statistically significant.[32]

Early-onset uveitis has been identified as an indicator of poor prognosis, with an increased likelihood of requiring biological therapy.[19–21] However, contrary to these studies, we found no significant difference in treatment resistance between patients diagnosed before and after the age of eight. This discrepancy may be due to the small sample size in our study.

A study investigating the efficacy of low-dose (<15 mg/m^2/week) and high-dose (>15 mg/m^2/week) MTX in pediatric uveitis reported an overall remission rate of 67%, with subcutaneous administration achieving higher remission rates than oral administration. In the high-dose MTX group, remission was achieved in 76.6% of cases, compared to 60% in the low-dose group, and remission was reached

more rapidly in the high-dose group.[35] Compared to this study, our remission rate with low-dose MTX was significantly lower, which may be due to geographical, ethnic, and genetic factors, as well as our limited sample size.

Studies on JIA-U have found that severe uveitis and ocular complications at initial presentation are poor prognostic factors for vision loss.[18,33,36] Another study evaluating inadequate response to MTX in JIA-U patients found no association between treatment resistance and the presence of ocular complications or severity of anterior chamber reaction at initial presentation.[19] However, the SHARE initiative suggested that early initiation of biological agents in cases with ocular complications at initial presentation may improve prognosis.[37] In childhood pars planitis, severe and prolonged inflammation, along with macular and optic disc edema, have been identified as poor prognostic factors.[20,21] Early initiation of anti-TNF agents in selected pars planitis cases has been recommended for achieving long-term remission and preventing ocular complications.[38]

In our study, there was no significant difference in the types of complications between patients who achieved remission with MTX and those who did not. However, among patients with at least one ocular complication at initial presentation, only 26.5% achieved remission with MTX, whereas the remission rate was 66.6% in patients without complications. Additionally, regression analysis revealed that patients with at least one ocular complication at diagnosis had a 10.7-fold higher risk of MTX treatment failure. Given that ocular complications develop in cases with prolonged severe inflammation and inadequate treatment, and these cases are more challenging to manage, the high rate of MTX resistance and need for additional therapies in patients with multiple complications is not surprising.[32–37] These findings highlight the critical importance of early diagnosis and treatment.

The limitations of our study include its retrospective design, the inclusion of different uveitic entities, and the short follow-up period. It would be more reliable to make a long-term and fixed-interval comparison, especially in the evaluation of remission and change in BCVA.

In conclusion, MTX is a frequently used, effective, and safe conventional immunosuppressive agent in pediatric NIU treatment. Delayed diagnosis and treatment, as well as inadequate management, unfortunately lead to ocular complications in pediatric uveitis cases, making MTX monotherapy insufficient in many instances. Larger studies with a higher number of cases are needed to determine the clinical characteristics and risk factors of patients who exhibit an inadequate response to MTX treatment.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The authors declare that the study received no funding.

Author contributions

CRediT: **Dilbade Yildiz Ekinci, MD**: Conceptualization, Data curation, Investigation, Methodology, Resources, Writing – original draft; : Formal analysis, Investigation, Methodology, Writing – review & editing. Conceptualization: DYE, MSC, data curation: DYE; formal analysis: MSC; Investigation: DYE, MSC; Methodology: DYE, MSC; Resources: DYE; Writing-original draft: DYE; Writing review and editing: MSC. All authors reviewed the results and approved the final version of the article.

References

1. Alqarni AM, Zeidler MP. How does methotrexate work? *Biochem Soc Trans*. 2020;48(2):559–567. doi: 10.1042/BST20190803.
2. Friedman B, Cronstein B. Methotrexate mechanism in treatment of rheumatoid arthritis. *Joint Bone Spine*. 2019;86(3):301–307. doi:10.1016/j.jbspin.2018.07.004.
3. Coates LC, Merola JF, Grieb SM, Mease PJ, Callis Duffin K. Methotrexate in psoriasis and psoriatic arthritis. *J Rheumatol Suppl*. 2020;96:31–35. doi: 10.3899/jrheum.200124.
4. Tan J, Renton WD, Whittle SL, et al. Methotrexate for juvenile idiopathic arthritis. *Cochrane Database Syst Rev*. 2024;2(2): CD003129. doi: 10.1002/14651858.CD003129.pub2.
5. Tirelli F, Zannin ME, Vittadello F, Agnolucci J, Mazzarolo M, Zulian F. Methotrexate monotherapy in juvenile idiopathic arthritis associated uveitis: myth or reality? *Ocul Immunol Inflamm*. 2022;30(7–8):1763–1767. doi: 10.1080/09273948.2021.1951303.
6. Priyadarssini M, Chandrashekar L, Rajappa M. Effect of methotrexate monotherapy on T-cell subsets in the peripheral circulation in psoriasis. *Clin Exp Dermatol*. 2019;44(5):491–497. doi: 10.1111/ced.13795.
7. Cronstein BN, Aune TM. Methotrexate and its mechanisms of action in inflammatory arthritis. *Nat Rev Rheumatol*. 2020;16 (3):145–154. doi: 10.1038/s41584-020-0373-9.
8. Maleki A, Anesi SD, Look-Why S, Manhapra A, Foster CS. Pediatric uveitis: a comprehensive review. *Surv Ophthalmol*. 2022;67(2):510 529. doi: 10.1016/j.survophthal.2021.06.006.
9. Simonini G, Paudyal P, Jones GT, Cimaz R, Macfarlane GJ. Current evidence of methotrexate efficacy in childhood chronic uveitis: a systematic review and meta-analysis approach. *Rheumatology (Oxford)*. 2013;52(5):825–831. doi: 10.1093/rheumatology/kes186.
10. Lahdenne P, Rapola J, Ylijoki H, Haapasaari J. Hepatotoxicity in patients with juvenile idiopathic arthritis receiving longterm methotrexate therapy. *J Rheumatol*. 2002;29(11):2442–2445.
11. Suwa A, Hirakata M, Satoh S, et al. Rheumatoid arthritis associated with methotrexate-induced pneumonitis: improvement with i. v. cyclophosphamide therapy. *Clin Exp Rheumatol*. 1999;17 (3):355–358.
12. Albrecht K, Müller-Ladner U. Side effects and management of side effects of methotrexate in rheumatoid arthritis. *Clin Exp Rheumatol*. Sep-Oct, 2010;28(5 Suppl 61):S95–101.
13. Prey S, Paul C. Effect of folic or folinic acid supplementation on methotrexate-associated safety and efficacy in inflammatory disease: a systematic review. *Br J Dermatol*. 2009;160(3):622–628. doi: 10.1111/j.1365-2133.2008.08876.x.
14. Curragh DS, O'Neill M, McAvoy CE, Rooney M, McLoone E. Pediatric uveitis in a well-defined population: improved outcomes with immunosuppressive therapy. *Ocul Immunol Inflamm*. 2018;26(6):978–985. doi:10.1080/09273948.2017.1305420.
15. Kalinina Ayuso V, van de Winkel EL, Rothova A, de Boer JH. Relapse rate of uveitis post-methotrexate treatment in juvenile idiopathic arthritis. *Am J Ophthalmol*. 2011;151(2):217–222. doi: 10.1016/j.ajo.2010.08.021.
16. Ramanan AV, Dick AD, Jones AP, et al. Adalimumab plus methotrexate for uveitis in juvenile idiopathic arthritis. *N Engl J Med*. April 27, 2017;376(17):1637–1646. doi: 10.1056/NEJMoa1614160.
17. Artornsombudh P, Pistilli M, Foster CS, et al. Factors predictive of remission of new-onset anterior uveitis. *Ophthalmology*. 2014;121 (3):778–784. doi: 10.1016/j.ophtha.2013.09.041.

18. Gregory AC, Kempen JH, Daniel E, et al. Systemic immunosuppressive therapy for eye diseases cohort study research group. risk factors for loss of visual acuity among patients with uveitis associated with juvenile idiopathic arthritis: the systemic immunosuppressive therapy for eye diseases study. *Ophthalmology*. 2013;120(1):186–192. doi: 10.1016/j.ophtha.2012.07.052.
19. Mapelli C, Miserocchi E, Nassisi Gaia Leone M, et al. Predictors of lack of response to methotrexate in juvenile idiopathic arthritis associated uveitis. *Rheumatology*. 2024:1–7. doi: 10.1093/rheumatology/keae079.
20. Kalinina Ayuso V, ten Cate HAT, van den Does P, Rothova A, de Boer JH. Young age as a risk factor for complicated course and visual outcome in intermediate uveitis in children. *Br J Ophthalmol*. 2011;95(5):646–651. doi: 10.1136/bjo.2010.184267.
21. Ozdal PC, Berker N, Tugal-Tutkun I. Pars planitis: epidemiology, clinical characteristics, management and visual prognosis. *J Ophthalmic Vis Res*. 2015;10(4):469–480. doi: 10.4103/2008-322X.176897.
22. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop. *Am J Ophthalmol*. 2005;140(3):509–516.
23. Deschenes J, Murray PI, Rao NA, Nussenblatt RB, International Uveitis Study Group. International Uveitis Study Group. International Uveitis Study Group (IUSG): clinical classification of uveitis. *Ocul Immunol Inflamm*. Jan-Feb, 2008;16(1):1–2. doi: 10.1080/09273940801899822.
24. Wang W, Zhou H, Liu L. Side effects of methotrexate therapy for rheumatoid arthritis: a systematic review. *Eur J Med Chem*. October 5, 2018;158:502–516. doi: 10.1016/j.ejmech.2018.09.027.
25. Nilüfer Yalçındağ F, Özdal P, Özyazgan Y, Batıoğlu F, Tugal-Tutkun I. BUST study group pediatric uveitis in Turkey: the national registry report II. Ocul Immunol Inflamm. December, 2023;31(10):1971–1977. doi: 10.1080/09273948.2022.2110900.
26. Siiskonen M, Hirn I, Pesälä R, et al. Prevalence, incidence and epidemiology of childhood uveitis. *Acta Ophthalmol*. 2021;99(2):e160–e163. doi: 10.1111/aos.14535.
27. Tuğal-Tutkun İ. An overview of pediatric uveitis. *Turk Arch Pediatr*. 2023;58(4):363–370. doi: 10.5152/TurkArchPediatr.2023.23086.
28. Curragh DS, O'Neill M, McAvoy CE, Rooney M, McLoone E. Pediatric uveitis in a well-defined population: improved outcomes with immunosuppressive therapy. *Ocul Immunol Inflammm*. 2018;26(6):978–985. doi: 10.1080/09273948.2017.1305420.
29. Ferrara M, Eggenschwiler L, Stephenson A, et al. The challenge of pediatric uveitis: tertiary referral center experience in the United States. *Ocul Immunol Inflammm*. 2019;27 (3):410–417. doi: 10.1080/09273948.2017.1420202.
30. Markomichelakis NN, Aissopou EK, Chatzistefanou KI, Aissopou EK, Chatzistefanou KI. Pediatric non-infectious uveitis: long-term outcomes and complications. *Ocul Immunol Inflamm*. December, 2023;31(10):2001–2008. doi: 10.1080/09273948.2022.2162422.
31. Seth NG, Kaur S, Yangzes S, et al. Ophthalmic complications in pediatric uveitis. *Ocul Immunol Inflamm*. November 17, 2021;29 (7–8):1375–1380. doi: 10.1080/09273948.2020.1762897.
32. Rosenberg KD, Feuer WJ, Davis JL. Ocular complications of pediatric uveitis. *Ophthalmology*. December, 2004;111 (12):2299–2306. doi: 10.1016/j.ophtha.2004.06.014.
33. Chia A, Lee V, Graham EM, Edelsten C. Factors related to severe uveitis at diagnosis in children with juvenile idiopathic arthritis in a screening program. *Am J Ophthalmol*. 2003;135(6):757–762. doi: 10.1016/S0002-9394(03)00225-3.
34. Kalinina Ayuso V, Ten Cate HA, van der Does P, Rothova A, de Boer JH. Male gender as a risk factor for complications in uveitis associated with juvenile idiopathic arthritis. *Am J Ophthalmol*. 2010;149(6):994–9.e5. doi: 10.1016/j.ajo.2010.01.016.
35. Wieringa WG, Armbrust W, Legger GE, Los LI. Efficacy of high-dose methotrexate in pediatric non-infectious uveitis. *Ocul Immunol & Inflammation*. 2019;27(8):1305–1313. doi: 10.1080/09273948.2018.
36. Dana MR, Merayo-Lloves J, Schaumberg DA, Foster CS. Visual outcomes prognosticators in juvenile rheumatoid arthritis-associated uveitis. *Ophthalmology*. 1997;104(2):236–244. doi: 10.1016/S0161-6420(97)30329-7.
37. Constantin T, Foeldvari I, Anton J, et al. Consensus-based recommendations for the management of uveitis associated with juvenile idiopathic arthritis: the SHARE initiative. *Ann Rheum Dis*. 2018;77 (8):1107–1117. doi: 10.1136/annrheumdis-2018-213131.
38. Khochtali S, Ozdal P, AlBloushi AF, Nabi W, Khairallah M. Pediatric pars planitis: a review. *Ocul Immunol Inflamm*. 2023;31 (10):1915–1929. doi: 10.1080/09273948.2023.2279683.

Ferrara *et al. Pediatric Rheumatology* (2018) 16:46
https://doi.org/10.1186/s12969-018-0255-8

Pediatric Rheumatology

REVIEW Open Access

Methotrexate in juvenile idiopathic arthritis: advice and recommendations from the MARAJIA expert consensus meeting

Giovanna Ferrara[1†], Greta Mastrangelo[2†], Patrizia Barone[3], Francesco La Torre[4], Silvana Martino[5], Giovanni Pappagallo[6], Angelo Ravelli[7], Andrea Taddio[8], Francesco Zulian[9], Rolando Cimaz[2*] On behalf of the Rheumatology Italian Study Group

Abstract

Background: Conventional pharmacological therapies for the treatment of juvenile idiopathic arthritis (JIA) consist of non-biological, disease-modifying antirheumatic drugs, among which methotrexate (MTX) is the most commonly prescribed. However, there is a lack of consensus-based clinical and therapeutic recommendations for the use of MTX in the management of patients with JIA. Therefore, the Methotrexate Advice and RecommendAtions on Juvenile Idiopathic Arthritis (MARAJIA) Expert Meeting was convened to develop evidence-based recommendations for the use of MTX in the treatment of JIA.

Methods: The preliminary executive committee identified a total of 9 key clinical issues according to the population, intervention, comparator, outcome (PICO) approach, and performed an evidence-based, systematic, literature review. During the subsequent Expert Meeting, the relevant evidence was assessed and graded, and 10 recommendations were made.

Results: Recommendations relating to the efficacy, optimal dosing and route of administration and duration of treatment with MTX in JIA, and to the issue of folic acid supplementation to prevent MTX side effects, use of MTX in the treatment of chronic JIA-associated uveitis, combination treatment with biologic agents, and the use of vaccinations in patients with JIA were developed. The selected topics were considered to represent clinically important issues facing clinicians caring for patients with JIA. Evidence was insufficient to formulate recommendations for the use of biomarkers predictive of treatment response.

Conclusions: These consensus recommendations provide balanced and evidence-based recommendations designed to have broad value for physicians and healthcare clinicians involved in the clinical management of patients with JIA.

Keywords: Juvenile idiopathic arthritis, Methotrexate, Consensus

Background

Juvenile idiopathic arthritis (JIA) is one of the most common chronic conditions of childhood. JIA comprises a group of heterogeneous forms of arthritis characterized by persistent joint inflammation lasting longer than 6 weeks and beginning before the age of 16 years and has an unknown cause [1]. According to the classification criteria of the International League of Associations for Rheumatology (ILAR), the term JIA covers seven mutually exclusive categories with differences in their clinical presentation, disease course and treatment response, namely systemic arthritis, oligoarthritis, polyarthritis (rheumatoid factor negative), polyarthritis (rheumatoid factor positive), psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis [1]. Conventional pharmacological therapies consist of non-biological, disease-modifying antirheumatic drugs (DMARD), among which methotrexate (MTX) is the most commonly prescribed [2].

* Correspondence: rolando.cimaz@meyer.it
†Giovanna Ferrara and Greta Mastrangelo contributed equally to this work.
[2]Rheumatology Unit, Anna Meyer Children Hospital and University of Florence, University of Florence, Florence, Italy
Full list of author information is available at the end of the article

© The Author(s). 2018 Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

To date, despite the wide use of MTX, there is a lack of consensus-based clinical and therapeutic recommendations for the use of MTX in the management of patients with JIA. Only two papers, one recently-published article from the Spanish Society of Paediatric Rheumatology (Sociedad Española de Reumatología Pediátrica; SERPE) [3], and an older article by the Pediatric Immunology and Rheumatology Division of the Centre for Child Health, Heinrich-Heine-University, Düsseldorf, Germany [4] currently deal with this task.

Thus, the aim of our group was to develop evidence-based recommendations for the use of MTX in the treatment of juvenile idiopathic arthritis. To this end, the Methotrexate Advice and RecommendAtions on Juvenile Idiopathic Arthritis (MARAJIA) Expert Meeting was convened in Milan, Italy.

Methodology

Development of the research topics

Establishing recommendations requires the use of formal methods, such as the nominal group technique (NGT), which is based on discussions by an Expert Panel to gather opinions and define a degree of consensus for each statement.

A preliminary executive committee comprising Rolando Cimaz, Giovanna Ferrara and Greta Mastrangelo was responsible for identifying key clinical issues using the PICO (Population – Intervention – Comparator - Outcome) system [5], with the aim of: 1) defining research questions, and 2) developing criteria for selecting studies to be reviewed by the Expert Panel in the development of clinical and therapeutic recommendations for the management of MTX in patients with JIA. The PICO framework is designed to help researchers to achieve relevant and precise questions that can be answered in a systematic review structure, and allows improved specificity and conceptual clarity of the clinical question by splitting the questions into smaller manageable components which are more straightforward to identify in the literature search process.

The approach facilitates the identification of a precise definition of a group of participants (Population), clear reporting of the drug exposures (Intervention) and the control group interventions (Comparator) under consideration, and well-defined and clearly specified Outcomes of the intervention being assessed. Finally, the type of Study design to be included in the review should be reported.

The executive committee identified nine clinically important research topics relating to the use of MTX in JIA using a structured PICO process. The topics covered efficacy and safety, dosages, routes of administration, tapering, and discontinuation of MTX, folic acid supplementation, efficacy in JIA-associated uveitis, add-on therapy with biologic drugs, biomarkers, and vaccination. The selected topics were considered to represent clinically important issues facing clinicians caring for patients with JIA.

Strategy for the literature search

A systematic search using PubMed and the Cochrane Library for human studies published in English until the present was conducted on the 30th of November 2016. The keywords used in the search were “juvenile idiopathic arthritis” and “methotrexate” (“arthritis, juvenile”[MeSH Terms] OR (“arthritis”[All Fields] AND “juvenile”[All Fields]) OR “juvenile arthritis”[All Fields] OR (“juvenile”[All Fields] AND “idiopathic”[All Fields] AND “arthritis”[All Fields]) OR “juvenile idiopathic arthritis”[All Fields]) AND (“methotrexate”[MeSH Terms] OR “methotrexate”[All Fields]).

Study selection and data extraction

All papers found with the first search were initially selected as appropriate to the intended purpose on the basis of the title. Papers inconsistent with the main topic (for example for disease or drug) were excluded. A second revision and selection was made reading the abstracts of remaining papers. Then all studies identified were read in their full text.

Critical appraisal of identified studies

Each of the included studies was assessed for level of evidence using Oxford criteria for evidence-based levels of evidence [6]. The levels of evidence used in the analyses are summarized in Table 1. Evidence levels are indicative of quality regarding confidence and study design. In

Table 1 Levels of evidence [6]

Levels of evidence	
1	Systematic review of all relevant randomized clinical trials or *n*-of-1 trials
2	Randomized trial or observational study with dramatic effect
3	Non-randomized controlled cohort/follow-up study (observational)
4	Case series, case-control study, or historically controlled study
5	Mechanism-based reasoning (expert opinion, based on physiology, animal or laboratory studies)
Grades of recommendation	
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies, or extrapolations from level 1 studies
C	Level 4 studies, or extrapolations from level 2 or 3 studies
D	Level 5 evidence or troubling, inconsistent or inconclusive studies of any level

defining the recommendations, the experts' assessment of the clinical conclusions of the studies was combined with the definition of the evidence levels.

Consensus process

Expert panel composition

The Expert Panel participating in the MARAJIA Expert Consensus Meeting held in Milan, Italy on the 12th of April, 2017 to identify recommendations for the use of MTX in the treatment of JIA consisted of Patrizia Barone, Rolando Cimaz, Francesco La Torre, Silvana Martino, Angelo Ravelli, Andrea Taddio, and Francesco Zulian, under the methodological guidance of Giovanni Pappagallo. Giovanna Ferrara and Greta Mastrangelo were involved in formulating the PICO research topics and drafting the recommendation statements.

All experts were pediatric rheumatologists, the majority from tertiary centers with longstanding expertise in pediatric rheumatic diseases.

Formulation of clinical recommendations

During the meeting, the Expert Panel considered the supporting research identified using the targeted literature search and formulated specific recommendation statements for each research topic. Ten clinical and therapeutic recommendations for the management of MTX were drafted and presented to the meeting with their supporting scientific evidence for discussion and voting by the Expert Panel towards reaching consensus.

The strength and relevance of the published evidence in support of a clinical intervention or treatment approach was evaluated, in addition taking into consideration the personal clinical experience of the panel participants. Each participant was required to express his or her expert opinion by rating the statement according to the following 7-point scale: 1) completely disagree; 2) somewhat disagree; 3) disagree a little; 4) neither agree nor disagree; 5) agree a little; 6) somewhat agree; 7) completely agree. A score of 6 or 7 was defined as "In favor", 3, 4 or 5 as "Uncertain", and 1 or 2 "Against".

Through this process, all research statements achieved acceptance, with a second round of voting not required for any statement. One hundred percent agreement (a unanimous score of 7 on the 7-point scale) was obtained on 5 statements (Statements 2, 3, 4, 7 and 8) and 83% agreement on Statements 1 and 6 (7 or 6) and Statement 5 (7 or 6 with a single score of 5 from one Advisor). The research questions are detailed in Table 2.

Research strategy and evidence selection

We obtained 843 references in our literature search. Among these, we selected 209 relevant references, of which 33 were clinical trials, 51 reviews, 1 Cochrane meta-analysis and 124 articles of other types.

A total of 472 references were excluded because they were judged not to be relevant, 139 because the studies were mainly about biologic drugs and there was an insufficient focus on MTX, and 23 because they were published in non-European languages. Six articles (2 clinical trials, 1 review, and 3 articles of other types) were subsequently included from an updated literature search (28 February 2017). A flow diagram of the study selection process is shown in Fig. 1.

Methotrexate in juvenile idiopathic arthritis: Recommendations for use

A summary of the recommendations for the use of MTX in JIA for each of the PICO research questions is presented in Table 2.

Research question 1: Efficacy and safety of methotrexate in juvenile idiopathic arthritis

Recommendation 1. *MTX is recommended as the first-line treatment in oligoarthritis that persists despite nonsteroidal anti-inflammatory drugs (NSAIDs) and intraarticular steroid (IAS) therapy, and in polyarticular disease (Evidence Grade 1A).*

MTX is also recommended in systemic arthritis with predominant joint inflammation, without active systemic features (Evidence Grade 4C).

Recommendation 2. *Clinical and laboratory monitoring of MTX toxicity is recommended every 4–8 weeks initially, and then every 12–16 weeks, unless risk factors are present (Evidence Grade 4C).*

PICO framework: P: children affected by JIA; I: administration of MTX; C: placebo or other therapies (salazopyrin, oral steroids, NSAIDs); O: efficacy and safety.

MTX is the most widely used DMARD in the treatment of JIA. A folic acid analog and an inhibitor of several different enzymes in the folate pathway, MTX exerts immunomodulatory and anti-inflammatory actions. Its efficacy was first demonstrated in a randomized controlled trial more than two decades ago [7]. MTX has been studied in further controlled clinical trials [8, 9] and has been established as the most common first-line DMARD treatment according to several national treatment guidelines [10–13]. In particular, considering the categories of JIA, NSAIDs and IAS therapy remain the first choice in oligoarthritis [1]. Furthermore, a recent multicenter, prospective, randomized, open-label trial [14] found that concomitant administration of MTX did not augment the effectiveness of intra-articular corticosteroid therapy.

MTX is recommended as first-line treatment in polyarthritis, and in systemic arthritis with predominant joint inflammation [2, 8, 11, 15]. However, initiation of sulfasalazine (SSZ) is recommended following IAS or an adequate

Table 2 Summary of recommendations for the use of methotrexate in juvenile idiopathic arthritis

PICO research questions and recommendations	Grade of evidence	Supporting references
Research question 1: Efficacy and safety of methotrexate in juvenile idiopathic arthritis		
1. MTX is recommended as the first-line treatment in oligoarthritis that persists despite nonsteroidal anti-inflammatory drugs (NSAIDs) and intraarticular steroid (IAS) therapy, and in polyarticular disease	1A	[2–4, 7–15, 20, 21, 23–25]
MTX is also recommended in systemic arthritis with predominant joint inflammation, without active systemic features	4C	[2–4, 7–15, 20–25]
2. Clinical and laboratory monitoring of MTX toxicity is recommended every 4-8 weeks initially, and then every 12-16 weeks, unless risk factors are present	4C	[1, 4, 12, 21, 26–38, 40–42]
Research question 2: Dosages of methotrexate in juvenile idiopathic arthritis		
3. A dose of 10-15 mg/m^2/week is recommended.	5D	[7, 9, 42]
Further increases in MTX dosage have not been associated with additional therapeutic benefit	1A	
Research question 3: Route of administration of methotrexate in juvenile idiopathic arthritis		
4. MTX may be given orally or subcutaneously once a week. If high doses (15 mg/m^2/week) are requested, the subcutaneous route is preferable due to increased bioavailability	4C	[9, 21, 43–49]
Research question 4: Tapering and discontinuation of methotrexate in juvenile idiopathic arthritis		
5. MTX could be discontinued after 6 months of stable remission	1A	[50–52]
Research question 5: Folic acid supplementation for the prevention of methotrexate toxicity in patients with juvenile idiopathic arthritis		
6. Folic or folinic acid supplementation is recommended to prevent MTX side effects.	1A	[53–57, 59–62]
The advised dose is approximately one third of the MTX dose, at least 24 hours after the weekly dose of MTX for folinic acid; for folic acid 1 mg/day skipping the day when MTX is administered	4C	
Research question 6: Efficacy of methotrexate in uveitis associated with juvenile idiopathic arthritis		
7. MTX is recommended for the treatment of JIA-related uveitis refractory to topical treatment	4C	[63–72, 74–79]
Research question 7: Add-on therapy with biologic drugs in juvenile idiopathic arthritis not responding to methotrexate		
8. The combination of MTX with a TNF-α inhibitor is recommended in patients who had an inadequate clinical response to MTX alone	3B	[11, 48, 80, 83–85, 88, 89]
Combination therapy is safe and may reduce the development of anti-drug antibodies	2B	[83, 88–90]
Research question 8: Molecular elements and genetic markers of response to methotrexate in juvenile idiopathic arthritis – Biomarkers		
9. No recommendation is made regarding the use of biomarkers in current clinical practice		[91–101]
Research question 9: Use of vaccination in patients with juvenile idiopathic arthritis treated with methotrexate		
10. Vaccination with non-live vaccines is not contraindicated during MTX treatment	2B	[101–119]
No recommendation can be formulated for live-attenuated vaccines, but the available data for measles, mumps, rubella (MMR) booster indicate that it is safe and adequately immunogenic		

Abbreviations: *IAS* intra-articular steroid, *JIA* juvenile idiopathic arthritis, *MMR* measles, mumps, rubella, *MTX* methotrexate, *NSAIDs* nonsteroidal anti-inflammatory drugs, *TNF-α* tumor necrosis factor-α

trial of NSAIDs for patients with the enthesitis-related arthritis category of JIA, with moderate activity [11]. Sulfasalazine has never been compared with MTX in treating JIA.

Currently, there are no published recommendations for the treatment of juvenile spondyloarthropathies. The ACR recommendations for the management of JIA suggest the use of sulfasalazine for patients with enthesitis-related arthritis. This recommendation is based on clinical experience and data from adult patients with ankylosing spondylitis. However, in the adult population it has been shown that sulfasalazine is ineffective in axial disease, while several observational studies have found that tumor necrosis factor (TNF)-α inhibitors are beneficial in juvenile spondyloarthropathies [16–19]. Furthermore, a recent randomized controlled trial demonstrated the efficacy of adalimumab in enthesitis-related arthritis [16, 18]. Available studies suggest that TNF-α inhibitors should be used when sulfasalazine is ineffective or earlier in moderate or highly active axial disease with established radiographic damage, such as erosions or joint-space narrowing.

MTX has been shown to be an effective drug in the indication, with 65–90% of patients successfully responding to treatment [9, 20–22]. MTX also significantly improved a wide range of health-related quality-of-life components, particularly in the physical domains [23].

Despite what has previously been reported in adult patients, MTX may also slow the radiologic progression of

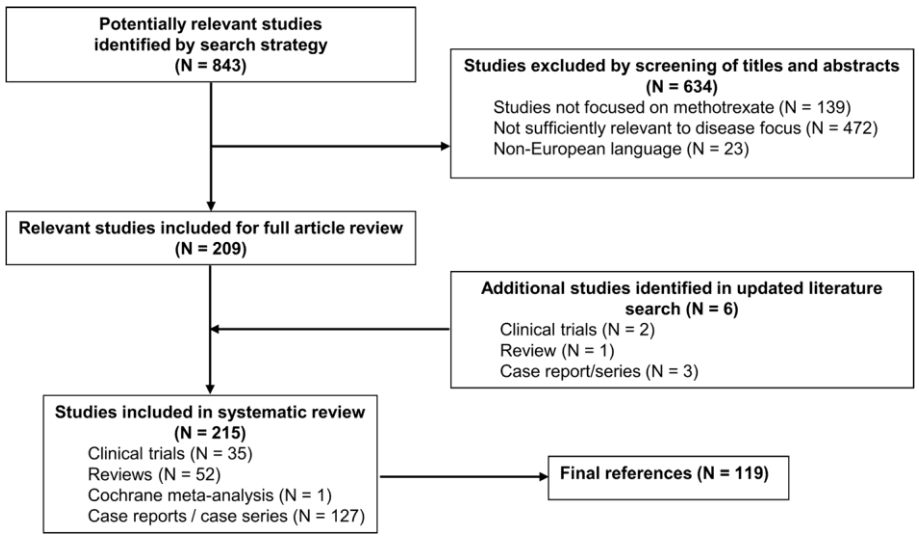


Fig. 1 Study selection process flow diagram

disease in JIA, acting as a disease-modifying drug, although the studies available involved few children [24, 25].

During 30 years of its use, MTX has shown a good safety profile, with few severe side effects reported [26]. Nevertheless, more than half of children were reported to have difficulties in taking it [27, 28]. The most common side effect of MTX include nausea or vomiting and abnormalities in liver function tests, the latest reported in 10–20% of patients [29, 30]. However, the transaminase levels usually normalize one or two weeks after stopping therapy. Others symptoms are mouth sores, rash, diarrhea and laboratory abnormalities such as leukopenia and hypogammaglobulinemia that may predispose to infections. Alopecia is seen in some patients, but hair grows back after stopping the medication. Since photosensitivity has been reported, limiting sun exposure and the use of sunscreen is advised. It is worth remembering that MTX is teratogenic, and it is necessary to use contraception while taking the drug and for 3–6 months after discontinuation [29].

MTX may cause cirrhosis and lung fibrosis, but these are extremely rare and have been reported only in adults with other comorbidities [31–33]. In the literature there are also few reports of lymphoma in children treated with MTX [34–36], but it has not been possible to determine whether these observations were merely coincidental, were causally linked to MTX, or were related to the underlying disease process. The issue of whether MTX treatment is an independent risk factor for various malignancies is controversial and remains unresolved. Long-term prospective cohort studies are needed to define the risk of hematological or other malignancies in MTX-treated patients.

Nodulosis is a rare MTX adverse event that has been described in JIA (accelerated nodulosis in two teenagers with rheumatoid factor [RF]-positive juvenile rheumatoid arthritis and one 3-year-old girl with systemic-onset disease). The nodules developed within six months after the initiation of MTX treatment and regressed after discontinuing therapy, or were successfully treated with hydroxychloroquine or colchicine [37–39].

Regarding laboratory monitoring in patients with JIA, there is only one guideline by Ortiz-Alvarez et al., derived from the American College of Rheumatology (ACR) guidelines for monitoring MTX toxicity in adults. They suggest a complete and differential blood count, liver function tests and albumin and serum creatinine levels every 4–8 week initially, and then every 12–16 week, unless risk factors are present [40]. Other authors also recommended hepatitis and varicella-zoster virus serology and tuberculin test before starting therapy [4]. MTX is contraindicated in children with reduced renal function.

Bulatović et al. [27] designed and validated the MTX Intolerance Severity Score (MISS) questionnaire to identify patients with MTX intolerance. The items investigated were: abdominal signs and symptoms (pain, nausea, vomiting) and behavioral symptoms (restless, crying, irritability, and refusal of MTX) before and after the administration of MTX. A cut-off score of 6 yielded the best sensitivity (88%) and specificity (80%). They found there was no difference in efficacy between the various routes of MTX administration. However, half of the 297 patients were MTX-intolerant. This was especially the case in patients who received parenteral MTX, who experienced more anticipatory behavioral symptoms prior to administration, compared to patients receiving oral MTX. However, the difference in the prevalence of gastrointestinal symptoms was not great.

Van Dijkhuizen et al. [41] also found more side effects among patients who received parenteral MTX. On the other hand, Klein et al. [21] found no difference in the prevalence of side effects between oral and parenteral MTX.

Overall, analysis of available studies and clinical experience of the participating experts show that MTX is usually well tolerated in patients with JIA.

Research question 2: Dosages of methotrexate in juvenile idiopathic arthritis

Recommendation 3. *A dose of 10–15 mg/m^2/week is recommended (Evidence Grade 5D). Further increases in MTX dosage have not been associated with additional therapeutic benefit (Evidence Grade 1A).*

PICO framework: P: children affected by JIA on treatment with MTX; I: low dosage of MTX (< 10 mg/m^2/week); C: high dosage of MTX (> 10 mg/m^2/week); O: efficacy and safety.

The therapeutic range of MTX for JIA is 8.5–15 mg/m^2/week. The first study by Giannini et al. showed that a dose of 5 mg/m^2/week was not superior to placebo, while 15 mg/m^2/week was superior to 10 mg/m^2/week [7].

Children seem to tolerate much higher doses than adults, and some series have described using 20 to 25 mg/m^2/week or 1.1 mg/kg/week in children with resistant disease with relative safety in the short-term [42]. However, a multinational, randomized controlled study confirmed this therapeutic range and showed no benefit of doses above 15 mg/m^2/week [9].

Research question 3: Route of administration of methotrexate in juvenile idiopathic arthritis

Recommendation 4. *MTX may be given orally or subcutaneously once a week. If high doses (15 mg/m^2/week) are requested, the subcutaneous route is preferable due to increased bioavailability* (*Evidence Grade 4C).*

PICO framework: P: children affected by JIA on treatment with MTX; I: subcutaneous administration of MTX; C: oral administration of MTX; O: efficacy, safety, and tolerability.

There is significant intraindividual and interindividual variability in the absorption and pharmacokinetics of MTX after oral administration [43, 44].

A pharmacokinetic study showed that factors such as age, body weight, creatinine clearance, gender, dose, and fasting state significantly influenced the absorption of MTX in adults with rheumatoid arthritis. The bioavailability of MTX has also been shown to be greater in the fasting state in children with JIA [45].

MTX should be taken on an empty stomach with water or clear beverages. Oral bioavailability generally is about 15% less than after intramuscular administration. The bioavailability of intramuscular and subcutaneous administration is similar, with the latter being generally more acceptable for children who require parenteral MTX [46, 47].

Several studies have reported the successful use of parenteral treatment in non-responders to oral MTX treatment, but there are no controlled comparative studies (only open-label studies are available). Alsufyani et al. found that patients switching from oral to subcutaneous administration of MTX had a 70% improvement in response [48].

Klein et al. in a retrospective study showed no differences in effectiveness between oral and parenteral administration of MTX, even if more patients on parenteral therapy discontinued it [21]. In clinical practice, MTX is preferentially administrated subcutaneously, and there is no sound study demonstrating greater efficacy for the oral route of MTX administration.

At doses over 15 mg/m^2/week, the parenteral route may be better because of the decreased oral bioavailability of the drug at high doses. It has been shown that subcutaneous administration of MTX has a 10–12% increased absorption compared with oral preparations [46, 49]. In discussion amongst the Panel members, it was noted that in clinical practice, treatment is usually started with MTX 15 mg/m^2/week, particularly in severe forms of JIA, where the patient is directly treated with MTX 15 mg/m^2/week. The Panel further suggested that, for the first administrations, the starting dose can be 10 mg/m^2/week, and then the dose can be increased at subsequent MTX administrations, if necessary. Ruperto et al. reported that MTX doses greater than 15 mg/m^2/week provided no additional clinical benefit, and that this dose should not be exceeded [9].

Research question 4: Tapering and discontinuation of methotrexate in juvenile idiopathic arthritis

Recommendation 5. *MTX could be discontinued after 6 months of stable remission (Evidence Grade 1A).*

PICO framework: P: children affected by JIA on treatment with MTX; I: tapering and discontinuing treatment six months after achieving remission; C: discontinuing MTX twelve months or longer after achieving remission; O: survival free of flares after stopping treatment.

MTX is a slow-acting drug, generally displaying its full therapeutic effect in 6–8 weeks (from 3 to 18 weeks among different studies), so there is general agreement to wait at least 12 weeks to assess its efficacy. On the contrary, there is a wide variability on the tapering and discontinuation of MTX doses in everyday clinical practice. There have been many studies in children treated with variable doses of MTX for variable periods in whom discontinuation of MTX was attempted after clinical “remission” of variable length was achieved [50].

The criteria for “remission” or “relapse” have usually not been well defined or standardized among various studies, and the assessment of outcomes has been nonblinded.

Only Foell et al. in a randomized clinical trial proved the safety of withdrawing MTX therapy after 6 months of stable remission versus 12 months. The results of this study that included 364 patients showed that a 12-month versus 6-month withdrawal of MTX did not reduce the relapse rate [51].

MTX withdrawal may result in disease flare in more than 50% of patients, and even more in younger children. A longer period on MTX treatment after remission may not prolong the duration of improvement after stopping treatment, but the duration of clinical remission may be predicted by the degree of subclinical synovial inflammation (using myeloid related proteins 8 and 14 [MRP8/MRP14]) at the time of stopping MTX [52].

Research question 5: Folic acid supplementation for the prevention of methotrexate toxicity in patients with juvenile idiopathic arthritis

Recommendation 6. *Folic or folinic acid supplementation is recommended to prevent MTX side effects (Evidence Grade 1A). The advised dose is approximately one third of the MTX dose, at least 24 h after the weekly dose of MTX for folinic acid; for folic acid 1 mg/day skipping the day when MTX is administered (Evidence Grade 4C).*

PICO framework: P: children affected by JIA on treatment with MTX; I: MTX and folic acid supplementation; C: MTX alone; O: frequency (prevalence/incidence) of nausea and dyspepsia.

MTX toxicity, such as hepatotoxicity, hematologic changes, gastrointestinal and mucocutaneous intolerance, has been hypothesized to be a result of an induced state of folate depletion. The addition of folate, therefore, can counteract the signs of toxicity, either as folic or folinic acid (a reduced form of folic acid), since they can function in biosynthetic pathways independent of dihydrofolate reductase.

In a double-blind placebo-controlled study in RA, 1–5 mg of folic acid led to a significant reduction of side effects whilst preserving the efficacy of MTX therapy, even if, in order to preserve the anti-inflammatory effect, a slightly higher dosage of MTX was necessary [53]. Several clinical studies showed also that folic acid supplementation is associated with a reduced MTX discontinuation rate [53–55]. According to available data, folic acid supplementation does not appear to interfere with the therapeutic efficacy of MTX [55–57]. Indeed, there is increasing evidence that the anti-inflammatory effect of MTX is mediated by adenosine and is unrelated to folic or folinic acid [58]. A randomized controlled study, which directly compared folic acid to folinic acid in rheumatoid arthritis, showed no difference between the two forms of supplementation [53].

Studies in children are limited. A 13-week, randomized, double-blind, placebo-controlled, crossover trial of folic acid (1 mg/day) or placebo combined with a stable dose of MTX in 19 children with juvenile rheumatoid arthritis reported no effect on the clinical efficacy of oral weekly MTX. No liver function tests abnormalities were observed, but no data about other toxicities were available [59]. According to the findings of the studies conducted in adults, the frequency of increased transaminases is reduced by 60% by folinic acid supplementation [57]. Furthermore, in a retrospective non-controlled study [60] the efficacy of folinic acid supplementation was investigated in a cohort of 43 children on an intermediate dose of MTX. A significant reduction in hepatotoxicity and gastrointestinal toxicity was shown, without compromising MTX efficacy.

Administration of folic or folinic acid 24 h apart from the administration of MTX, in a dose of approximately one-third of the MTX dose, has been used to prevent MTX toxicity manifestations [61].

However, in limited cases, it is reported that at high doses folic acid supplementation seems to be associated with disease flares [62].

According to available data, it is not possible to make firm recommendations about routine folate supplementation in children receiving MTX treatment. However, data from adult studies and limited pediatric data can provide helpful information. Low-dose (1 mg/day) folic acid supplementation does not affect the anti-inflammatory efficacy of MTX and counteracts the signs of gastrointestinal and mucosal toxicities associated with it. The advisable dose is approximately one-third of the MTX dose, at least 24 h after the weekly dose of MTX, or 1 mg/day skipping the day when MTX is administered (Grade 4C). Folic acid supplementation does not appear to interfere with the therapeutic efficacy of MTX and seems to be associated with a reduced MTX discontinuation rate.

Research question 6: Efficacy of methotrexate in uveitis associated with juvenile idiopathic arthritis

Recommendation 7. *MTX is recommended for the treatment of JIA-related uveitis refractory to topical treatment (Evidence Grade 4C).*

PICO framework: P: children affected by JIA and uveitis; I: administration of MTX; C: placebo or other therapies (e.g., oral steroids); O: efficacy and safety.

Although there is a lack of randomized controlled studies on the subject, the available data suggest that MTX is useful for preventing the onset of uveitis and improving disease activity in cases of JIA. In particular, a systematic review and meta-analysis of prospective studies carried out by Simonini et al. found that there was a 73% (95% confidence interval 66–81%) likelihood of improving intraocular inflammation in patients treated with MTX [63]. The systematic review was based on data from nine retrospective chart reviews [63–72]. The number of children in studies varied from 3 to 25, and

the dose of MTX ranged from 7.5 to 30 mg/m^2, with 15 mg/m^2 the most commonly used. Ninety-five of 135 children were responders to MTX. The outcome measures to assess the effectiveness of MTX were collected according to the Standardization of Uveitis Nomenclature working group criteria [73]. It was reported that additional topical steroids or systemic immunosuppressive drugs were often required. However, the lack of randomized controlled trials means that treatment with immunosuppressive drugs is supported only at evidence level III: expert opinion, clinical experience or descriptive studies [74].

Additionally, Charuvanij and colleagues [75] reviewed the medication history in 43 children with JIA and anterior uveitis. Topical corticosteroids alone permitted satisfactory disease control in few patients (16%). The addition of MTX controlled the uveitis in three-quarters of patients, but additional systemic immunosuppressive drug (infliximab) was required in 6 children, with disease control in 4 patients.

The lack of evidence from randomized controlled trials limits our understanding of MTX effectiveness in the indication and of the best time to start therapy, even though MTX is largely used in chronic uveitis, mostly when associated with JIA.

Heiligenhaus et al. [76] suggest adding an immunosoppressive drug (i.e. MTX) to steroids when the inflammation in the eyes has not resolved within 12 weeks under treatment with topical corticosteroids maximally 3 times daily or, in cases of recurring uveitis, under a systemic corticosteroid dosage of more than 0.15 mg/kg body weight or if new uveitis complications develop. The preferred dose is 15 mg/m^2/week (maximum 25 mg/m^2/week) [77]. Evidence from several sources suggested that if MTX is effective in controlling inflammation, treatment should be maintained for 12 months from when inactive uveitis has been confirmed. In patients with poor visual prognosis, MTX treatment should be maintained over 24 months [77].

In terms of preventing the onset of uveitis in children during early treatment with MTX Papadopoulou et al. [78] performed a retrospective study of 254 patients with JIA. Eighty-six patients (33.9%) were treated with MTX and 168 patients (66.1%) did not receive MTX. Over the 2-year follow-up, the frequency of uveitis was lower in patients who had received MTX than in untreated patients (10.5% vs 20.2%, respectively, $p = 0.049$). The majority of patients in the study had persistent and extended oligoarthritis (61.8 and 22.4%, respectively); 14.2% of patients had RF-negative polyarthritis. As expected, patients treated with MTX had a greater frequency of polyarticular disease, which is well known to have a lower incidence of uveitis. However, the distribution of the main risk factors for uveitis (proportion of female and antinuclear antibodies- positive subjects) and the median age at disease onset were comparable between the two groups. In a longitudinal analysis from a nationwide pediatric rheumatology database [79] the influence of MTX, TNF-α inhibitors, and a combination of the 2 medications on uveitis occurrence in JIA patients was analyzed. In a total of 3512 patients the use of any of these drugs in the year before uveitis onset significantly reduced the risk for uveitis, and the use of MTX within the first year of disease and of the combination of MTX with a TNF-α inhibitor had the highest protective effect.

In a recent systematic review [63], MTX seems an effective therapy for uveitis associated with JIA.

Research question 7: Add-on therapy with biologic drugs in patients with juvenile idiopathic arthritis not responding to methotrexate

Recommendation 8. *The combination of MTX with a TNF-α inhibitor is recommended in patients who had an inadequate clinical response to MTX alone (Evidence Grade 3B). Combination therapy is safe and may reduce the development of anti-drug antibodies (Evidence Grade 2B).*

PICO framework: P: children affected by JIA on treatment with MTX who did not achieve remission; I: MTX plus TNF-α inhibitors (etanercept and adalimumab); C: MTX alone; O: efficacy and safety.

The ACR recommendations [11] propose the addition of a TNF-α inhibitor (etanercept or adalimumab) for patients who had a partial previous clinical response to MTX with persistent disease activity, recommending, after starting combination therapy, that treatment with MTX be continued or not depending on the patient's previous response to it.

Two retrospective cohort studies recommended completion of a maximal response timeframe and to achieve the maximum effective dose by the parenteral route before considering combination therapy [48, 80].

Studies in adult patients with RA revealed a superiority of combining MTX and etanercept versus MTX only [81, 82]. This combination has also been successfully used in children and adolescents, despite a lack of double-blind, randomized controlled trials [83].

A 3-year, open-label, prospective multicenter study of children and adolescents (aged 2–18 years) with polyarticular, systemic, or extended oligoarticular JIA receiving MTX ($n = 197$), etanercept ($n = 103$), or both ($n = 294$) showed good safety and efficacy in all three groups. The results of this study indicated that patients with polyarticular (RF-positive or negative) or systemic JIA benefit from etanercept or etanercept plus MTX treatment [84]. Improvements in joint counts and physician's global assessment scores were similar across three different arms, and improvements were maintained for three years in those continuing to receive medication.

In a randomized, double-blind, stratified, placebo-controlled, multicenter, medication-withdrawal study with a 16-week open-label lead-in phase, a 32-week double-blind withdrawal phase, and an open-label extension phase, 171 children with active juvenile rheumatoid arthritis underwent stratification according to MTX use (85 patients receiving MTX, 86 not receiving MTX) and received adalimumab every other week for 16 weeks. Subsequently, those that had an ACR Pediatric 30% (ACR Pedi 30) response at week 16 (74% of patients not receiving MTX and 94% of those receiving MTX) were randomly assigned to receive adalimumab or placebo in a double-blind fashion every other week for up to 32 weeks. At 48 weeks, the percentages of patients treated with MTX who had ACR Pedi 30, 50, 70, or 90 responses were significantly greater for those receiving adalimumab than for those receiving placebo; the differences between patients not treated with MTX who received adalimumab and those who received placebo were not significant. The study was not statistically powered to detect differences between patients receiving and those not receiving MTX; however, the proportions of patients with ACR Pedi 30, 50, 70, or 90 responses were somewhat higher among those receiving adalimumab in combination with MTX than among those receiving adalimumab without MTX [85].

A diminished response to treatment with certain TNF-α inhibitors may be associated with the development of anti-drug antibodies [86], and concomitant use of MTX reduces the immunogenicity of these drugs [85, 87].

Concerning safety, several studies reported that MTX combined with anti-TNF-α does not increase its toxicity [83, 88–90].

MTX in combination with biologic therapy is safe and may reduce the development of anti-drug antibodies in addition to improving response.

Research question 8: Molecular elements and genetic markers of response to methotrexate in juvenile idiopathic arthritis – Biomarkers

Recommendation 9. *No recommendation is made regarding the use of biomarkers in current clinical practice.*

PICO framework: P: children affected by JIA undergoing treatment with MTX; I: evaluating the concentration of MTX polyglutamates and genetics variants in MTX responders; C: polyglutamate levels and genetic variants in patients with JIA non-responders to MTX; O: response to MTX in children with JIA.

Although MTX is the first choice in JIA, it is known that about one-third of patients fail to respond. Given the time lag between MTX treatment initiation and the patient response (about 3 months), it would be particularly useful to determine a priori the probability of beneficial therapeutic response [91, 92].

In fact, the delay in identifying the optimal treatment at an early stage of disease can influence long-term joint damage. Several biomarkers have been investigated so far. Recent studies found that the effect of MTX in JIA is associated with MTX polyglutamate intracellular concentrations: elevated long chain MTX polyglutamate levels are associated with lower disease activity indexes (JADAS) during 1 year of MTX treatment in JIA [93–95].

Other studies have evaluated the effects of genetic variants in the complex pathway of candidate genes involved in MTX pharmacokinetics and pharmacodynamics on the response to the medication in children with JIA. These studies found that genetic variants that predict MTX response in JIA are those in 5-aminoimidazole-4-carboxamide ribonucleotide-transformylase (ATIC), inosine triphosphate-pyrophosphatase (ITPA) and SLC19A1 genes [96–99].

Pastore et al. showed that reduced activity of ITPA, an enzyme involved in nucleotides' homeostasis, is related to reduced MTX efficacy in patients with JIA [100]. The same group also found that a common functional variant in ATIC gene is associated with good response to MTX, while a variant in ITPA is associated with reduced response to MTX. However, there are suggestions that genetic variability, specifically single-nucleotide polymorphisms (SNP), in MTX metabolic pathways may be a better marker for MTX toxicity than for efficacy [99].

The conclusions of these studies may suggest that patients with variants associated with lack of efficacy for MTX should be switched more rapidly to a more aggressive treatment, but studies specifically addressing this issue are still lacking. In the future, therapy personalization in JIA may be achieved by a pharmacological approach integrating pharmacokinetic and pharmacogenomic evaluations. However, the supporting evidence is not yet sufficiently robust to form the basis of a recommendation.

Therefore, it was determined that the place of pharmacokinetic and pharmacogenomic analysis performed before MTX treatment in patients with JIA to identify those predisposed to better responses currently undefined and, furthermore, in current clinical practice no assessment of the biomarkers predictive of treatment response is carried out. Therefore, it was decided that no recommendation regarding the use of biomarkers in the treatment of patients with JIA should be made.

Research question 9: Use of vaccination in patients with juvenile idiopathic arthritis treated with methotrexate

Recommendation 10. *Vaccination with non-live vaccines is not contraindicated during MTX treatment (Evidence Grade 2B).*

No recommendation can be formulated for live-attenuated vaccines, but the available data for measles, mumps, rubella (MMR) booster indicate that it is safe and adequately immunogenic.

PICO framework: P: children affected by JIA on treatment with MTX; I: vaccinations during treatment with MTX; C: no vaccinations during treatment with MTX; O: safety and efficacy of vaccinations, safety of drugs.

Considering that children with JIA have an increased risk of infection, which contributes to the morbidity of their disease, non-live vaccines, and live-attenuated vaccines can be recommended in these patients. However, the presence of immunosuppressive drugs can interfere with effectiveness and safety of vaccinations.

In 2011, the European League Against Rheumatism (EULAR) published recommendations regarding the vaccination of children with rheumatic diseases [101], based on a systematic literature review published in that same year [102]. The EULAR guidelines recommend adherence to the national vaccination guidelines for live-attenuated vaccines in pediatric patients unless the patients are on high-dose immunosuppressants, high-dose cortisone or biological agents. Booster vaccinations against varicella, yellow fever, and measles, mumps, rubella (MMR) can be considered in patients receiving MTX less than15mg/m^2 or low-dose corticosteroids. However, it should be noted that the MTX summary of product characteristics states that live vaccines are contraindicated in patients taking MTX.

Recently Groot et colleagues provided an update to July 2014 of the systematic literature study of 2011 [103]. Eight studies on MTX and vaccinations, counting in total 420 patients, were available in the Groot review concerning the most common vaccines, i.e., seasonal influenza virus and H1N1, hepatitis B virus (HBV), meningococcus C, pneumococcus, measles, mumps and rubella (MMR), varicella zoster virus (VZV), bacillus Calmette-Guérin (BCG) [104–111]. Further we found five more articles about the above-mentioned vaccines including subgroups of patients on MTX [112–116], and one more concerning the bivalent human papillomavirus (HPV) vaccine [117].

In a prospective controlled observational cohort study, the immunogenicity of the bivalent HPV 16/18 vaccine in 68 patients with JIA was compared to 55 healthy controls, showing that all participants were seropositive up to 12 months after vaccination. No deleterious effect of MTX on antibodies was detected in the subgroup of 24 patients on MTX. No relevant differences in adverse events were found, and HPV vaccination did not aggravate JIA disease activity [117].

In two prospective open-label studies, influenza vaccine response and safety among patients treated with MTX were compared with a control group. Both studies showed that influenza vaccination in JIA induces a lower but effective protective antibody response with an adequate disease safety profile [109, 111].

Kasapcopur et al. compared responsiveness and safety of hepatitis B vaccination in 39 children affected by JIA and 41 healthy children. No effect of MTX on antibody concentration or response rate and no increase in disease activity were observed. A vaccination schedule at 0, 1, 6 months appeared to be the most effective [105].

The Neisseria meningitidis C (NeisVac-C) vaccine, is also safe and immunogenic in patients with JIA [115]. A retrospective cohort study showed that persistence of MenC-specific immunoglobulin (Ig)G antibodies in patients with JIA is similar to healthy controls and there is no effect of MTX on the decline of antibody levels over time, unlike biologicals [107].

Farmaki and colleagues observed that patients with JIA, when using MTX, had a similar response and seroprotection rate to the 7-valent pneumococcal vaccine (PCV7) as in healthy controls [114]. The only study evaluating the 23-valent polysaccharide pneumococcal vaccine in patients with JIA also demonstrated vaccine safety and effectiveness [116].

In a randomized, multicenter, open-label clinical equivalence trial, 137 patients with JIA aged 4 to 9 years (60 using MTX and 15 using biologics) were randomly assigned to receive MMR booster vaccination (n = 68) or no vaccination (control group; n = 69). Disease activity during complete follow-up did not differ between revaccinated patients and controls and seroprotection rates at 12 months after vaccination were higher in revaccinated patients. It seems that MTX and biologics did not affect humoral responses, but low patient numbers precluded definite conclusions. Moreover, no disease due to infections with attenuated viruses occurred in patients treated with immunosuppressive drugs [113]. A retrospective cross-sectional study [104], a retrospective observational multicenter cohort study [108] and a prospective case-control study [110] confirm these results.

In a prospective study [112], safety and immunogenicity of the VZV vaccine among 25 patients with pediatric rheumatic diseases treated with MTX and corticosteroids were compared to 18 healthy children. The vaccine proved to be safe in MTX treated patients, and no severe treatment-related adverse effects were observed during the one year follow up period. Both patients and controls had a low seroconversion rate one year after vaccination. However, a recent study [118] showed a low seroconversion rate in susceptible healthy children after one dose of vaccine, and indeed the US Centers for Disease Control and Prevention (CDC) guidelines advocate the use of 2 doses [119]. In clinical practice, a booster dose of VZV vaccine is normally administered to patients who fail to exhibit an immunological response after the first dose.

Kiray et al. demonstrated that there is no effect of MTX on purified protein derivative (PPD) induration size several years after BCG vaccination [106]. The PPD positivity rate was similar in MTX users and nonusers, even if the response to PPD was significantly lower in BCG-vaccinated

children with JIA compared to healthy children. However, because of the lack of safety data, BCG vaccinations should not be administered to patients on immunosuppressive drugs (including MTX) or biologicals.

According to available data, no detrimental effect of MTX on the short-term immunogenicity or on the persistence of antibodies over time and no relevant increase in vaccine-associated adverse events were found in patients treated with MTX. Non-live vaccines are generally adequately immunogenic and safe. It appears that live-attenuated vaccines can be safely and effectively administered to patients with JIA on MTX, unless they are also on additional immunosuppressive drugs or biologicals. In these cases, evidence on safety is scarce. Live-attenuated booster vaccinations can be considered on an individual basis, although the data do not currently support the formulation of a specific recommendation for live-attenuated vaccines. There is no evidence in pediatric patients about the safe time intervals for the administration of live vaccines after cessation of immunosuppressive/immunomodulatory drugs such as MTX.

Discussion

Although MTX is accepted as the most effective non-biologic agent for the treatment of patients with JIA, there is a wide variability in everyday practice in the use of MTX in the management of JIA. Therefore, the adoption of a consensus approach by a group of practitioners expert in the use of the drug in treating patients with JIA has the potential to guide clinicians and improve the understanding and management of this condition.

The recommendations presented in these consensus guidelines developed by the panel of experts participating in the MARAJIA Expert Consensus Meeting are based on a high level of evidence provided in large measure by robust data from randomized controlled clinical trials. Based on a set of key clinical issues developed using the PICO system and a rigorous approach to evidence review and the formulation of the research questions adopted to reduce the introduction of biases and to ensure balanced and evidence-based recommendations, we identified sound scientific support to guide the use of MTX in patients with JIA. Our consensus-based analysis integrated the scientific evidence from the literature with clinical experience to provide a set of recommendations we believe are of value in helping clinicians optimize the treatment of their patients with a diagnosis of JIA.

Conclusions

These consensus recommendations relating to the efficacy, optimal dosing and route of administration and duration of treatment with MTX in JIA, and to the important issues of folic acid supplementation to prevent MTX side effects, use of MTX in the treatment of chronic JIA-associated uveitis, combination treatment with biologic agents, and the use of vaccinations in patients with JIA provide balanced and evidence-based recommendations designed to have broad value for physicians and healthcare clinicians. We did not at this time find sufficient evidence to justify pharmacokinetic and pharmacogenomic analysis prior to MTX treatment in current clinical practice, as insufficient evidence is available on biomarkers able to predict treatment response.

Abbreviations

ACR: American College of Rheumatology; BCG: Bacillus Calmette- Guérin; DMARD: Disease-modifying antirheumatic drugs; EULAR: European League Against Rheumatism; HBV: Hepatitis B virus; HPV: Human papillomavirus; IAS: Intraarticular steroid; Ig: Immunoglobulin; ILAR: International League of Associations for Rheumatology; JIA: Juvenile idiopathic arthritis; MARAJIA: Methotrexate Advice and RecommendAtions on Juvenile Idiopathic Arthritis; MISS: MTX Intolerance Severity Score; MMR: Measles, mumps, rubella; MTX: Methotrexate; NSAIDs: Nonsteroidal anti-inflammatory drugs; PICO: Population – Intervention – Comparator – Outcome; PPD: Purified protein derivative; RF: Rheumatoid factor; TNF-α: Tumor necrosis factor-α; VZV: Varicella zoster virus

Acknowledgements

The MARAJIA project was developed with the unconditional support of Alfasigma.

The authors thank Ray Hill, an independent medical writer acting on behalf of Springer Healthcare Communications, who provided medical writing support funded by Alfasigma.

Funding

The project received no direct funding.

Authors' contributions

Project conception: RC. Formulation of PICO and the first draft of the manuscript: RC, GF, GM. Analysis and critical review of recommendations: all authors. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable. No patient data was included in this work.

Competing interests

The authors declare they have no competing interests.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Author details

[1]University of Trieste, Trieste, Italy. [2]Rheumatology Unit, Anna Meyer Children Hospital and University of Florence, University of Florence, Florence, Italy. [3]Department of Pediatrics, University of Catania, Catania, Italy. [4]Pediatric Rheumatology Section, Pediatric Onco-Hematology Unit, Vito Fazzi Hospital, Lecce, Italy. [5]Clinica Pediatrica Università di Torino, Day-Hospital Immunoreumatologia, Turin, Italy. [6]Epidemiology & Clinical Trials Office, General Hospital, Mirano VE, Italy. [7]Pediatria II – Reumatologia, Istituto Giannina Gaslini, and Università degli Studi di Genova, Genoa, Italy. [8]Institute for Maternal and Child Health - IRCCS "Burlo Garofolo", Trieste, and University of Trieste, Trieste, Italy. [9]Department of Pediatrics, Rheumatology Unit, University of Padua, Padua, Italy.

Received: 27 February 2018 Accepted: 8 June 2018
Published online: 11 July 2018

References

1. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International league of associations for rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol. 2004;31:390–2.
2. Blazina S, Markelj G, Avramovic MZ, Toplak N, Avčin T. Management of juvenile idiopathic arthritis: a clinical guide. Paediatr Drugs. 2016;18:397–412.
3. Calvo I, Anton J, Lopez Robledillo JC, de Inocencio J, Gamir ML, Merino R, et al. Recommendations for the use of methotrexate in patients with juvenile idiopathic arthritis. An Pediatr (Barc). 2016;84(177):e1–8.
4. Niehues T, Lankisch P. Recommendations for the use of methotrexate in juvenile idiopathic arthritis. Paediatr Drugs. 2006;8:347–56.
5. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from https://handbook.cochrane.org..
6. OCEBM Levels of Evidence Working Group. The Oxford levels of evidence 2. Oxford, UK: Oxford Centre for Evidence-Based Medicine; 2011.
7. Giannini EH, Brewer EJ, Kuzmina N, Shaikov A, Maximov A, Vorontsov I, et al. Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.a.-U.S.S.R. double-blind, placebo-controlled trial. The pediatric rheumatology collaborative study group and the cooperative Children's study group. N Engl J Med. 1992;326:1043–9.
8. Woo P, Southwood TR, Prieur AM, Dore CJ, Grainger J, David J, et al. Randomized, placebo-controlled, crossover trial of low-dose oral methotrexate in children with extended oligoarticular or systemic arthritis. Arthritis Rheum. 2000;43:1849–57.
9. Ruperto N, Murray KJ, Gerloni V, Wulffraat N, de Oliveira SK, Falcini F, et al. A randomized trial of parenteral methotrexate comparing an intermediate dose with a higher dose in children with juvenile idiopathic arthritis who failed to respond to standard doses of methotrexate. Arthritis Rheum. 2004;50:2191–201.
10. Bader-Meunier B, Wouters C, Job-Deslandre C, Cimaz R, Hofer M, Pillet P, et al. Guidelines for diagnosis and treatment of oligoarticular and polyarticular juvenile idiopathic arthritis. Arch Pediatr. 2010;17:1085–9.
11. Beukelman T, Patkar NM, Saag KG, Tolleson-Rinehart S, Cron RQ, DeWitt EM, et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Res (Hoboken). 2011;63:465–82.
12. Guellac N, Niehues T. Interdisciplinary and evidence-based treatment guideline for juvenile idiopathic arthritis. Klin Padiatr. 2008;220:392–402.
13. Niehues T, Horneff G, Michels H, Hock MS, Schuchmann L, Working Groups Pediatric Rheumatology G, et al. Evidence-based use of methotrexate in children with rheumatic diseases: a consensus statement of the working groups pediatric rheumatology Germany (AGKJR) and pediatric rheumatology Austria. Rheumatol Int. 2005;25:169–78.
14. Ravelli A, Davi S, Bracciolini G, Pistorio A, Consolaro A, van Dijkhuizen EH, et al. Intra-articular corticosteroids versus intra-articular corticosteroids plus methotrexate in oligoarticular juvenile idiopathic arthritis: a multicentre, prospective, randomised, open-label trial. Lancet. 2017;389:909–16.
15. Ringold S, Weiss PF, Beukelman T, EM DW, Ilowite NT, Kimura Y, et al. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. Arthritis Rheum. 2013;65:2499–512.
16. Otten MH, Prince FH, Twilt M, Ten Cate R, Armbrust W, Hoppenreijs EP, et al. Tumor necrosis factor-blocking agents for children with enthesitis-related arthritis–data from the dutch arthritis and biologicals in children register, 1999-2010. J Rheumatol. 2011;38:2258–63.
17. Horneff G, Burgos-Vargas R, Constantin T, Foeldvari I, Vojinovic J, Chasnyk VG, et al. Efficacy and safety of open-label etanercept on extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis and psoriatic arthritis: part 1 (week 12) of the CLIPPER study. Ann Rheum Dis. 2014;73:1114–22.
18. Horneff G, Fitter S, Foeldvari I, Minden K, Kuemmerle-Deschner J, Tzaribacev N, et al. Double-blind, placebo-controlled randomized trial with adalimumab for treatment of juvenile onset ankylosing spondylitis (JoAS): significant short term improvement. Arthritis Res Ther. 2012;14:R230.
19. Burgos-Vargas R, Tse SM, Horneff G, Pangan AL, Kalabic J, Goss S, et al. A randomized, double-blind, placebo-controlled multicenter study of adalimumab in pediatric patients with enthesitis-related arthritis. Arthritis Care Res (Hoboken). 2015;67:1503–12.
20. Fráňová J, Fingerhutová Š, Kobrová K, Srp R, Němcová D, Hoza J, et al. Methotrexate efficacy, but not its intolerance, is associated with the dose and route of administration. Pediatr Rheumatol. 2016;14:36.
21. Klein A, Kaul I, Foeldvari I, Ganser G, Urban A, Horneff G. Efficacy and safety of oral and parenteral methotrexate therapy in children with juvenile idiopathic arthritis: an observational study with patients from the German methotrexate registry. Arthritis Care Res (Hoboken). 2012;64:1349–56.
22. Silverman E, Mouy R, Spiegel L, Jung LK, Saurenmann RK, Lahdenne P, et al. Leflunomide or methotrexate for juvenile rheumatoid arthritis. N Engl J Med. 2005;352:1655–66.
23. Cespedes-Cruz A, Gutierrez-Suarez R, Pistorio A, Ravelli A, Loy A, Murray KJ, et al. Methotrexate improves the health-related quality of life of children with juvenile idiopathic arthritis. Ann Rheum Dis. 2008;67:309–14.
24. Ravelli A, Viola S, Ramenghi B, Beluffi G, Zonta LA, Martini A. Radiologic progression in patients with juvenile chronic arthritis treated with methotrexate. J Pediatr. 1998;133:262–5.
25. Harel L, Wagner-Weiner L, Poznanski AK, Spencer CH, Ekwo E, Magilavy DB. Effects of methotrexate on radiologic progression in juvenile rheumatoid arthritis. Arthritis Rheum. 1993;36:1370–4.
26. Graham LD, Myones BL, Rivas-Chacon RF, Pachman LM. Morbidity associated with long-term methotrexate therapy in juvenile rheumatoid arthritis. J Pediatr. 1992;120:468–73.
27. Bulatović M, Heijstek MW, Verkaaik M, van Dijkhuizen EH, Armbrust W, Hoppenreijs EP, et al. High prevalence of methotrexate intolerance in juvenile idiopathic arthritis: development and validation of a methotrexate intolerance severity score. Arthritis Rheum. 2011;63:2007–13.
28. Mulligan K, Wedderburn LR, Newman S. The experience of taking methotrexate for juvenile idiopathic arthritis: results of a cross-sectional survey with children and young people. Pediatr Rheumatol Online J. 2015;13:58.
29. Braun J, Rau R. An update on methotrexate. Curr Opin Rheumatol. 2009;21:216–23.
30. Hashkes PJ, Laxer RM. Update on the medical treatment of juvenile idiopathic arthritis. Curr Rheumatol Rep. 2006;8:450–8.
31. Hashkes PJ, Balistreri WF, Bove KE, Ballard ET, Passo MH. The long-term effect of methotrexate therapy on the liver in patients with juvenile rheumatoid arthritis. Arthritis Rheum. 1997;40:2226–34.
32. Kugathasan S, Newman AJ, Dahms BB, Boyle JT. Liver biopsy findings in patients with juvenile rheumatoid arthritis receiving long-term, weekly methotrexate therapy. J Pediatr. 1996;128:149–51.
33. Salliot C, van der Heijde D. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. Ann Rheum Dis. 2009;68:1100–4.
34. Cleary AG, McDowell H, Sills JA. Polyarticular juvenile idiopathic arthritis treated with methotrexate complicated by the development of non-Hodgkin's lymphoma. Arch Dis Child. 2002;86:47–9.
35. Krugmann J, Sailer-Hock M, Muller T, Gruber J, Allerberger F, Offner FA. Epstein-Barr virus-associated Hodgkin's lymphoma and legionella pneumophila infection complicating treatment of juvenile rheumatoid arthritis with methotrexate and cyclosporine a. Hum Pathol. 2000;31:253–5.
36. Munro R, Porter DR, Sturrock RD. Lymphadenopathy in a patient with systemic onset juvenile chronic arthritis. Ann Rheum Dis. 1998;57:513–7.
37. Falcini F, Taccetti G, Ermini M, Trapani S, Calzolari A, Franchi A, et al. Methotrexate-associated appearance and rapid progression of rheumatoid nodules in systemic-onset juvenile rheumatoid arthritis. Arthritis Rheum. 1997;40:175–8.
38. Muzaffer MA, Schneider R, Cameron BJ, Silverman ED, Laxer RM. Accelerated nodulosis during methotrexate therapy for juvenile rheumatoid arthritis. J Pediatr. 1996;128:698–700.
39. Merrill J, Cronstein B, Shen C, Goodman S, Paget S, Mitnick H, et al. Reversal of new but not old rheumatoid nodules by colchicine: evidence from an in vitro model and case reports of 14 patients [abstract]. Arthritis Rheum. 1996;39:1272.
40. Ortiz-Alvarez O, Morishita K, Avery G, Green J, Petty RE, Tucker LB, et al. Guidelines for blood test monitoring of methotrexate toxicity in juvenile idiopathic arthritis. J Rheumatol. 2004;31:2501–6.

41. van Dijkhuizen EH, Pouw JN, Scheuern A, Hugle B, Hardt S, Ganser G, et al. Methotrexate intolerance in oral and subcutaneous administration in patients with juvenile idiopathic arthritis: a cross-sectional, observational study. Clin Exp Rheumatol. 2016;34:148–54.
42. Reiff A, Shaham B, Wood BP, Bernstein BH, Stanley P, Szer IS. High dose methotrexate in the treatment of refractory juvenile rheumatoid arthritis. Clin Exp Rheumatol. 1995;13:113–8.
43. Petty RE, Laxer RM, Lindsley C, Wedderburn LR. Textbook of pediatric rheumatology 7th edition. Philadelphia. USA: Saunders; 2016.
44. Ravelli A, Di Fuccia G, Molinaro M, Ramenghi B, Zonta L, Regazzi MB, et al. Plasma levels after oral methotrexate in children with juvenile rheumatoid arthritis. J Rheumatol. 1993;20:1573–7.
45. Dupuis LL, Koren G, Silverman ED, Laxer RM. Influence of food on the bioavailability of oral methotrexate in children. J Rheumatol. 1995;22:1570–3.
46. Jundt JW, Browne BA, Fiocco GP, Steele AD, Mock D. A comparison of low dose methotrexate bioavailability: oral solution, oral tablet, subcutaneous and intramuscular dosing. J Rheumatol. 1993;20:1845–9.
47. Pinkerton CR, Welshman SG, Glasgow JF, Bridges JM. Can food influence the absorption of methotrexate in children with acute lymphoblastic leukaemia? Lancet. 1980;2:944–6.
48. Alsufyani K, Ortiz-Alvarez O, Cabral DA, Tucker LB, Petty RE, Malleson PN. The role of subcutaneous administration of methotrexate in children with juvenile idiopathic arthritis who have failed oral methotrexate. J Rheumatol. 2004;31:179–82.
49. Tuková J, Chládek J, Němcová D, Chládková J, Doležalová P. Methotrexate bioavailability after oral and subcutaneous dministration in children with juvenile idiopathic arthritis. Clin Exp Rheumatol. 2009;27:1047–53.
50. Gottlieb BS, Keenan GF, Lu T, Ilowite NT. Discontinuation of methotrexate treatment in juvenile rheumatoid arthritis. Pediatrics. 1997;100:994–7.
51. Foell D, Wulffraat N, Wedderburn LR, Wittkowski H, Frosch M, Gerss J, et al. Methotrexate withdrawal at 6 vs 12 months in juvenile idiopathic arthritis in remission: a randomized clinical trial. JAMA. 2010;303:1266–73.
52. Foell D, Frosch M, Schulze zur Wiesch A, Vogl T, Sorg C, Roth J. Methotrexate treatment in juvenile idiopathic arthritis: when is the right time to stop? Ann Rheum Dis. 2004;63:206–8.
53. van Ede AE, Laan RF, Rood MJ, Huizinga TW, van de Laar MA, van Denderen CJ, et al. Effect of folic or folinic acid supplementation on the toxicity and efficacy of methotrexate in rheumatoid arthritis: a forty-eight week, multicenter, randomized, double-blind, placebo-controlled study. Arthritis Rheum. 2001;44:1515–24.
54. Pavy S, Constantin A, Pham T, Gossec L, Maillefert JF, Cantagrel A, et al. Methotrexate therapy for rheumatoid arthritis: clinical practice guidelines based on published evidence and expert opinion. Joint Bone Spine. 2006;73:388–95.
55. Shiroky JB, Neville C, Esdaile JM, Choquette D, Zummer M, Hazeltine M, et al. Low-dose methotrexate with leucovorin (folinic acid) in the management of rheumatoid arthritis. Results of a multicenter randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 1993;36:795–803.
56. Prey S, Paul C. Effect of folic or folinic acid supplementation on methotrexate-associated safety and efficacy in inflammatory disease: a systematic review. Br J Dermatol. 2009;160:622–8.
57. Shea B, Swinden MV, Ghogomu ET, Ortiz Z, Katchamart W, Rader T, et al. Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. J Rheumatol. 2014;41:1049–60.
58. Dervieux T, Furst D, Lein DO, Capps R, Smith K, Walsh M, et al. Polyglutamation of methotrexate with common polymorphisms in reduced folate carrier, aminoimidazole carboxamide ribonucleotide transformylase, and thymidylate synthase are associated with methotrexate effects in rheumatoid arthritis. Arthritis Rheum. 2004;50:2766–74.
59. Hunt PG, Rose CD, McIlvain-Simpson G, Tejani S. The effects of daily intake of folic acid on the efficacy of methotrexate therapy in children with juvenile rheumatoid arthritis. A controlled study. J Rheumatol. 1997;24:2230–2.
60. Ravelli A, Migliavacca D, Viola S, Ruperto N, Pistorio A, Martini A. Efficacy of folinic acid in reducing methotrexate toxicity in juvenile idiopathic arthritis. Clin Exp Rheumatol. 1999;17:625–7.
61. West SG. Methotrexate hepatotoxicity. Rheum Dis Clin N Am. 1997;23:883–915.
62. Modesto C, Castro L. Folinic acid supplementation in patients with juvenile rheumatoid arthritis treated with methotrexate. J Rheumatol. 1996;23:403–4.
63. Simonini G, Paudyal P, Jones GT, Cimaz R, Macfarlane GJ. Current evidence of methotrexate efficacy in childhood chronic uveitis: a systematic review and meta-analysis approach. Rheumatology (Oxford). 2013;52:825–31.
64. Foeldvari I, Wierk A. Methotrexate is an effective treatment for chronic uveitis associated with juvenile idiopathic arthritis. J Rheumatol. 2005;32:362–5.
65. Gion N, Stavrou P, Foster CS. Immunomodulatory therapy for chronic tubulointerstitial nephritis-associated uveitis. Am J Ophthalmol. 2000;129:764–8.
66. Heiligenhaus A, Mingels A, Heinz C, Ganser G. Methotrexate for uveitis associated with juvenile idiopathic arthritis: value and requirement for additional anti-inflammatory medication. Eur J Ophthalmol. 2007;17:743–8.
67. Kalinina Ayuso V, van de Winkel EL, Rothova A, de Boer JH. Relapse rate of uveitis post-methotrexate treatment in juvenile idiopathic arthritis. Am J Ophthalmol. 2011;151:217–22.
68. Kaplan-Messas A, Barkana Y, Avni I, Neumann R. Methotrexate as a first-line corticosteroid-sparing therapy in a cohort of uveitis and scleritis. Ocul Immunol Inflamm. 2003;11:131–9.
69. Malik AR, Pavesio C. The use of low dose methotrexate in children with chronic anterior and intermediate uveitis. Br J Ophthalmol. 2005;89:806–8.
70. Samson CM, Waheed N, Baltatzis S, Foster CS. Methotrexate therapy for chronic noninfectious uveitis: analysis of a case series of 160 patients. Ophthalmology. 2001;108:1134–9.
71. Shetty AK, Zganjar BE, Ellis GS Jr, Ludwig IH, Gedalia A. Low-dose methotrexate in the treatment of severe juvenile rheumatoid arthritis and sarcoid iritis. J Pediatr Ophthalmol Strabismus. 1999;36:125–8.
72. Weiss AH, Wallace CA, Sherry DD. Methotrexate for resistant chronic uveitis in children with juvenile rheumatoid arthritis. J Pediatr. 1998;133:266–8.
73. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature working group. Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop. Am J Ophthalmol. 2005;140:509–16.
74. Simonini G, Cantarini L, Bresci C, Lorusso M, Galeazzi M, Cimaz R. Current therapeutic approaches to autoimmune chronic uveitis in children. Autoimmun Rev. 2010;9:674–83.
75. Charuvanij S, Guzman J, Lyons C, Petty R. Determination of response to treatment of anterior uveitis with juvenile idiopathic arthritis and isolated chronic idiopathic uveitis [abstract]. Arthritis Rheum. 2009;60:258.
76. Heiligenhaus A, Michels H, Schumacher C, Kopp I, Neudorf U, Niehues T, et al. Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis. Rheumatol Int. 2012;32:1121–33.
77. Bou R, Adan A, Borras F, Bravo B, Calvo I, De Inocencio J, et al. Clinical management algorithm of uveitis associated with juvenile idiopathic arthritis: interdisciplinary panel consensus. Rheumatol Int. 2015;35:777–85.
78. Papadopoulou C, Kostik M, Böhm M, Nieto-Gonzalez JC, Gonzalez-Fernandez MI, Pistorio A, et al. Methotrexate therapy may prevent the onset of uveitis in juvenile idiopathic arthritis. J Pediatr. 2013;163:879–84.
79. Tappeiner C, Schenck S, Niewerth M, Heiligenhaus A, Minden K, Klotsche J. Impact of antiinflammatory treatment on the onset of uveitis in juvenile idiopathic arthritis: longitudinal analysis from a nationwide pediatric rheumatology database. Arthritis Care Res (Hoboken). 2016;68:46–54.
80. Albers HM, Wessels JA, van der Straaten RJ, Brinkman DM, Suijlekom-Smit LW, Kamphuis SS, et al. Time to treatment as an important factor for the response to methotrexate in juvenile idiopathic arthritis. Arthritis Rheum. 2009;61:46–51.
81. Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med. 1999;340:253–9.
82. Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet. 2004;363:675–81.
83. Schmeling H, Mathony K, John V, Keysser G, Burdach S, Horneff G. A combination of etanercept and methotrexate for the treatment of refractory juvenile idiopathic arthritis: a pilot study. Ann Rheum Dis. 2001;60:410–2.
84. Giannini EH, Ilowite NT, Lovell DJ, Wallace CA, Rabinovich CE, Reiff A, et al. Long-term safety and effectiveness of etanercept in children with selected categories of juvenile idiopathic arthritis. Arthritis Rheum. 2009;60:2794–804.
85. Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med. 2008;359:810–20.

86. Murias S, Alcobendas R, Pascual-Salcedo D, Remesal A, Peralta J, Merino R. Anti-adalimumab antibodies in paediatric rheumatology patients: a pilot experience. Rheumatology (Oxford). 2014;53:2124–6.
87. Krieckaert CL, Nurmohamed MT, Wolbink GJ. Methotrexate reduces immunogenicity in adalimumab treated rheumatoid arthritis patients in a dose dependent manner. Ann Rheum Dis. 2012;71:1914–5.
88. Russo RA, Katsicas MM, Zelazko M. Etanercept in systemic juvenile idiopathic arthritis. Clin Exp Rheumatol. 2002;20:723–6.
89. Quartier P, Taupin P, Bourdeaut F, Lemelle I, Pillet P, Bost M, et al. Efficacy of etanercept for the treatment of juvenile idiopathic arthritis according to the onset type. Arthritis Rheum. 2003;48:1093–101.
90. Lahdenne P, Vahasalo P, Honkanen V. Infliximab or etanercept in the treatment of children with refractory juvenile idiopathic arthritis: an open label study. Ann Rheum Dis. 2003;62:245–7.
91. Schmeling H, Horneff G, Benseler SM, Fritzler MJ. Pharmacogenetics: can genes determine treatment efficacy and safety in JIA? Nat Rev Rheumatol. 2014;10:682–90.
92. Pastore S, Stocco G, Favretto D, De Iudicibus S, Taddio A, d'Adamo P, et al. Genetic determinants for methotrexate response in juvenile idiopathic arthritis. Front Pharmacol. 2015;6:52.
93. Calasan MB, den Boer E, de Rotte MC, Vastert SJ, Kamphuis S, de Jonge R, et al. Methotrexate polyglutamates in erythrocytes are associated with lower disease activity in juvenile idiopathic arthritis patients. Ann Rheum Dis. 2015;74:402–7.
94. Chabner BA, Allegra CJ, Curt GA, Clendeninn NJ, Baram J, Koizumi S, et al. Polyglutamation of methotrexate. Is methotrexate a prodrug? J Clin Invest. 1985;76:907–12.
95. Vilca I, Munitis PG, Pistorio A, Ravelli A, Buoncompagni A, Bica B, et al. Predictors of poor response to methotrexate in polyarticular-course juvenile idiopathic arthritis: analysis of the PRINTO methotrexate trial. Ann Rheum Dis. 2010;69:1479–83.
96. Cobb J, Cule E, Moncrieffe H, Hinks A, Ursu S, Patrick F, et al. Genome-wide data reveal novel genes for methotrexate response in a large cohort of juvenile idiopathic arthritis cases. Pharmacogenomics J. 2014;14:356–64.
97. Hinks A, Moncrieffe H, Martin P, Ursu S, Lal S, Kassoumeri L, et al. Association of the 5-aminoimidazole-4-carboxamide ribonucleotide transformylase gene with response to methotrexate in juvenile idiopathic arthritis. Ann Rheum Dis. 2011;70:1395–400.
98. de Rotte MC, Bulatović M, Heijstek MW, Jansen G, Heil SG, van Schaik RH, et al. ABCB1 and ABCC3 gene polymorphisms are associated with first-year response to methotrexate in juvenile idiopathic arthritis. J Rheumatol. 2012;39:2032–40.
99. Avramovič MZ, Dolžan V, Toplak N, Accetto M, Lusa L, Avčin T. Relationship between polymorphisms in methotrexate pathway genes and outcome of methotrexate treatment in a cohort of 119 patients with juvenile idiopathic arthritis. J Rheumatol. 2017;44:1216–23.
100. Pastore S, Stocco G, Moressa V, Zandona L, Favretto D, Malusa N, et al. 5-Aminoimidazole-4-carboxamide ribonucleotide-transformylase and inosine-triphosphate-pyrophosphatase genes variants predict remission rate during methotrexate therapy in patients with juvenile idiopathic arthritis. Rheumatol Int. 2015;35:619–27.
101. Heijstek MW, Ott de Bruin LM, Bijl M, Borrow R, van der Klis F, Kone-Paut I, et al. EULAR recommendations for vaccination in paediatric patients with rheumatic diseases. Ann Rheum Dis. 2011;70:1704–12.
102. Heijstek MW, Ott de Bruin LM, Borrow R, van der Klis F, Kone-Paut I, Fasth A, et al. Vaccination in paediatric patients with auto-immune rheumatic diseases: a systemic literature review for the European league against rheumatism evidence-based recommendations. Autoimmun Rev. 2011;11:112–22.
103. Groot N, Heijstek MW, Wulffraat NM. Vaccinations in paediatric rheumatology: an update on current developments. Curr Rheumatol Rep. 2015;17:46.
104. Heijstek MW, van Gageldonk PG, Berbers GA, Wulffraat NM. Differences in persistence of measles, mumps, rubella, diphtheria and tetanus antibodies between children with rheumatic disease and healthy controls: a retrospective cross-sectional study. Ann Rheum Dis. 2012;71:948–54.
105. Kasapcopur O, Cullu F, Kamburoglu-Goksel A, Cam H, Akdenizli E, Calykan S, et al. Hepatitis B vaccination in children with juvenile idiopathic arthritis. Ann Rheum Dis. 2004;63:1128–30.
106. Kiray E, Kasapcopur O, Bas V, Kamburoglu-Goksel A, Midilli K, Arisoy N, et al. Purified protein derivative response in juvenile idiopathic arthritis. J Rheumatol. 2009;36:2029–32.
107. Stoof SP, Heijstek MW, Sijssens KM, van der Klis F, Sanders EA, Teunis PF, et al. Kinetics of the long-term antibody response after meningococcal C vaccination in patients with juvenile idiopathic arthritis: a retrospective cohort study. Ann Rheum Dis. 2014;73:728–34.
108. Heijstek MW, Pileggi GC, Zonneveld-Huijssoon E, Armbrust W, Hoppenreijs EP, Uiterwaal CS, et al. Safety of measles, mumps and rubella vaccination in juvenile idiopathic arthritis. Ann Rheum Dis. 2007;66:1384–7.
109. Woerner A, Sauvain MJ, Aebi C, Otth M, Bolt IB. Immune response to influenza vaccination in children treated with methotrexate or/and tumor necrosis factor-alpha inhibitors. Hum Vaccin. 2011;7:1293–8.
110. Borte S, Liebert UG, Borte M, Sack U. Efficacy of measles, mumps and rubella revaccination in children with juvenile idiopathic arthritis treated with methotrexate and etanercept. Rheumatology (Oxford). 2009;48:144–8.
111. Aikawa NE, Campos LM, Goldenstein-Schainberg C, Saad CG, Ribeiro AC, Bueno C, et al. Effective seroconversion and safety following the pandemic influenza vaccination (anti-H1N1) in patients with juvenile idiopathic arthritis. Scand J Rheumatol. 2013;42:34–40.
112. Pileggi GS, de Souza CB, Ferriani VP. Safety and immunogenicity of varicella vaccine in patients with juvenile rheumatic diseases receiving methotrexate and corticosteroids. Arthritis Care Res (Hoboken). 2010;62:1034–9.
113. Heijstek MW, Kamphuis S, Armbrust W, Swart J, Gorter S, de Vries LD, et al. Effects of the live attenuated measles-mumps-rubella booster vaccination on disease activity in patients with juvenile idiopathic arthritis: a randomized trial. JAMA. 2013;309:2449–56.
114. Farmaki E, Kanakoudi-Tsakalidou F, Spoulou V, Trachana M, Pratsidou-Gertsi P, Tritsoni M, et al. The effect of anti-TNF treatment on the immunogenicity and safety of the 7-valent conjugate pneumococcal vaccine in children with juvenile idiopathic arthritis. Vaccine. 2010;28:5109–13.
115. Zonneveld-Huijssoon E, Ronaghy A, Van Rossum MA, Rijkers GT, van der Klis FR, Sanders EA, et al. Safety and efficacy of meningococcal c vaccination in juvenile idiopathic arthritis. Arthritis Rheum. 2007;56:639–46.
116. Aikawa NE, Franca IL, Ribeiro AC, Sallum AM, Bonfa E, Silva CA. Short and long-term immunogenicity and safety following the 23-valent polysaccharide pneumococcal vaccine in juvenile idiopathic arthritis patients under conventional DMARDs with or without anti-TNF therapy. Vaccine. 2015;33:604–9.
117. Heijstek MW, Scherpenisse M, Groot N, Tacke C, Schepp RM, Buisman AM, et al. Immunogenicity and safety of the bivalent HPV vaccine in female patients with juvenile idiopathic arthritis: a prospective controlled observational cohort study. Ann Rheum Dis. 2014;73:1500–7.
118. Michalik DE, Steinberg SP, Larussa PS, Edwards KM, Wright PF, Arvin AM, et al. Primary vaccine failure after 1 dose of varicella vaccine in healthy children. J Infect Dis. 2008;197:944–9.
119. Marin M, Guris D, Chaves SS, Schmid S, Seward JF. Advisory committee on immunization practices of the Centers for Disease Control and Prevention (CDC). Prevention of varicella: recommendations of the advisory committee on immunization practices (ACIP). MMWR Recomm Rep. 2007;56:1–40.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

BMC

Check for updates

Arthritis Care & Research
Vol. 75, No. 5, May 2023, pp 975–982
DOI 10.1002/acr.24963
© 2022 American College of Rheumatology.

American College of Rheumatology
Empowering Rheumatology Professionals

New and Updated Recommendations for the Treatment of Juvenile Idiopathic Arthritis–Associated Uveitis and Idiopathic Chronic Anterior Uveitis

Ivan Foeldvari,[1] Ilaria Maccora,[2] Harry Petrushkin,[3] Najiha Rahman,[4] Jordi Anton,[5] Joke de Boer,[6] Joan Calzada-Hernández,[5] Elisa Carreras,[7] Jesus Diaz,[5] Clive Edelsten,[8] Sheila T. Angeles-Han,[9] Arnd Heiligenhaus,[10] Elisabetta Miserocchi,[11] Susan Nielsen,[12] Rotraud K. Saurenmann,[13] Nicole Stuebiger,[14] Karoline Baquet-Walscheid,[10] Daniel Furst,[15] and Gabriele Simonini[2]

Objective. The Multinational Interdisciplinary Working Group for Uveitis in Childhood identified the need to update the current guidelines, and the objective here was to produce this document to guide clinicians managing children with juvenile idiopathic arthritis–associated uveitis (JIAU) and idiopathic chronic anterior uveitis (CAU).

Methods. The group analyzed the literature published between December 2014 and June 2020 after a systematic literature review conducted by 2 clinicians. Pediatric rheumatologists were paired with ophthalmologists to review the eligible 37 publications. The search criteria were selected to reflect those used for the 2018 Single Hub and Access point for pediatric Rheumatology in Europe (SHARE) recommendations, in order to provide an update, rather than a replacement for that publication. The summary of the current evidence for each SHARE recommendation was presented to the expert committee. These recommendations were then discussed and revised during a video consensus meeting on January 22, 2021, with 14 voting participants, using a nominal group technique to reach consensus.

Results. JIAU treatment was extended to include CAU. Fourteen recommendations regarding treatment of JIAU und CAU with >90% agreement were accepted.

Conclusion. An update to the previous 2018 SHARE recommendations for the treatment of children with JIAU with the addition of CAU was created using an evidence-based consensus process. This guideline should help support clinicians to care for children and young people with CAU.

INTRODUCTION

Pediatric chronic anterior uveitis (CAU) is a cause of significant visual morbidity (1,2). It is the most common extraarticular manifestation of juvenile idiopathic arthritis (JIA) but can occur in isolation. The Single Hub and Access point for pediatric Rheumatology in Europe (SHARE) recommendations for the management of JIA-associated uveitis (JIAU) (2) were published in 2018, but the literature they were based on was only reviewed up to December 2014. Subsequently, adalimumab was approved to treat CAU in children, and a number of other biologics and small molecule agents have become available to clinicians. While physicians now accept that idiopathic CAU and JIAU should be managed in the same way, there are no guidelines focused on CAU. The Multinational Interdisciplinary Working Group for Uveitis in Childhood (MIWGUC) (3) identified the need to update the current

[1]Ivan Foeldvari, MD: Schön Klinik Hamburg Eilbek, Hamburg, Germany; [2]Ilaria Maccora, MD, Gabriele Simonini, MD: Meyer Children's Hospital, University of Florence, Florence, Italy; [3]Harry Petrushkin, MD: Moorfields Eye Hospital and Great Ormond Street Hospital, NHS Foundation Trust, London, UK; [4]Najiha Rahman, MD: Moorfields Eye Hospital, NHS Foundation Trust, London, UK; [5]Jordi Anton, MD, Joan Calzada-Hernández, MD, Jesus Diaz, MD: Hospital Sant Joan de Déu, Universitat de Barcelona, Barcelona, Spain; [6]Joke de Boer, MD: University Medical Center Utrecht, Utrecht, The Netherlands; [7]Elisa Carreras, MD: Barraquer Eye Hospital, Dubai, United Arab Emirates; [8]Clive Edelsten, MD: Great Ormond Street Hospital, NHS Foundation Trust, London, UK; [9]Sheila T. Angeles-Han, MD: Cincinnati Children's Hospital Medical Center and University of Cincinnati, Cincinnati, Ohio; [10]Arnd Heiligenhaus, MD, Karoline Baquet-Walscheid, MD: St. Franziskus Hospital, Muenster, and University of Duisburg-Essen, Essen, Germany; [11]Elisabetta Miserocchi, MD: San Raffaele Scientific Institute, Milan, Italy; [12]Susan Nielsen, MD: Rigshospitalet, Copenhagen, Denmark; [13]Rotraud K. Saurenmann, MD: Kantonsspital Winterthur, Winterthur, Switzerland; [14]Nicole Stuebiger, MD: Universitätsklinikum Hamburg-Eppendorf, Augenklinik, Hamburg, Germany; [15]Daniel Furst, MD: University of California, Los Angeles, University of Washington, Seattle, and University of Florence, Florence, Italy.

Author disclosures are available at https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Facr.24963&file=acr24963-sup-0001-Disclosureform.pdf.

Address correspondence via email to Ivan Foeldvari, MD, at foeldvari@t-online.de and Harry Petrushkin, MD, at harrypetrushkin@gmail.com.

Submitted for publication December 21, 2021; accepted in revised form May 24, 2022.

70

SIGNIFICANCE & INNOVATIONS

- This updated guideline includes new medications.
- The switching between drugs is discussed in case of nonresponse or partial response.

guidelines and worked to produce this document, which should serve to guide clinicians managing children with JIAU and idiopathic CAU.

MATERIALS AND METHODS

The MIWGUC consists of an international expert panel which has already published outcome measures in pediatric uveitis. The MIWGUC working group for this project consisted of 8 pediatric rheumatologists and 8 ophthalmologists with expertise in pediatric uveitis. The group analyzed the literature published between December 2014 and June 2020 after a systematic literature review conducted by 2 clinicians. A pediatric rheumatologist was paired with a pediatric ophthalmologist to review the eligible 37 publications associated with an assigned topic. This article summarizes data from studies done by others involving human participants, and therefore for this report no formal review and approval by an appropriate institutional review board or ethics committee was required.

Systematic literature search. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement was used to conduct a literature search (4), and a systematic review was performed to identify the existing evidence in the PubMED/MEDLINE, EMBASE, and Cochrane libraries from December 2014 to June 2020 by 2 independent researchers (IM and NR). The search criteria were selected to reflect those used for the 2018 SHARE recommendations, to serve as an update rather than a replacement for that publication.

The following key words were used: "arthritis, juvenile rheumatoid" [MeSH] or (JIA or JRA) or (juvenile* or child* or paediatric*) and (rheumatoid or rheumatic or idiopathic or chronic or systemic) and (arthritis or arthritides or polyarthritis or oligoarthritis) or ("still's disease" or "still disease" or "stills disease") and (juvenile* or child* or paediatric* or paediatric*) and (uveitis [MeSH] or iridocyclitis or uveitides or iritis or vitritis or panuveitis or pan-uveitis or cyclitis) OR ("uveitis" or "uveitis*" or "panuveitis" or "iridocyclitis" or "iritis" or "vitreitis" or "chronic uveitis" or "chronic iridocyclitis" or "recurrent uveitis" or "refractory uveitis" or "non-infectious uveitis" or "autoimmune uveitis" or "inflamma$ ocul$" or "inflamma$ eye") and (methotrexate or methotrexate or mtx or mycofenolate or mmf or TNF OR "TNFi" OR "TNF-inhibitor" OR "antiTNFα" or TNFα OR adalimumab or infliximab or etanercept or golimumab or certolizumab or tocilizumab or "anti-il6" or "il6" or "antiil6" or abatacept or "ctla4" or "janus kinase inhibitor*" or "baricitinib" or "tofacitinib" or "il1" or "il-1" or "anti-il1" or "canakinumab" or "cd20' or "anti-cd20" or 'anticd20" or "rituximab" or "il17" or "il23" or "tcz" or "abt" OR "RTX" OR "JAK" OR "JAK-inhibitor") NOT (behcet OR behçet OR sarcoidosis OR blau). Only publications in English were reviewed.

Two independent reviewers (IM and NR) identified relevant articles based on the title and abstract (Figure 1). When there was a disagreement whether to include an article, it was resolved through discussion with a third reviewer (IF or GS). Publications selected for analysis were required to: 1) include patients with a diagnosis of JIAU (according to International League of Associations for Rheumatology classification) or idiopathic CAU, 2) describe patients managed with systemic treatment (biologic and nonbiologic disease-modifying antirheumatic drugs [DMARDs]), 3) be original articles, 4) include at least 2 patients, and 5) have at least 6 months of follow-up data.

Exclusion criteria included: 1) patients with other systemic causes associated with uveitis (i.e., Blau syndrome, Behçet's syndrome, or autoinflammatory diseases), 2) patients with intermediate or posterior uveitis, 3) single case reports, reviews, meeting, and conference abstracts, 4) exclusively adult patients, and 5) articles in press.

The 2 experts independently assessed the methodologic quality of articles meeting the inclusion criteria. Each reviewer extracted data using a predefined scoring form for each study that included information about demographic data, primary and secondary outcomes of the study, methodology, medications, MIWGUC definitions (where available) applied regarding remission, inactivity, the presence of structural complications, discontinuation of topical glucocorticoids, and the validity of the study (3).

Establishment of recommendations. As part of the EULAR standard operating procedure (2), one of the reviewers (IM) supervised by GS described the main results and conclusions of each article, along with their validity and level of evidence. These descriptions were collated by 2 experts (IF and GS) and used to formulate provisional recommendations that were reviewed by a panel of 3 experts.

The consensus meeting. The consensus meeting was moderated by DF, one of the authors. The summary of the current evidence for each SHARE recommendation was presented to the expert committee. These recommendations were then discussed and revised during the online video consensus meeting on January 22, 2021, with 14 voting participants, using a nominal group technique to reach consensus (2). Two nonvoting observers (IM and DF) presented the current results of the literature search for each SHARE recommendation. The results of the current findings and the need to change or keep previous recommendations were discussed. At the end of the discussion, either a new recommendation

21514658, 2023, 5, Downloaded from https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.24963 by Amanda LaVoy - Wiley Online Library on [22/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

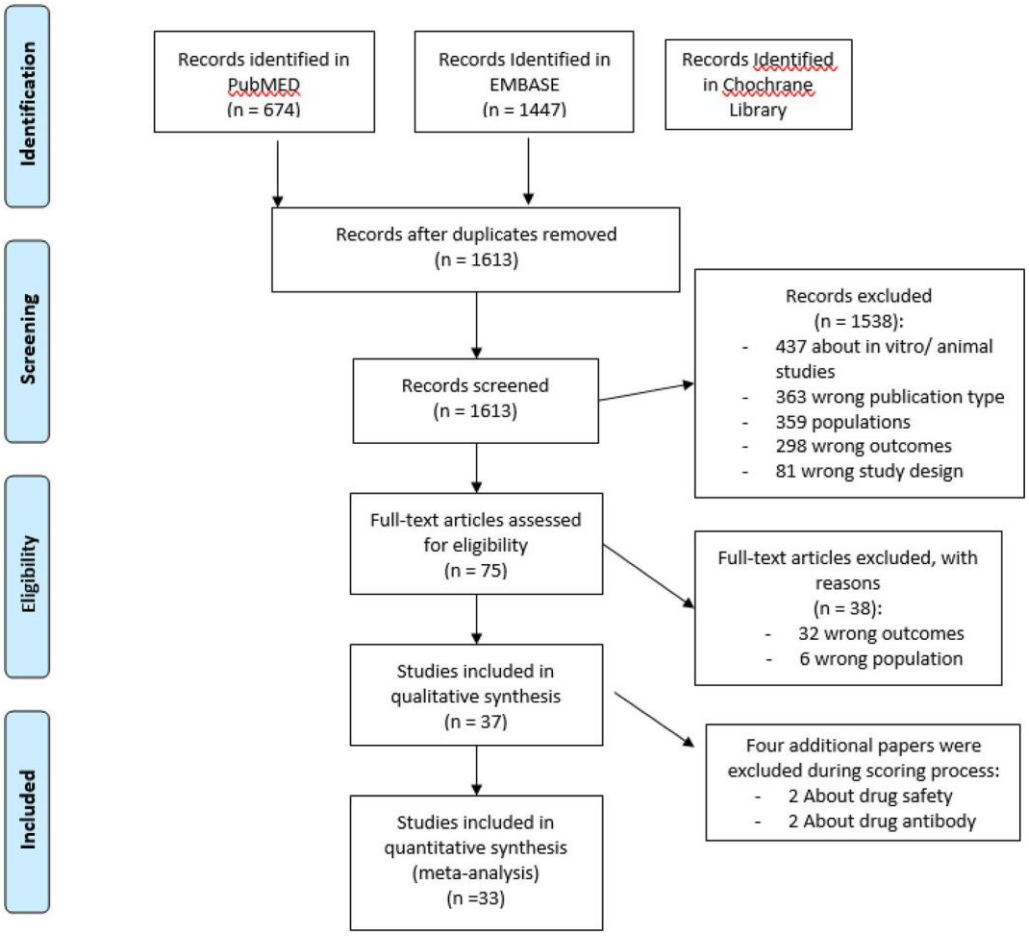


Figure 1. Flow sheet systematic literature review.

was formulated, or the original SHARE recommendation remained unchanged. Proposed recommendations were accepted when ≥90% (11 of 14) of the experts agreed. The grade of evidence of the recommendations was based on the level of evidence of the different studies included and their scores voted by the MIWGUC (2).

RESULTS

The literature search retrieved 2,121 initial citations, 508 of which were duplicates and were removed. Following title and abstract screening, 37 articles met the inclusion criteria (Figure 1) to be scored and used as material for the final recommendations The 2018 SHARE recommendations (1) were designed to provide guidance on treatment of patients with JIAU. The participants recognized that most patients who present with a painless CAU not associated with JIA (regardless of antinuclear antibody [ANA] status) have an analogous disease and should be treated in the same way as JIAU (3,5). This concept is in line with European Medical Agency recognition of this similarity, which led to the licensing of adalimumab for the treatment of both JIAU and CAU.

The recent Childhood Arthritis and Rheumatology Research Alliance guideline for JIAU (1) also does not differentiate regarding recommendations between JIAU and CAU. Furthermore, data from a population-based nationwide study in Germany recently demonstrated that ANA-positive CAU and JIAU did not significantly differ in clinical course (5). A national consensus statement from the UK echoed the idea that patients with CAU and JIAU should be managed in a similar fashion (6).

Notably, a small proportion of patients have CAU due to several other causes (viral, Fuch's heterochromic cyclitis, and post infectious, etc.) that fall outside this guidance. These exceptions are the case regardless of ANA status. The clinician ultimately has discretion whether or not a patient fits into the JIAU/CAU treatment model.

Recommendations for starting therapy. Active uveitis in JIAU and in CAU usually requires immediate treatment. No discussion occurred regarding when to start therapy in the 2014 SHARE recommendation. The word "usually" has been kept, as a clinician may sometimes choose to observe mild uveitis, or new uveitis following a period of quiescence if there has been a

21514658, 2023, 5, Downloaded from https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.24963 by Amanda LaVoy , Wiley Online Library on [22/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

precipitating event such as a bacterial or viral illness (7,8). The outcome of voting was level of evidence 2B, strength of evidence B (13 of 14 voting YES with 1 missing vote).

Recommendations regarding topical therapy. Topical glucocorticoids (usually prednisolone acetate 1% or dexamethasone 0.1%) are the first-line treatment for JIAU and CAU. Consensus was reached on this recommendation. The outcome of voting was level of evidence 4D, strength of evidence D (13 of 14 voting YES with 1 missing vote).

Topical and systemic nonsteroidal antiinflammatory drugs (NSAIDs) have no demonstrable effect as monotherapy. Since the 2014 SHARE guideline, no articles have been published examining the effect of oral or topical NSAIDs in JIAU or CAU. However, the usefulness of topical and systemic NSAIDs has been described in other forms of uveitis (8). Therefore, the previous recommendation "Topical and systemic NSAIDs have no demonstrable effect as monotherapy but may be used as additional therapy" was removed. The panel agreed that topical or systemic NSAIDs could be used as additional therapy. While no published evidence exists for systemic NSAIDs use for CAU, some experts still use them. "NSAIDs have no demonstrable effect as monotherapy" was the agreed statement the panel voted on. The outcome of voting was level of evidence 3C, strength of evidence D (13 of 14 voting YES with 1 missing vote).

Recommendations regarding systemic treatments. Systemic immunosuppression is recommended for active JIAU and CAU if there are poor prognostic factors and/or if persistent disease is present, regardless of laterality. Systemic immunosuppression is recommended in active JIAU and CAU in the presence of poor prognostic factors (1,5–8). These factors include ocular complications, male sex, and uveitis preceding arthritis (7). Furthermore, persistent uveitis predisposes to poorer outcomes, including a higher risk of ocular complications and blindness. Persistent disease was defined as active uveitis lasting >3 months per the Standardization of Uveitis Nomenclature criteria (9). Structural complications are associated with anterior chamber cell and flare grade (3). These include posterior synechia, band keratopathy, glaucoma, cataract, hypotony, macular edema, and dense vitreous body opacification, and lead to ocular damage (1,3,5,7,8). These factors have all been considered as complications defining damage by the MIWGUC proposal (3). The age at the onset of uveitis and ANA positivity are associated with uveitis occurrence in JIA patients, but they are not related to poor prognosis (3,7,8). Heiligenhaus et al have described in the ICON-JIA study an association between older ages at JIA diagnosis and the rate of ocular complications during follow-up, which can be explained by a longer period of uveitis, with insidious onset of flare before JIA diagnosis (8). The group agreed that systemic immunosuppression should not be delayed due to unilateral involvement.

Updates to 2018 SHARE recommendations were: 1) to extend the recommendation of systemic DMARDs to any time of the disease in the setting of active uveitis and poor prognostic factors or persistent disease, not restricting the recommendation to the first visit, 2) to include mention of the fact that unilaterality should not be a limitation for systemic immunosuppression, and 3) to define persistent disease. The outcome of voting was level of evidence 2A, strength of evidence B (13 of 14 voting YES with 1 missing vote).

Acceptable frequency of topical glucocorticoids for maintenance therapy. Systemic immunosuppression is recommended if clinical inactivity could not be achieved with 3 drops or less of topical dexamethasone 0.1% or prednisolone acetate 1%. Topical glucocorticoids (preferably prednisolone 1% or dexamethasone 0.1%) are the first-line treatments for JIAU and CAU. However, the use of high doses of topical glucocorticoids leads to cataract formation and increases the risk of glaucoma.

The maximum acceptable dose of topical glucocorticoids is still controversial. Thorne et al found that children receiving low doses of topical glucocorticoids (3 or fewer drops daily) over moderate periods had a low risk of developing cataracts (10). Kothari et al described an increased risk of ocular hypertension in children receiving 2 or more drops of glucocorticoids daily, and that the risk increases with higher doses (11,12).

Although the level of evidence is low, the authors agreed to recommend the addition of systemic immunosuppression if clinical inactivity (3) according the MIWGUC definition cannot be achieved with 3 drops or less of topical glucocorticoids over a period of 3 months, at the maximum (Table 1). MIWGUC members were clear that 3 drops per day was an absolute maximum, and many members felt that patients should be managed on <2 drops of glucocorticoid per day.

Updates to 2018 SHARE recommendations were: 1) to introduce the "3-months criteria" before starting systemic immunosuppression, unless poor prognostic factors are present, and 2) to introduce "inactivity" as defined by MIWGUC. The outcome of voting was level of evidence 2A, strength of evidence B (13 of 14 voting YES with 1 missing vote).

Table 1. Inactive uveitis is defined by both eyes fulfilling the following conditions at a specific assessment*

Slit lamp total number of AC cells: 0 inflammatory cells†
Absence of optic disc edema
Absence of macular edema
Absence of vitreous haze (<0.5+)
Ophthalmologist global assessment of uveitis activity on VAS score (range 0–100 mm) must be 0

* AC = anterior chamber; VAS = visual analog scale.
† In aphakia patients some cells may be present in the anterior vitreous.

21514658, 2023, 5, Downloaded from https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.24963 by Amanda LaVoy , Wiley Online Library on [22/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Use of systemic glucocorticoids. Systemic glucocorticoids should be considered a bridging therapy to synthetic DMARDs, not a medium- to long-term treatment strategy. There was consensus (1 vote missing) that short-term systemic glucocorticoids should be considered only as bridging therapy while waiting for DMARDs to take effect. Glucocorticoids may also be used for a variety of other reasons in JIAU and CAU. These include rescue treatment in the context of hypotony or macular edema due to active inflammation and perioperative cover for cataract and glaucoma surgery. Systemic glucocorticoid monotherapy lasting longer than 3 months is not recommended. The outcome of voting was level of evidence 2B, strength of evidence B (13 of 14 voting YES with 1 missing vote).

Role of methotrexate (MTX). MTX is usually the first synthetic DMARD used for the management of JIAU and CAU. Although the level of evidence is only moderate, the panel agreed that there was sufficient experience with MTX to recommend it as a first-line agent (13–15). MTX is generally well tolerated and considered safe for long-term use. In case of MTX intolerance, a change in the mode of administration, adjustment of the dose, increase in folic acid dose, or premedication with antinausea medication may reduce the gastrointestinal symptoms. Additionally, cataract and glaucoma may be prevented by glucocorticoid sparing from early treatment with MTX, and controlling inflammation. The outcome of voting was level of evidence 3C, strength of evidence C (13 of 14 voting YES with 1 missing vote).

Role of mycophenolate mofetil (MMF). MMF or mycophenolic acid is an option for the treatment of JIAU and CAU. While MMF is not recommended as treatment for arthritis associated with JIA, it can be used to manage JIAU and CAU if arthritis is not a feature of the disease. In general, MMF is well tolerated by children, and gastrointestinal side effects are rare (13,16). The outcome of voting was level of evidence 4D, strength of evidence D (13 of 14 voting YES with 1 missing vote).

Switching treatment to adalimumab. In case of inefficacy or intolerance to MTX and/or other conventional synthetic DMARDs, adding or switching to adalimumab is recommended. There was unanimous agreement that adalimumab should be recommended when there is inefficacy or intolerance to MTX. Since 2013, 2 randomized controlled trials and other articles have reported on the efficacy of adalimumab in patients with JIAU and CAU (12,13,17–29) These trials provided high-quality evidence supporting the use of adalimumab for JIAU and CAU. A meta-analysis by Maccora et al found that adalimumab was superior to both etanercept (x^2 = 26.8, $P < 0.0001$) and infliximab (x^2 = 13.4, $P < 0.0002$) in the management of JIAU and CAU (22). The group agreed that sufficient evidence exists to recommend adalimumab as a first-line over other tumor necrosis factor inhibitors (TNFi). The outcome of voting was level of evidence 1B, strength of evidence A (14 of 14 voting YES).

Adalimumab failures. In case of lack or loss of efficacy, increasing the dose and/or switching from every other week up to weekly dosing may be considered, before switching to another agent. There was 100% agreement (14 of 14) with the statement from the earlier SHARE recommendations. However, members agreed that a very low quality of evidence existed and that increasing the frequency of dosing was not always possible in their country of practice (12,21,27,30). Loss of efficacy may suggest the formation of antidrug antibodies, and the panel recommended testing for antidrug antibodies to determine this possibility before dose increase (31).

For children treated with adalimumab at a standard dose who have an inadequate response to therapy, the group suggested escalating the dose and/or frequency to above-standard dosing used for uveitis prior to switching to another monoclonal antibody TNFi. Although consensus was not reached regarding a specific dose or frequency, multiple reports have indicated success using weekly adalimumab (12,21,27). The outcome of voting was level of evidence 4D, strength of evidence D (14 of 14 voting YES).

The next step after adalimumab failure. In the case of adalimumab failure, using another TNFi (excluding etanercept) or tocilizumab is reasonable. At present, sufficient evidence does not exist to recommend 1 agent based on clinical efficacy. The group did not feel that there was sufficient evidence to recommend the use of tocilizumab over infliximab, golimumab, or certolizumab (20,23,28,32–43). The APTITUDE trial did not meet its primary endpoint, and tocilizumab is not always used in the event of adalimumab failure (39). APTITUDE reported a 40% response rate at the interim time point and a 33% response rate by the end of the trial. Of note, 1 patient who exited the trial early was classified as a responder, bringing the response rate to 38% (the trial needed to attain a response rate of 36.4% to meet its primary endpoint). Given these data, we did not feel that APTITUTE could really be cited as evidence that tocilizumab was "ineffective." The outcome of voting was level of evidence 3B, strength of evidence B (14 of 14 voting YES).

Use of etanercept in the treatment of anterior uveitis. Based on the current evidence, etanercept should not be considered for uveitis. The group agreed that etanercept, while very useful for arthritis, should not be used to manage uveitis based on current literature (22). The outcome of voting was level of evidence 1B, strength of evidence A (14 of 14 voting YES).

TNFi with the highest efficacy for the management of uveitis. Among TNFi currently available, the strongest evidence for efficacy is for adalimumab (1B) followed by infliximab

21514658, 2023, 5, Downloaded from https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.24963 by Amanda LaVoy - Wiley Online Library on [22/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

(2A), golimumab, and certolizumab. Consensus was reached that sufficient evidence exists to recommend infliximab over golimumab or certolizumab (22) after adalimumab. The group agreed that very few occasions occur where infliximab would be used as a first-line biologic. The outcome of voting was level of evidence 1B, strength of evidence B (14 of 14 voting YES).

Medications to use following an insufficient response to TNFi (except etanercept) and tocilizumab. Abatacept, JAK inhibitors, and/or rituximab may be considered in patients refractory to TNFi and tocilizumab. There was 100% agreement (14 of 14) with the statement. However, members agreed that no specific data were available to recommend abatacept over JAK inhibition or rituximab at present.

Abatacept. Panel members agreed that experience was limited with abatacept for patients who have failed MTX and TNFi agents. Three articles outlined retrospective experience with abatacept in this group (44–46). Tappeiner et al described 21 such patients, of whom 52% (11 of 21) achieved initial quiescence while on abatacept (44). Three further patients were described by Marrani et al (45), all of whom achieved inactivity. Birolo et al (46) compared patients who were TNFi-naive against TNFi failures, and 54.8% (17 of 31) patients went into remission at 12 months, although no significant difference was found between the 2 groups in terms of response.

JAK inhibition. At the time of writing, a multicenter randomized controlled trial was underway comparing baricitinib to placebo for the management of ANA-positive CAU (JAHW trial, ClinicalTrials.gov identifier: NCT04088409) (47). Miserocchi et al described 3 patients treated with baricitinib and 1 with tofacitinib who responded favorably. Bauermann et al reported a patient also treated with tofacitinib whose anterior uveitis and macular edema resolved (48,49).

Rituximab. Minimal data exist concerning the use of rituximab for anterior uveitis. Miserocchi et al described 8 patients who had failed first- and second-line agents (50). All patients showed an improvement in uveitis activity after rituximab, although 2 required extra treatment for joint involvement. The outcome of voting was level of evidence 4, strength of evidence C (14 of 14 voting YES).

Discarded statements. In the 2018 SHARE guidance, the following statements were made, which the panel in this update voted unanimously to remove or replace:

"Tocilizumab, rituximab, and abatacept might be potential options for cases refractory to previous TNFi therapy." No mention was made at the time of JAK inhibitors for the management of CAU nor was there a discussion on the efficacy of tocilizumab. Cases are now published of patients with JIAU treated with the following therapies: abatacept (44–46), tofacitinib and baricitinib (48,49), and rituximab (50). The above statement has been replaced with statement 14.

Table 2. List of recommendations with level of evidence based on literature review and expert opinion*

Recommendation	Level of evidence	Voting
Active uveitis in JIAU and in CAU usually requires immediate treatment†	2B	13/14
Topical glucocorticoids (usually prednisolone acetate 1% or dexamethasone 0.1%) are the first-line treatment for JIAU und CAU‡	4D	13/14
Topical and systemic NSAIDs have no demonstrable effect as monotherapy†	3C	13/14
Systemic immunosuppression in active uveitis is recommended if poor prognostic factors and persistent disease are present, regardless of laterality†	2A	13/14
Systemic immunosuppression is recommended if clinical inactivity could not be achieved with 2 drops or less of topical dexamethasone or prednisolone 1%§	2A	13/14
If considering systemic glucocorticoids for JIAU and in CAU, they should be considered as a bridging therapy to DMARDs§	2B	13/14
Usually MTX is the first immunosuppressive drug for JIAU and in CAU	3C	13/14
Mycophenolate mofetil or mycophenolic acid is an option for the treatment of JIAU and in CAU	4D	13/14
In case of inefficacy or intolerance to MTX and/or other conventional synthetic DMARDs, adding or switching to adalimumab is recommended	1B	14/14
In case of lack or loss of efficacy, increasing the dose and/or switching from every other week up to weekly adalimumab might be considered before switching to another therapy	4D	14/14
In the case of adalimumab failure, one may use other TNFi (excepting etanercept) or tocilizumab, and at present sufficient evidence does not exist to separate their clinical efficacy	3C	14/14
Based on the current evidence, etanercept should not be considered for JIAU and in CAU	1B	14/14
Among the TNFi, the strongest evidence for efficacy is for adalimumab followed by infliximab (1B) over golimumab (2A) or certolizumab (3B)	1B, 2A, 3B	14/14
Abatacept, JAK inhibitors, and/or rituximab may be considered in patients refractory to TNFi and tocilizumab	4D	14/14

* 1A = meta-analysis of cohort studies; 1B = meta-analysis of case–control studies; 2A = controlled study without randomization; 2B = quasi-experimental study; 3 = descriptive study; 4 = expert opinion. CAU = chronic anterior uveitis; DMARD = disease-modifying antirheumatic drug; JIAU = juvenile idiopathic arthritis–associated uveitis; MTX = methotrexate; NSAID = nonsteroidal antiinflammatory drug; TNFi = tumor necrosis factor inhibitor.
† Word change compared to previous SHARE recommendations.
‡ Same statement as previous SHARE recommendation.
§ New statement compared to previous recommendation.

21514658, 2023, 5, Downloaded from https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.24963 by Amanda LaVoy , Wiley Online Library on [22/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

"The use of adalimumab is recommended in patients with uveitis refractory/resistant to DMARD therapy, principally methotrexate." This statement has been replaced by statement 10.

"Based on the current evidence, etanercept should not be considered for JIAU." This statement has been replaced by statement 13.

"The use of TNFi treatment strategies (adalimumab > infliximab > golimumab) is recommended in patients with JIAU refractory/resistant to DMARD therapy, principally MTX." This statement has been replaced by statement 14.

DISCUSSION

This is an update of the previous 2014 SHARE recommendations for the treatment of children with JIAU with the addition of CAU (Table 2). The recommendations have been established using a combination of systematic literature review and consensus by pediatric rheumatologists and ophthalmologists using nominal group technique. All recommendations were accepted with >90% agreement.

Although the quality of evidence was low in several recommendations, 7 of them reached a good level of evidence. The landscape has changed significantly following the publication of the ADUVITE (18) and SYCAMORE (17) trials, with adalimumab now being a commonly used medication for the management of uveitis in children who are still active despite DMARD therapy.

The tocilizumab trial in patients with TNFi-refractory JIAU (APTITUDE) (39) failed to reach its primary endpoint, but one-third of patients appeared to benefit from the drug. The group agreed that these data were compelling enough to recommend tocilizumab for patients who still had active JIAU or CAU despite conventional synthetic DMARD and adalimumab therapy. Based on the lack of evidence regarding other biologics, the recommendations regarding golimumab, certolizumab, abatacept, rituximab, and tocilizumab or baricitinib were therefore conditional. However, the JAHW trial is currently recruiting patients to determine whether baricitinib may be of use as a first- or second-line agent after nonresponse to a DMARD in children with uveitis (47). A major limitation of the recommendations is the rarity of good-quality trials in pediatric uveitis. Multinational collaborations are crucial to drive randomized controlled trials in rare diseases such as CAU and JIAU and to allow recommendations to be based more on evidence rather than on experience.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Foeldvari had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Foeldvari.

Acquisition of data. Foeldvari, Maccora, Petrushkin, Rahman, Anton, de Boer, Calzada-Herna´ndez, Carreras, Diaz, Edelsten, Angeles-Han, Heiligenhaus, Miserocchi, Nielsen, Saurenmann, Stuebiger, Baquet-Walscheid, Furst, Simonini.

Analysis and interpretation of data. Foeldvari, Maccora, Petrushkin, Rahman, Anton, de Boer, Calzada-Herna´ndez, Carreras, Diaz, Edelsten, Angeles-Han, Heiligenhaus, Miserocchi, Nielsen, Saurenmann, Stuebiger, Baquet-Walscheid, Furst, Simonini.

REFERENCES

1. Angeles-Han ST, Ringold S, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the screening, monitoring, and treatment of juvenile idiopathic arthritis–associated uveitis. Arthritis Care Res (Hoboken) 2019;71:703–16.
2. Constantin T, Foeldvari I, Anton J, et al. Consensus-based recommendations for the management of uveitis associated with juvenile idiopathic arthritis: the SHARE initiative. Ann Rheum Dis 2018;77:1107–17.
3. Heiligenhaus A, Foeldvari I, Edelsten C, et al. Proposed outcome measures for prospective clinical trials in juvenile idiopathic arthritis–associated uveitis: a consensus effort from the Multinational Interdisciplinary Working Group for Uveitis in Childhood. Arthritis Care Res (Hoboken) 2012;64:1365–72.
4. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.
5. Heiligenhaus A, Klotsche J, Niewerth M, et al. Similarities in clinical course and outcome between juvenile idiopathic arthritis (JIA)-associated and ANA-positive idiopathic anterior uveitis: data from a population-based nationwide study in Germany. Arthritis Res Ther 2020;22:81.
6. Solebo AL, Rahi JS, Dick AD, et al. Areas of agreement in the management of childhood non-infectious chronic anterior uveitis in the UK. Br J Ophthalmol 2020;104:11–6.
7. Angeles-Han ST, Yeh S, Vogler LB. Updates on the risk markers and outcomes of severe juvenile idiopathic arthritis-associated uveitis. Int J Clin Rheumatol 2013;8:10.2217/ijr.12.83.
8. Heiligenhaus A, Klotsche J, Tappeiner C, et al. Predictive factors and biomarkers for the 2-year outcome of uveitis in juvenile idiopathic arthritis: data from the Inception Cohort of Newly diagnosed patients with Juvenile Idiopathic Arthritis (ICON-JIA) study. Rheumatology (Oxford) 2019;58:975–86.
9. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature for reporting clinical data: results of the first international workshop. Am J Ophthalmol 2005;140:509–16.
10. Thorne JE, Woreta FA, Dunn JP, et al. Risk of cataract development among children with juvenile idiopathic arthritis-related uveitis treated with topical glucocorticoids. Ophthalmology 2020;127:S21–6.
11. Kothari S, Foster CS, Pistilli M, et al. The risk of intraocular pressure elevation in pediatric noninfectious uveitis. Ophthalmology 2015;122:1987–2001.
12. Lee J, Koreishi AF, Zumpf KB, et al. Success of weekly adalimumab in refractory ocular inflammatory disease. Ophthalmology 2020;127:1431–3.
13. Curragh DS, O'Neill M, McAvoy CE, et al. Pediatric uveitis in a well-defined population: improved outcomes with immunosuppressive therapy. Ocular Immunol Inflamm 2018;26:978–85.
14. Simonini G, Paudyal P, Jones GT, et al. Current evidence of methotrexate efficacy in childhood chronic uveitis: a systematic review and meta-analysis approach. Rheumatology (Oxford) 2013;52:825–31.
15. Papadopoulou C, Kostik M, Böhm M, et al. Methotrexate therapy may prevent the onset of uveitis in juvenile idiopathic arthritis. J Pediatr 2013;163:879–84.

21514658, 2023, 5, Downloaded from https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.24963 by Amanda LaVoy , Wiley Online Library on [22/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

16. Sobrin L, Christen W, Foster CS. Mycophenolate mofetil after methotrexate failure or intolerance in the treatment of scleritis and uveitis. Ophthalmology 2008;115:1416–21.
17. Ramanan AV, Dick AD, Jones AP, et al. Adalimumab plus methotrexate for uveitis in juvenile idiopathic arthritis. N Engl J Med 2017;376:1637–46.
18. Quartier P, Baptiste A, Despert V, et al. ADJUVITE: a double-blind, randomised, placebo-controlled trial of adalimumab in early onset, chronic, juvenile idiopathic arthritis-associated anterior uveitis. Ann Rheum Dis 2018;77:1003–11.
19. Salek SS, Pradeep A, Guly C, et al. Uveitis and juvenile psoriatic arthritis or psoriasis. Am J Ophthalmol 2018;185:68–74.
20. McCracken C, Yeh S, Jenkins K, et al. Timing of infliximab and adalimumab initiation despite methotrexate in children with chronic noninfectious anterior uveitis. Eye (Lond) 2019;33:629–39.
21. Liberman P, Berkenstock MK, Burkholder BM, et al. Escalation to weekly adalimumab for the treatment of ocular inflammation. Ocul Immunol Inflamm 2021;29:1564–8.
22. Maccora I, Fusco E, Marrani E, et al. Changing evidence over time: updated meta-analysis regarding anti-TNF efficacy in childhood chronic uveitis. Rheumatology (Oxford) 2021;60:568–87.
23. Lerman MA, Lewen MD, Kempen JH, et al. Uveitis reactivation in children treated with tumor necrosis factor alpha inhibitors. Am J Ophthalmol 2015;160:193–200.
24. Lazarevi´c D, Nikoli´c I, Ratkovic´-Jankovi´c M, et al. Outcome of juvenile idiopathic arthritis associated uveitis in two disease subtypes. Arch Rheumatol 2017;32:26–31.
25. La Torre F, Cattalini M, Teruzzi B, et al. Efficacy of adalimumab in young children with juvenile idiopathic arthritis and chronic uveitis: a case series. BMC Res Notes 2014;7:316.
26. Horton S, Jones AP, Guly CM, et al. Adalimumab in juvenile idiopathic arthritis-associated uveitis: 5-year follow-up of the Bristol participants of the SYCAMORE trial. Am J Ophthalmol 2019;207:170–4.
27. Correll CK, Bullock DR, Cafferty RM, et al. Safety of weekly adalimumab in the treatment of juvenile idiopathic arthritis and pediatric chronic uveitis. Clin Rheumatol 2018;37:549–53.
28. Cecchin V, Zannin ME, Ferrari D, et al. Longterm safety and efficacy of adalimumab and infliximab for uveitis associated with juvenile idiopathic arthritis. J Rheumatol 2018;45:1167–72.
29. Breitbach M, Tappeiner C, Böhm MR, et al. Discontinuation of long-term adalimumab treatment in patients with juvenile idiopathic arthritis-associated uveitis. Graefes Arch Clin Exp Ophthalmol 2017;255:171–7.
30. Roberts JE, Nigrovic PA, Lo MS, et al. Weekly adalimumab, an effective alternative for refractory uveitis in children. J Clin Rheumatol 2022;28:e301–4.
31. Skrabl-Baumgartner A, Seidel G, Langner-Wegscheider B, et al. Drug monitoring in long-term treatment with adalimumab for juvenile idiopathic arthritis-associated uveitis. Arch Dis Child 2019;104:246–50.
32. Mesquida M, Molins B, Llorenç V, et al. Long-term effects of tocilizumab therapy for refractory uveitis-related macular edema. Ophthalmology 2014;121:2380–6.
33. Quesada-Masachs E, Caballero CM. Subcutaneous tocilizumab may be less effective than intravenous tocilizumab in the treatment of juvenile idiopathic arthritis-associated uveitis. J Rheumatol 2017;44:260–1.
34. Silpa-Archa S, Oray M, Preble JM, et al. Outcome of tocilizumab treatment in refractory ocular inflammatory diseases. Acta Ophthalmol 2016;94:e400–6.
35. Tappeiner C, Mesquida M, Ada´n A, et al. Evidence for tocilizumab as a treatment option in refractory uveitis associated with juvenile idiopathic arthritis. J Rheumatol 2016;43:2183–8.
36. Calvo-Río V, Santos-Go´mez M, Calvo I, et al. Anti–interleukin-6 receptor tocilizumab for severe juvenile idiopathic arthritis–associated uveitis refractory to anti–tumor necrosis factor therapy: a multicenter study of twenty-five patients. Arthritis Rheumatol 2017;69:668–75.
37. Grönlund MM, Remes-Pakarinen T, Kröger L, et al. Efficacy and safety of tocilizumab in a real-life observational cohort of patients with polyarticular juvenile idiopathic arthritis. Rheumatology (Oxford) 2020;59:732–41.
38. Dipasquale V, Atteritano M, Fresta J, et al. Tocilizumab for refractory uveitis associated with juvenile idiopathic arthritis: a report of two cases. J Clin Pharm Ther 2019;44:482–5.
39. Ramanan AV, Dick AD, Guly C, et al. Tocilizumab in patients with anti-TNF refractory juvenile idiopathic arthritis-associated uveitis (APTITUDE): a multicentre, single-arm, phase 2 trial. Lancet Rheumatol 2020;2:e135–41.
40. Miraldi Utz V, Bulas S, Lopper S, et al. Effectiveness of long-term infliximab use and impact of treatment adherence on disease control in refractory, non-infectious pediatric uveitis. Pediatr Rheumatol Online J 2019;17:79.
41. Ashkenazy N, Saboo US, Abraham A, et al. Successful treatment with infliximab after adalimumab failure in pediatric noninfectious uveitis. J AAPOS 2019;23:151.e1–5.
42. Palmou-Fontana N, Calvo-Río V, Martín-Varillas JL, et al. Golimumab in refractory uveitis associated to juvenile idiopathic arthritis: multicentre study of 7 cases and literature review. Clin Exp Rheumatol 2018;36:652–7.
43. Sharon Y, Chu DS. Certolizumab pegol: tumor necrosis factor inhibitor for refractory uveitis. Am J Ophthalmol Case Rep 2020;18:100633.
44. Tappeiner C, Miserocchi E, Bodaghi B, et al. Abatacept in the treatment of severe, longstanding, and refractory uveitis associated with juvenile idiopathic arthritis. J Rheumatol 2015;42:706–11.
45. Marrani E, Paganelli V, Libero C de, et al. Long-term efficacy of abatacept in pediatric patients with idiopathic uveitis: a case series. Graefes Arch Clin Exp Ophthalmol 2015;253:1813–6.
46. Birolo C, Zannin ME, Arsenyeva S, et al. Comparable efficacy of abatacept used as first-line or second-line biological agent for severe juvenile idiopathic arthritis-related uveitis. J Rheumatol 2016;43:2068–73.
47. Ramanan AV, Guly CM, Keller SY, et al. Clinical effectiveness and safety of baricitinib for the treatment of juvenile idiopathic arthritis-associated uveitis or chronic anterior antinuclear antibody-positive uveitis: study protocol for an open-label, adalimumab active-controlled phase 3 clinical trial (JUVE-BRIGHT). Trials 2021;22:689.
48. Bauermann P, Heiligenhaus A, Heinz C. Effect of Janus kinase inhibitor treatment on anterior uveitis and associated macular edema in an adult patient with juvenile idiopathic arthritis. Ocul Immunol Inflamm 2019;27:1232–4.
49. Miserocchi E, Giuffrè C, Cornalba M, et al. JAK inhibitors in refractory juvenile idiopathic arthritis-associated uveitis. Clin Rheumatol 2020;39:847–51.
50. Miserocchi E, Modorati G, Berchicci L, et al. Long-term treatment with rituximab in severe juvenile idiopathic arthritis-associated uveitis. Br J Ophthalmol 2016;100:782–6.

21514658, 2023, 5, Downloaded from https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.24963 by Amanda LaVoy , Wiley Online Library on [22/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Check for updates

Arthritis Care & Research
Vol. 71, No. 6, June 2019, pp 703–716
DOI 10.1002/acr.23871
© 2019, American College of Rheumatology

American College of Rheumatology
Empowering Rheumatology Professionals

SPECIAL ARTICLE

2019 American College of Rheumatology/Arthritis Foundation Guideline for the Screening, Monitoring, and Treatment of Juvenile Idiopathic Arthritis–Associated Uveitis

Sheila T. Angeles-Han,[1] Sarah Ringold,[2] Timothy Beukelman,[3] Daniel Lovell,[1] Carlos A. Cuello,[4] Mara L. Becker,[5] Robert A. Colbert,[6] Brian M. Feldman,[7] Gary N. Holland,[8] Polly J. Ferguson,[9] Harry Gewanter,[10] Jaime Guzman,[11] Jennifer Horonjeff,[12] Peter A. Nigrovic,[13] Michael J. Ombrello,[6] Murray H. Passo,[14] Matthew L. Stoll,[3] C. Egla Rabinovich,[15] H. Nida Sen,[16] Rayfel Schneider,[7] Olha Halyabar,[17] Kimberly Hays,[14] Amit Aakash Shah,[18] Nancy Sullivan,[19] Ann Marie Szymanski,[6] Marat Turgunbaev,[18] Amy Turner,[18] and James Reston[19]

Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology (ACR) are intended to provide guidance for particular patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to the recommendations within this guideline to be voluntary, with the ultimate determination regarding their application to be made by the health care provider in light of each patient's individual circumstances. Guidelines and recommendations are intended to promote beneficial or desirable outcomes but cannot guarantee any specific outcome. Guidelines and recommendations developed and endorsed by the ACR are subject to periodic revision as warranted by the evolution of medical knowledge, technology, and practice. ACR recommendations are not intended to dictate payment or insurance decisions. These recommendations cannot adequately convey all uncertainties and nuances of patient care.

The American College of Rheumatology is an independent, professional, medical and scientific society that does not guarantee, warrant, or endorse any commercial product or service.

Objective. To develop recommendations for the screening, monitoring, and treatment of uveitis in children with juvenile idiopathic arthritis (JIA).

Methods. Pediatric rheumatologists, ophthalmologists with expertise in uveitis, patient representatives, and methodologists generated key clinical questions to be addressed by this guideline. This was followed by a systematic literature review and rating of the available evidence according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology. A group consensus process was used to compose the final recommendations and grade their strength as conditional or strong.

Results. Due to a lack of literature with good quality of evidence, recommendations were formulated on the basis of available evidence and a consensus expert opinion. Regular ophthalmic screening of children with JIA is recommended because of the risk of uveitis, and the frequency of screening should be based on individual risk factors. Regular ophthalmic monitoring of children with uveitis is recommended, and intervals should be based on ocular examination findings and treatment regimen. Ophthalmic monitoring recommendations were strong primarily because

This article is published simultaneously in *Arthritis & Rheumatology*.

Supported by the American College of Rheumatology and the Arthritis Foundation. Dr. Angeles-Han's work was supported by the NIH (grant K23-EY-021760 from the National Eye Institute), the Rheumatology Research Foundation, and the Cincinnati Children's Hospital Medical Center Research Innovation and Pilot fund. Drs. Colbert and Ombrello's work was supported by the NIH (grants AR-041184 and AR-041198, respectively, from the Intramural Research Program of the National Institute of Arthritis and Musculoskeletal and Skin Diseases). Dr. Ferguson's work was supported by the NIH (grant AR-059-703). Dr. Nigrovic's work was supported by the Fundación Bechara. Dr. Sen's work was supported by the Intramural Research Program of the National Eye Institute, NIH (grant EY-000356-16).

[1]Sheila T. Angeles-Han, MD, MSc, Daniel Lovell, MD, MPH: Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, Ohio; [2]Sarah Ringold, MD, MS: Seattle Children's Hospital, Seattle, Washington; [3]Timothy Beukelman, MD, MSCE, Matthew L. Stoll, MD, PhD, MSCS: University

of concerns of vision-threatening complications of uveitis with infrequent monitoring. Topical glucocorticoids should be used as initial treatment to achieve control of inflammation. Methotrexate and the monoclonal antibody tumor necrosis factor inhibitors adalimumab and infliximab are recommended when systemic treatment is needed for the management of uveitis. The timely addition of nonbiologic and biologic drugs is recommended to maintain uveitis control in children who are at continued risk of vision loss.

Conclusion. This guideline provides direction for clinicians and patients/parents making decisions on the screening, monitoring, and management of children with JIA and uveitis, using GRADE methodology and informed by a consensus process with input from rheumatology and ophthalmology experts, current literature, and patient/parent preferences and values.

INTRODUCTION

Uveitis is the most common extraarticular manifestation of juvenile idiopathic arthritis (JIA) and can be a chronic or acute disease. Chronic anterior uveitis (CAU) develops in 10–20% of children with JIA, is usually asymptomatic, and there is rarely external evidence of inflammation (1,2). Acute anterior uveitis (AAU) is a distinctly different form of uveitis. It is typically associated with HLA–B27 and occurs in children with spondyloarthritis (i.e., those with enthesitis-related or psoriatic arthritis). AAU differs from CAU in that AAU is episodic, unilateral, characterized by the sudden onset of erythema, pain, and photophobia, and generally does not require systemic treatment (3).

Uncontrolled CAU can lead to sight-threatening complications such as synechiae, cataracts, and glaucoma in 25–50% and vision loss in 10–20% of children with uveitis (2,4–6). Early detection through regular ophthalmic screening with timely and appropriate treatment can improve visual outcomes and prevent complications (5,7).

Because CAU is often asymptomatic until ocular complications arise, the American Academy of Pediatrics (AAP) published recommendations in 2006 for routine ophthalmic screening in children with arthritis (8). These recommendations were based on an older arthritis nomenclature and did not include uveitis screening in all JIA categories such as psoriatic, enthesitis-related, and undifferentiated arthritis. To fill this gap, in 2012, Heiligenhaus and colleagues from the German Uveitis in Childhood Study Group ("German recommendations") proposed ophthalmic screening schedules based on the International League of Associations for Rheumatology (ILAR) JIA classification scheme (9). These 2 publications, however, did not address the monitoring of children with an established diagnosis of uveitis or the treatment of uveitis. Thus, recommendations for both monitoring and treatment of uveitis in children with JIA are needed.

Initial treatment of children with JIA-associated uveitis typically includes topical glucocorticoids. In those who are refractory to or dependent on topical glucocorticoids, there are no accepted North American guidelines for the use of systemic immunosuppressive therapy. Methotrexate is the usual first-line systemic immunosuppressive agent, followed by tumor necrosis factor inhibitor (TNFi) biologics, particularly the monoclonal antibodies infliximab and adalimumab (10). Despite the frequency with which these drugs are used for uveitis, only 1 large randomized controlled trial (RCT) studying children with JIA-associated uveitis has been published (11). Guidance is needed for the acceptable duration and frequency of topical glucocorticoids prior to initiation of nonbiologic disease-modifying antirheumatic drugs (DMARDs) and systemic biologic therapy, and for the approach to initiation, escalation, and modification of systemic therapy. Optimization of treatment strategies is crucial to improve vision outcomes.

of Alabama, Birmingham; [4]Carlos A. Cuello, MD, PhD: McMaster University, Hamilton, Ontario, Canada; [5]Mara L. Becker, MD, MSCE: Children's Mercy Hospital, Kansas City, Missouri; [6]Robert A. Colbert, MD, PhD, Michael J. Ombrello, MD, Ann Marie Szymanski, MD: National Institutes of Health, Bethesda, Maryland; [7]Brian M. Feldman, MD, MSc, FRCPC, Rayfel Schneider, MBBCh: The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada; [8]Gary N. Holland, MD: UCLA Stein Eye Institute, David Geffen School of Medicine at UCLA, Los Angeles, California; [9]Polly J. Ferguson, MD: University of Iowa Carver College of Medicine, Iowa City; [10]Harry Gewanter, MD: Children's Hospital of Richmond, Virginia Commonwealth University, Richmond; [11]Jaime Guzman, MD, MSc, FRCPC: BC Children's Hospital, Vancouver, British Columbia, Canada; [12]Jennifer Horonjeff, PhD: Columbia University Medical Center, New York, New York; [13]Peter A. Nigrovic, MD: Brigham & Women's Hospital and Boston Children's Hospital, Boston, Massachusetts; [14]Murray H. Passo, MD, MEd, Kimberly Hays, MD: Medical University of South Carolina, Charleston; [15]C. Egla Rabinovich, MD, MPH: Duke University, Durham, North Carolina; [16]H. Nida Sen, MD, MHSc: National Eye Institute, National Institutes of Health, Bethesda, Maryland; [17]Olha Halyabar, MD: Boston Children's Hospital, Boston, Massachusetts; [18]Amit Aakash Shah, MD, MPH, Marat Turgunbaev, MD, MPH, Amy Turner: American College of Rheumatology, Atlanta, Georgia; [19]Nancy Sullivan, BA, James Reston, PhD, MPH: ECRI Institute, Plymouth Meeting, Pennsylvania.

Dr. Beukelman has received consulting fees from Bristol-Myers Squibb, Sobi, UCB, and Novartis (less than $10,000 each). Dr. Lovell has received consulting fees from AstraZeneca, Amgen, Abbott, Wyeth Pharmaceuticals, Pfizer, Hoffmann-La Roche, Novartis, UCB, Takeda, Janssen, GlaxoSmithKline, Boehringer Ingelheim, Celgene, Bristol-Myers Squibb, and AbbVie (less than $10,000 each). Dr. Nigrovic has received consulting fees from Bristol-Myers Squibb, Pfizer, AbbVie, Novartis, and Sobi (less than $10,000 each) and research grants from Sobi, Novartis, AbbVie, and Genentech (support of the FROST study of systemic JIA through CARRA). Dr. Stoll has received speaking fees from Novartis (less than $10,000). Dr. Rabinovich has received consulting fees from AbbVie (less than $10,000). Dr. Schneider has received consulting fees from Novartis and Sobi (less than $10,000 each). No other disclosures relevant to this article were reported.

Address correspondence to Sheila T. Angeles-Han, MD, MSc, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, MLC 4010, Cincinnati, OH 45229. E-mail: Sheila.Angeles-Han@cchmc.org.

Submitted for publication August 31, 2018; accepted in revised form February 27, 2019.

21514658, 2019, 6, Downloaded from https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.23871 by Cochrane Colombia, Wiley Online Library on [02/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

To address this need, the American College of Rheumatology (ACR) and the Arthritis Foundation (AF) convened expert panels of pediatric rheumatologists and ophthalmologists to develop the first ACR/AF recommendations for the screening, monitoring, and treatment of JIA-associated CAU and AAU. Recognizing the importance of close collaboration and communication between pediatric rheumatologists and ophthalmologists, this guideline was developed in collaboration with experts from both specialties. Patient and parent panels also provided input. Overall, clinicians, parents, and patients should use a shared decision-making process that considers patients' preferences and values. Recommendations for the treatment of children with JIA manifesting as non-systemic polyarthritis, sacroiliitis, and enthesitis were developed concomitantly and are presented separately (12).

METHODS

Methodology overview. This guideline followed the ACR guideline development process (http://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines). This process uses the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology (www.gradeworkinggroup.org) to rate the quality of the available evidence and to develop the recommendations (13–15). ACR policy guided disclosures and the management of potential conflicts of interest (participant disclosures are available at https://www.rheumatology.org/Portals/0/Files/JIA-Guideline-Disclosures.pdf). Supplementary Appendix 1 (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23871/abstract) presents the full methods in detail.

Guideline development teams. This work involved 5 groups: 1) a Core Leadership Team, consisting of 4 pediatric rheumatologists, supervised and coordinated the project and drafted the clinical questions and manuscript; 2) a Literature Review Team, led by an experienced literature review consultant, completed the literature search and data abstraction; 3) an Expert Panel, composed of 9 pediatric rheumatologists and 1 ophthalmologist with expertise in the management of uveitis in children, developed the clinical Patient/Population, Intervention, Comparison, and Outcomes (PICO) questions and decided on the scope of the guideline project; 4) a Voting Panel, including 15 pediatric rheumatologists, 2 ophthalmologists, both of whom were uveitis specialists, and 2 adult

Table 1. Terms, definitions, and medication interventions*

Terms/medications	Definition/name
Terms	
Controlled uveitis	Inactive OR grade <1+ anterior chamber cells without new complications due to active inflammation per Standardization of Uveitis Nomenclature criteria†
Complications due to active inflammation‡	New development of peripheral anterior synechiae, posterior synechiae, inflammatory membranes, or cystoid macular edema
Additional signs of active inflammation	Fresh keratic precipitates, increased flare, and hypotony
Complications representing cumulative damage	Cataract, glaucoma/elevated intraocular pressure, hypotony, or sequelae of keratic precipitates (hyalinized spots or ghost keratic precipitates)§
Loss of control‡	Increase of anterior chamber cells to grade 1+ or more or new signs of inflammation/complications of inflammation†
New uveitis activity	No history of prior uveitis or loss of control of previously controlled uveitis
Systemic therapy	Nonbiologic DMARDs and biologics
Medications included in the guideline	
Glucocorticoids	Topical eye drops
	Systemic (all oral)
Nonbiologic DMARDs	Methotrexate
	Leflunomide
	Mycophenolate
	Cyclosporine
Biologic DMARDs	Monoclonal TNF inhibitor (adalimumab, infliximab)
	Etanercept
	Abatacept
	Tocilizumab

* DMARDs = disease-modifying antirheumatic drugs; TNF = tumor necrosis factor.
† Grade 1+ anterior chamber cells = 6–15 cells per field in a 1-mm × 1-mm slit beam.
‡ Loss of control of uveitis, active uveitis, and complications can lead to partial or permanent vision loss.
§ These are not reversible changes and should not be indications to change treatment in the absence of active inflammation.

21514658, 2019, 6, Downloaded from https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.23871 by Cochrane Colombia, Wiley Online Library on [02/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

patients with JIA, assisted with developing the scope of the project and refining PICO questions, reviewed the collated evidence, and voted on the recommendations; and 5) a Parent and Patient Panel, consisting of 9 adult patients with JIA and 2 parents of children with JIA and uveitis, reviewed the collated evidence and provided input on their values and preferences, within the context of a separate voting meeting. Supplementary Appendix 2 (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23871/abstract) presents rosters of the team and panel members. In accordance with ACR policy, the principal investigator and the leader of the Literature Review Team were free of potential conflicts of interest, and in all teams, >50% of the members were free of potential conflicts of interest.

PICO question development and importance of outcomes. The Core Leadership Team drafted the initial project scope, key principles, and relevant clinical PICO questions. These were then presented to the guideline development groups for their review at a scoping face-to-face meeting in which the project plan was defined. GRADE criteria provided the framework for judging the overall quality of evidence (13).

During the scoping meeting, the guideline scope, key terms, and definitions were discussed and agreed upon (Table 1). The Expert Panel chose the following 3 areas of focus: 1) ophthalmic screening for uveitis in children with JIA, 2) ophthalmic monitoring of established uveitis in children with JIA, and 3) use of topical and systemic glucocorticoids and systemic immunosuppressant medications to treat uveitis. This guideline pertains to children with JIA and either CAU or AAU. The Expert Panel defined "controlled uveitis" as an inactive OR grade of <1+ anterior chamber (AC) cells without new complications due to active inflammation per Standardization of Uveitis Nomenclature (SUN) criteria (16). "Loss of control" of uveitis was defined as an increase of AC cells to grade 1+ or more or new signs of inflammation/complications of inflammation. A grade of 1+ AC cells is 6–15 cells/field in a 1-mm × 1-mm slit beam, as seen through a biomicroscope. The term "new uveitis activity" included either new activity in patients with no history of uveitis or recurrent activity in patients with loss of control of previously controlled uveitis. Complications due to active inflammation, additional signs of active inflammation, and complications representing cumulative damage were also defined (Table 1). Loss of control of uveitis, active uveitis, and complications can lead to partial or permanent vision loss.

Critical and important outcomes varied based on the type of recommendation (Table 2). Critical outcomes related to screening included new diagnosis of uveitis and new diagnosis of uveitis with any ocular complications (Table 2). Critical outcomes related to monitoring included loss of control of uveitis and new complications due to inflammation. Critical outcomes related to medication use included loss of control of uveitis, incidence of loss of control of uveitis (rate or frequency of loss of control of uveitis, i.e., number of episodes over time), control of uveitis at 1 month and 3 months, new glucocorticoid-related ocular complications (cataracts, glaucoma/increased intraocular pressure [IOP], infection), and new ocular complications due to inflammation, incident uveitis, and recurrence of uveitis. Other important outcomes for monitoring were severity and level of inflammation and for medication use were side effects of systemic therapy, time to control of uveitis, and time to loss of control of uveitis.

Table 2. Critical and important outcomes*

Type of recommendation	Outcome
Screening	
Critical outcomes	New diagnosis of uveitis
	New diagnosis of uveitis with ANY ocular complications
Monitoring	
Critical outcomes	Loss of control of uveitis
	New complications due to inflammation
Important outcomes	Severity/level of inflammation
Treatment	
Critical outcomes	Loss of control of uveitis
	Incidence of loss of control of uveitis
	Control of uveitis at 1 month and 3 months
	New ocular glucocorticoid complications (cataracts, glaucoma/increased intraocular pressure, infection)
	New ocular complications due to inflammation
	Incident uveitis
	Recurrence of uveitis
Important outcomes	Side effects of systemic therapy
	Time to control of uveitis
	Time to loss of control of uveitis

* Vary depending on the recommendation.

Synthesis of the literature and grading of the evidence. Systematic searches of the published English language literature included OVID Medline, PubMed, Embase, and the Cochrane Library (including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, and Health Technology Assessments) from inception through June 12, 2017 (see Supplementary Appendix 3, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23871/abstract); updated searches were conducted on October 13, 2017. DistillerSR software (https://dis-

21514658, 2019, 6, Downloaded from https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.23871 by Cochrane Colombia, Wiley Online Library on [02/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

tillercer.com/products/distillersr-systematic-reviewsoftware/) (Supplementary Appendix 4, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23871/abstract) facilitated duplicate screening of literature search results. Reviewers entered extracted data into RevMan software (http://tech.cochrane.org/revman) and evaluated the risk of bias of primary studies using the Cochrane risk of bias tool (http://handbook.cochrane.org/). RevMan files were exported into GRADEpro software to formulate a GRADE summary of a table showing the GRADE summary of findings (see Supplementary Appendix 5, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23871/abstract) for each PICO question (17).

When data were available, the evidence summaries included the benefits and harms for outcomes of interest across studies, the relative effect (with effect size and 95% confidence interval), the number of participants, and the absolute effects. We rated the quality of evidence (also called certainty) for each critical and important outcome as high, moderate, low, or very low quality, taking into account risk of bias, inconsistency, indirectness, imprecision, and other considerations as per the GRADE recommendations.

Moving from evidence to recommendations. GRADE methodology specifies that panels make recommendations based on the balance of benefits and harms, the quality of the evidence (i.e., confidence in effect estimates), and parents/patients' values and preferences. Deciding on the balance between desirable and undesirable outcomes requires estimating the relative value patients place on those outcomes. When the literature did not provide clear evidence, recommendations were based on the values/preferences input from the members of the Parent and Patient Panel and on the experience of the Voting Panel members (including physicians and the 2 patients present).

Consensus building. The Voting Panel voted on the direction and strength of the recommendation related to each PICO question. Recommendations required a 70% level of agreement; if 70% agreement was not achieved during an initial vote, Voting Panel members held additional discussions before re-voting, including rewording of recommendations if needed, until consensus was attained (18). For all conditional recommendations, a written explanation is provided, describing the reasons for this decision and conditions under which the alternative may be preferable. A second round of voting occurred after the face-to-face meeting for recommendations with additional questions. In some instances, the Voting Panel combined PICO questions into 1 recommendation for clarity. Some PICO questions were dropped during the consensus meeting due to insufficient evidence to make a formal recommendation (see Supplementary Appendix 6, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23871/abstract).

Moving from recommendations to practice. These recommendations are designed to help health care providers work with parents/patients in selecting therapies. Health care providers and parents/patients must take into consideration all active disease domains, comorbidities, and the patient's functional status when choosing the optimal therapy for an individual patient.

RESULTS/RECOMMENDATIONS

The literature searches retrieved 1,704 initial citations, 131 duplications were removed, and 1,537 unique uveitis citations were identified. Full-length articles were abstracted and graded for evidence related to the 34 PICO questions. The available evidence was very low-quality for all PICO questions, mainly because of the lack of evidence and the indirectness of the evidence. Most articles were based on observational studies, which are considered to be low-quality in the GRADE system.

How to interpret the recommendations

1. A *strong recommendation* means that the Voting Panel was confident that the desirable effects of following the recommendation outweigh the undesirable effects (or vice versa), so the course of action would apply to all or almost all patients, and only a small proportion would not want to follow the recommendation. Due to the risk of ocular complication with resultant vision loss with irregular or infrequent monitoring, and because ophthalmic examinations are low-risk, all recommendations on ophthalmic monitoring examinations of children with uveitis were strong despite the very low quality of evidence. Patients were concerned about the consequences of infrequent monitoring and agreed there was little disadvantage to monitoring, including the potential cost and inconvenience of frequent visits.
2. A *conditional recommendation* means the Voting Panel believed that the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of patient preference and lack of strong evidence, conditional recommendations are preference-sensitive and always warrant a shared decision-making approach. All of the treatment recommendations were conditional, except for 1 related to tapering topical glucocorticoids (Recommendation 18).
3. All of the recommendations had a very low quality of evidence; thus, most of the recommendations are conditional.
4. All of the recommendations are meant to apply to children with JIA at risk of and with associated uveitis, *regardless of activity of arthritis and other manifestations of JIA*.
5. When deciding on the frequency of ophthalmic monitoring and treatment, close collaboration and communication be-

21514658, 2019, 6, Downloaded from https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.23871 by Cochrane Colombia, Wiley Online Library on [02/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 3. Recommendations for ophthalmic screening, ophthalmic monitoring, and treatment of children with JIA-associated uveitis*

Recommendation
Recommendations for ophthalmic screening
In children and adolescents with JIA at high risk of developing uveitis:†
• Ophthalmic screening every 3 months is conditionally recommended (Recommendation 1, PICO 1).
Recommendations for ophthalmic monitoring
In children and adolescents with JIA and controlled uveitis who are:
• Tapering or discontinuing topical glucocorticoids, ophthalmic monitoring within 1 month after each change of topical glucocorticoids is ***strongly*** recommended over monitoring less frequently (Recommendation 2, PICO 3). • On stable therapy, ophthalmic monitoring no less frequently than every 3 months is ***strongly*** recommended over monitoring less frequently (Recommendation 3, PICO 2). • Tapering or discontinuing systemic therapy, ophthalmic monitoring within 2 months of changing systemic therapy is ***strongly*** recommended over monitoring less frequently (Recommendation 4, PICO 4).
Recommendations for glucocorticoid use
In children and adolescents with JIA and active CAU:
• Using prednisolone acetate 1% topical drops is conditionally recommended over difluprednate topical drops (Recommendation 5, PICO 10). • Adding or increasing topical glucocorticoids for short-term control is conditionally recommended over adding systemic glucocorticoids (Recommendation 6, PICO 11).
In children and adolescents with JIA and CAU still requiring 1–2 drops/day of prednisolone acetate 1% (or equivalent) for uveitis control:
• If not on systemic therapy, adding systemic therapy in order to taper topical glucocorticoids is conditionally recommended over not adding systemic therapy and maintaining topical glucocorticoids only (Recommendation 8, PICO 7). • If still requiring 1–2 drops/day of prednisolone acetate 1% (or equivalent) for at least 3 months and on systemic therapy, changing or escalating systemic therapy is conditionally recommended over maintaining current systemic therapy (Recommendation 9, PICO 8).
In children and adolescents with JIA who develop new CAU activity despite stable systemic therapy:‡
• Topical glucocorticoids prior to changing/escalating systemic therapy is conditionally recommended over changing/escalating systemic therapy immediately (Recommendation 7, PICO 12).
Recommendations for DMARDs and biologics
In children and adolescents with JIA and active CAU who are/have:
• Starting systemic treatment for uveitis, using subcutaneous methotrexate is conditionally recommended over oral methotrexate (Recommendation 10, PICO 13). • Starting a TNFi, starting a monoclonal antibody TNFi is conditionally recommended over etanercept (Recommendation 12, PICO 15). • Severe active CAU and sight-threatening complications, starting methotrexate and a monoclonal antibody TNFi immediately is conditionally recommended over methotrexate as monotherapy (Recommendation 11, PICO 22). • Inadequate response to one monoclonal TNFi at standard JIA dose, escalating the dose and/or frequency of the monoclonal TNFi to above standard is conditionally recommended over switching to another monoclonal antibody TNFi (Recommendation 13, PICO 20). • Failed a first monoclonal antibody TNFi at above-standard dose and/or frequency, changing to another monoclonal antibody TNFi is conditionally recommended over a biologic in another category (Recommendation 14, PICO 21). • Failed methotrexate and 2 monoclonal antibody TNFi at above-standard dose and/or frequency, abatacept or tocilizumab are conditionally recommended as biologic DMARD options, and mycophenolate, leflunomide, or cyclosporine as alternative nonbiologic options (Recommendation 15, PICO 23).
Recommendations for education about and treatment of AAU
In children and adolescents with spondyloarthritis:
• ***Strongly*** recommend education regarding the warning signs of AAU for the purpose of decreasing delay in treatment, duration of symptoms, or complications of iritis (Recommendation 16, PICO 32). • Well controlled with systemic immunosuppressive therapy (DMARD, biologics) who develop an isolated short-lived episode of AAU, conditionally recommend against switching systemic immunosuppressive therapy immediately in favor of treating with topical glucocorticoids first (Recommendation 17, PICO 34).

(continued)

21514658, 2019, 6, Downloaded from https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.23871 by Cochrane Colombia, Wiley Online Library on [02/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 3. (*Cont'd*)

Recommendation
Recommendations for tapering therapy for uveitis
In children and adolescents with JIA and CAU that is controlled on systemic therapy but remain on 1–2 drops/day of prednisolone acetate 1% (or equivalent):
• Tapering topical glucocorticoids first is ***strongly*** recommended over systemic therapy (Recommendation 18, PICO 6).
In children and adolescents with JIA and uveitis that is well controlled on DMARD and biologic systemic therapy only:
• Conditionally recommend that there be at least 2 years of well-controlled disease before tapering therapy (Recommendation 19, PICO 29).

* Each recommendation had very low quality level of evidence. JIA = juvenile idiopathic arthritis; PICO = Patient/Population, Intervention, Comparison, and Outcomes; CAU = chronic anterior uveitis; DMARDs = disease-modifying antirheumatic drugs; TNFi = tumor necrosis factor inhibitor; AAU = acute anterior uveitis.
† High-risk children are those with oligoarthritis, polyarthritis (rheumatoid factor negative), psoriatic arthritis, or undifferentiated arthritis who are also antinuclear antibody positive, younger than 7 years of age at JIA onset, and have JIA duration of 4 years or less.
‡ Definition of new CAU activity: no prior uveitis or loss of control of previously controlled uveitis.

tween rheumatology and ophthalmology subspecialists is crucial. Points to consider include degree of ocular inflammation, presence of complications, use of topical glucocorticoids, and level of IOP.

6. Recommendations on topical glucocorticoids pertain to prednisolone acetate 1% or equivalent dosing with other types of topical glucocorticoids.
7. Recommendations on systemic therapy pertain to nonbiologic DMARDs and biologics and not systemic glucocorticoids.
8. Recommendations that consider TNFi biologics pertain to etanercept, adalimumab, and infliximab only. Monoclonal antibody TNFi refers to adalimumab and infliximab, due to lack of data and experience with other agents (golimumab, certolizumab, or biosimilars) for uveitis in pediatric patients. Only adalimumab, infliximab, etanercept, abatacept, and tocilizumab were discussed, because data on the use of other biologics for treatment of uveitis are lacking.

Recommendation for ophthalmic screening of children with JIA (Table 3 and Figure 1A)

Recommendation 1. *In children and adolescents with JIA at high risk of developing uveitis, ophthalmic screening every 3 months is conditionally recommended over screening at a different frequency.*

The Voting Panel agreed with combining the screening recommendations of the AAP Sections on Rheumatology and Ophthalmology and the German Uveitis in Childhood Study Group (German recommendations) (8,9). AAP recommendations are based on the older classification scheme "juvenile rheumatoid arthritis," which does not include ILAR categories of psoriatic JIA, enthesitis-related arthritis, and undifferentiated arthritis. The screening schedule suggested by the German recommendations incorporates these categories and recommends screening high-risk children every 3 months, similar to the AAP recommendations. Based on the combined AAP and German recommendations, high-risk children are those with oligoarthritis, polyarthritis (rheumatoid factor negative), psoriatic arthritis, or undifferentiated arthritis who are also antinuclear antibody (ANA) positive, younger than 7 years of age at JIA onset, and have JIA duration of 4 years or less. Low- or moderate-risk children are those with high-risk JIA categories but who are ANA negative, age 7 years or older at JIA onset, or have JIA duration of more than 4 years, and those with systemic JIA, polyarthritis (rheumatoid factor positive), and enthesitis-related arthritis. Low- or moderate-risk children should be screened every 6–12 months depending on their combination of risk factors. Because children who have enthesitis-related arthritis or are carrying the HLA–B27 genotype are at risk of both AAU and CAU, they require screening as well. This recommendation was conditional, based on the low quality of evidence, although several reports have described factors that increase the risk of developing uveitis (19–24). Some children have significant eye disease at the time of screening under the current schedule, but there is a lack of data showing that more frequent screening is beneficial. Patients and parents supported the recommended frequency of screening and expressed a desire for frequent screening.

Recommendations for ophthalmic monitoring of children with JIA diagnosed with uveitis (Table 3 and Figure 1B)

Recommendation 2. *In children and adolescents with JIA and controlled uveitis who are tapering or discontinuing topical glucocorticoids, ophthalmic monitoring within 1 month after each change of topical glucocorticoids is strongly recommended over monitoring less frequently.*

Recommendation 3. *In children and adolescents with JIA and controlled uveitis on stable therapy, ophthalmic monitoring*

21514658, 2019, 6, Downloaded from https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.23871 by Cochrane Colombia, Wiley Online Library on [02/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

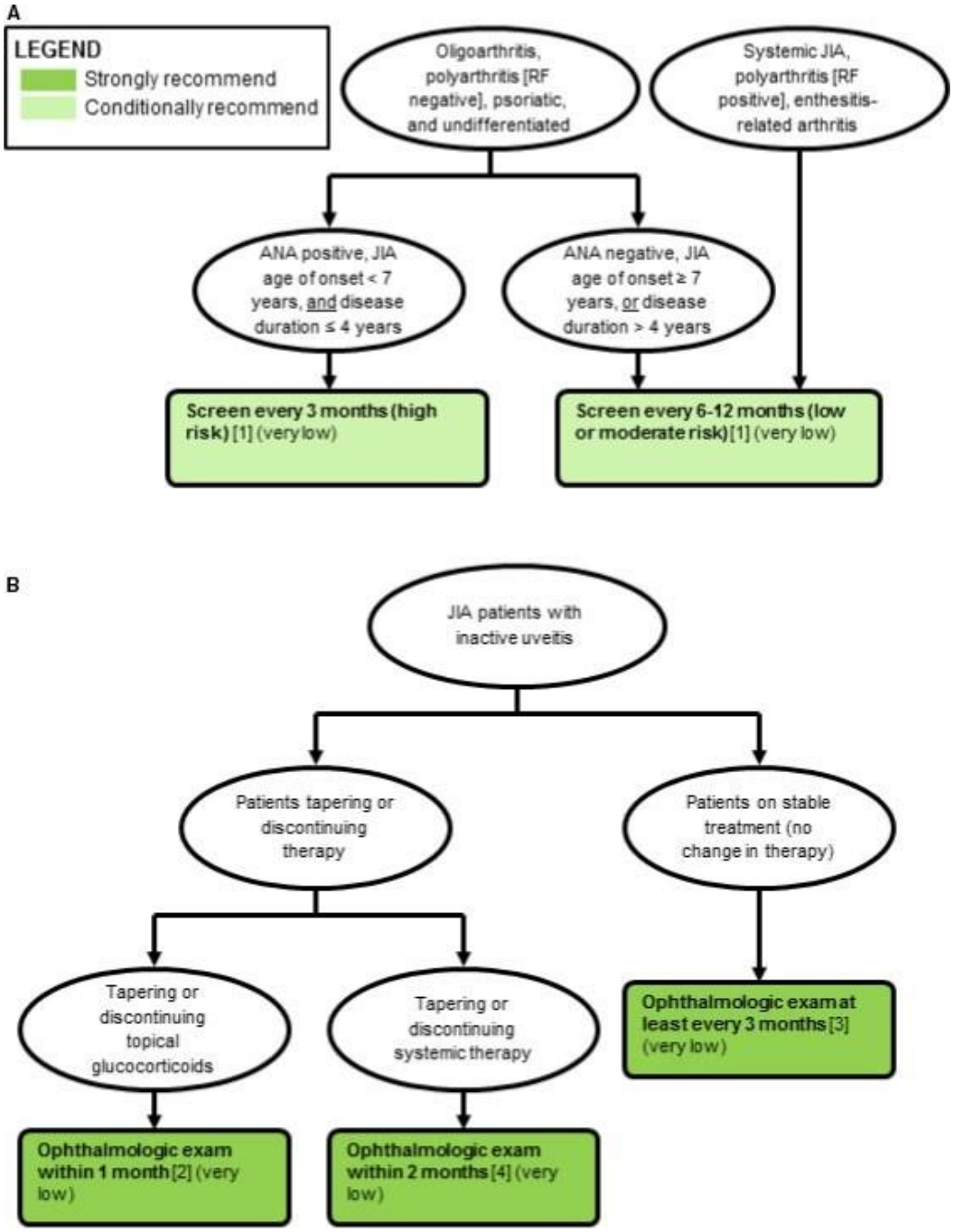


Figure 1. A, Ophthalmic screening examinations (see also Table 1). B, Ophthalmic monitoring examinations (see also Table 3). No recommendations were made for patients with uncontrolled chronic anterior uveitis. Patient/Population, Intervention, Comparison, and Outcomes (PICO) questions are shown in brackets, and quality of evidence is shown in parentheses. JIA = juvenile idiopathic arthritis; RF = rheumatoid factor; ANA = antinuclear antibody.

no less frequently than every 3 months is strongly recommended over monitoring less frequently.

Recommendation 4. *In children and adolescents with JIA and controlled uveitis who are tapering or discontinuing systemic therapy, ophthalmic monitoring within 2 months of changing systemic therapy is strongly recommended over monitoring less frequently.*

The need for regular monitoring of children with established uveitis was emphasized. The Voting Panel recommends that children with controlled CAU on stable medication should be monitored at 3-month intervals, and those tapering or discontinuing therapy should be monitored at intervals shorter than 3 months, either within 1 month after each change in topical glucocorticoids, and within 2 months of a change in systemic therapy (Figure 1B). Although the quality of evidence was very

21514658, 2019, 6, Downloaded from https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.23871 by Cochrane Colombia, Wiley Online Library on [02/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

low, the recommendations for monitoring were strong due to the potential for harmful consequences of irregular or infrequent monitoring of children with CAU, which could lead to substantial loss of vision and ocular complications from undetected exacerbation of inflammation (20,25). Patients were generally concerned about the consequences of infrequent monitoring and agreed that there was little disadvantage to having frequent ophthalmic examinations. The Voting Panel agreed that the frequency of monitoring may be influenced by the half-life of the systemic therapy and by the expected time for efficacy.

The Voting Panel was not able to reach consensus on a standard schedule of ophthalmic monitoring in children and adolescents with *uncontrolled* CAU; thus, no formal recommendation was made. The Voting Panel agreed, however, that regular monitoring is needed for uncontrolled uveitis, and that in most cases, examinations could occur at 2–6-week intervals tailored to the frequency of topical glucocorticoid administration, IOP, degree of inflammation, and presence of complications, as agreed on by the treatment team.

Recommendations for glucocorticoid use (Table 3 and Figure 2)

Recommendation 5. *In children and adolescents with JIA and active CAU, using prednisolone acetate 1% topical drops is conditionally recommended over difluprednate topical drops.*

Recommendation 6. *In children and adolescents with JIA and active CAU, adding or increasing topical glucocorticoids for short-term control is conditionally recommended over adding systemic glucocorticoids.*

Frequent administration of topical glucocorticoids should be used as initial therapy to control inflammation, followed by tapering as soon as the AC cellular reaction comes under control. The recommendation was conditional based on the very low quality of evidence (26). Prednisolone acetate 1% topical drops are the preferred topical glucocorticoid based on better corneal penetration compared with other eye drops and the fact that there is less experience with difluprednate, which has an increased risk of glucocorticoid-induced IOP and cataract formation (27,28). However, because long-term comparison data between both formulations are lacking, this recommendation was conditional. Patient compliance should be taken into consideration, because prednisolone acetate 1% requires more frequent administration due to its lower potency compared with difluprednate. The Voting Panel recognized that in selected patients, systemic glucocorticoids can be used as short-term bridging therapy. The Voting Panel did not seek consensus to make a recommendation on the use of periocular or intraocular glucocorticoids.

Recommendation 7. *In children and adolescents with JIA who develop new CAU activity despite stable systemic therapy, topical glucocorticoids prior to changing/escalating systemic therapy is conditionally recommended over changing/escalating systemic therapy immediately.*

Initially, topical glucocorticoids should be given to children with uncontrolled uveitis, whether there is a new diagnosis or exacerbation of previously controlled uveitis, unless there is a contraindication. Adding, changing, or escalating (increasing the dose or frequency) systemic therapy should be considered in those children who continue to require prednisolone acetate 1% 1–2 drops/day (or equivalent) (Recommendations 8 and 9). This recommendation was conditional based on very low quality of data.

Recommendation 8. *In children and adolescents with JIA and CAU still requiring 1–2 drops/day of prednisolone acetate 1% (or equivalent) for uveitis control, and not on systemic therapy, adding systemic therapy in order to taper topical glucocorticoids is conditionally recommended over not adding systemic therapy and maintaining on topical glucocorticoids only.*

The risk of elevated IOP and cataracts increases with greater frequency of administration of topical glucocorticoids (drops/day) and longer duration of therapy. Kothari et al found that topical glucocorticoids at a dosage of ≥2 drops/day was a strong risk factor for IOP elevation, which increased with a greater number of drops daily (29). Another retrospective cohort study showed that ≤3 drops/day of prednisolone is preferred to ≥4 drops/day to decrease the risk of developing cataracts (30). The Voting Panel recommends adding systemic DMARD therapy in children needing ongoing topical glucocorticoids to control uveitis, with the ultimate goal of discontinuation of topical glucocorticoids. These recommendations were conditional due to very low quality of data, and because there may be reasons why a dosage of 1–2 drops/day of topical prednisolone is unacceptable, such as the presence of complications from use of topical glucocorticoids, contraindications to topical glucocorticoids, and difficulty in compliance with multiple drops per day. Nevertheless, prednisolone at a dosage of 1–2 drops/day may be appropriate as monotherapy if there are no issues with ocular complications such as elevated IOP and cataracts, no difficulties with the use of topical glucocorticoids, and there is regular close follow-up with an ophthalmologist.

Recommendation 9. *In children and adolescents with JIA and CAU still requiring 1–2 drops/day of prednisolone acetate 1% (or equivalent) for at least 3 months and on systemic therapy for uveitis control, changing or escalating systemic therapy is conditionally recommended over maintaining current systemic therapy.*

The Voting Panel agreed on 3 months as the threshold for adding or changing systemic therapy in children who require topical glucocorticoids to maintain uveitis control. Nevertheless, changes in systemic therapy may be warranted earlier, depending on findings on the ocular examination, the duration of topical and systemic therapy, and the presence of existing complications. The recommendation was conditional because of the very low quality of the

21514658, 2019, 6, Downloaded from https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.23871 by Cochrane Colombia, Wiley Online Library on [02/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

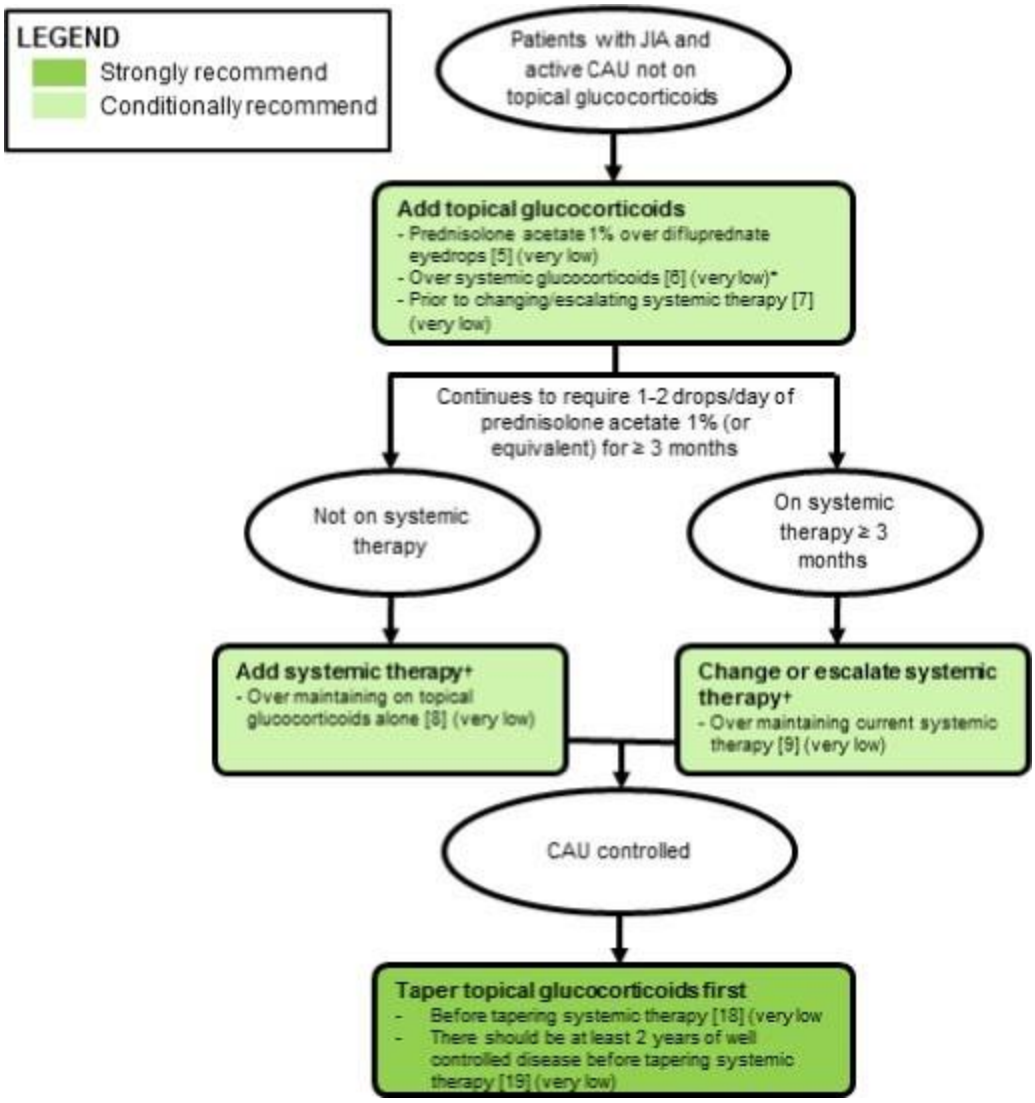


Figure 2. Recommendations for topical glucocorticoids in patients with juvenile idiopathic arthritis (JIA) and chronic anterior uveitis (CAU) (see also Table 3). Systemic therapy is defined as disease-modifying antirheumatic drugs and biologics. Topical glucocorticoids refer to prednisolone acetate 1% (or equivalent). Doses of prednisolone acetate 1% greater than 1–2 drops/eye/day may be needed initially but increase the risk of ocular complications. Topical glucocorticoids should be used as short-term therapy (≤3 months). The goal is to discontinue topical glucocorticoid use, due to risk of glaucoma and cataracts. Periocular and intraocular injections are administered at the discretion of the treating ophthalmologist. The recommendation numbers are shown in brackets, and quality of evidence is shown in parentheses. * = In selected patients, systemic glucocorticoids can be used as short-term bridging therapy. † = Can escalate dose or frequency of current therapy; 3 months is the threshold for adding or changing systemic therapy in children who require topical glucocorticoids to maintain uveitis control. Changes in systemic therapy may be warranted earlier, depending on findings on the ocular examination, the duration of topical and systemic therapy, and the presence of existing complications.

evidence, the variation in the severity of a child's disease presentation, child and family preference for topical medication over systemic therapy, and the specific systemic therapy being considered.

Recommendations for DMARDS and biologics (Table 3)

Recommendation 10. *In children and adolescents with JIA and CAU who are starting systemic treatment for uveitis, using subcutaneous methotrexate is conditionally recommended over oral methotrexate.*

Recommendation 11. *In children and adolescents with JIA with severe active CAU and sight-threating complications, starting methotrexate and a monoclonal antibody TNFi immediately is conditionally recommended over methotrexate as monotherapy.*

Methotrexate and monoclonal antibody TNFi are the mainstays of systemic treatment of uveitis. Subcutaneous

21514658, 2019, 6, Downloaded from https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.23871 by Cochrane Colombia, Wiley Online Library on [02/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

methotrexate was considered preferable to oral administration for uveitis, but this recommendation was conditional given the lack of strong data on differential efficacy and the notion that family preferences regarding the route of administration may differ. In children with severe active uveitis and sight-threatening complications, combining methotrexate with a monoclonal antibody TNFi at the time of initiation of systemic immunosuppressive treatment was recommended over methotrexate as monotherapy. Severe uveitis could be considered as the presence of ocular structural complications due to uveitis or complications of topical steroid therapy (31). This recommendation was conditional based on the lack of direct evidence from studies, the risk of permanent vision loss, and anticipated differences in patient values and preferences.

Recommendation 12. *In children and adolescents with JIA and active CAU starting a TNFi, starting a monoclonal antibody TNFi is conditionally recommended over etanercept.*

Monoclonal antibody TNFi, specifically adalimumab and infliximab, were conditionally recommended over etanercept for active CAU. Although there is a paucity of direct comparisons, a benefit of using monoclonal antibody TNFi has been shown. The Voting Panel was not able to make recommendations on the preferred TNFi treatment for children with active JIA to prevent uveitis onset or for children with known CAU to prevent uveitis flares, due to lack of evidence (32–36). The Voting Panel also did not make a recommendation on preference between adalimumab and infliximab for use as the initial TNFi.

Recommendation 13. *In children and adolescents with JIA and active CAU who have an inadequate response to 1 monoclonal antibody TNFi at standard JIA dose, escalating the dose and/or frequency to above standard is conditionally recommended over switching to another monoclonal antibody TNFi.*

Recommendation 14. *In children and adolescents with JIA and active CAU who have failed a first monoclonal antibody TNFi at above-standard dose and/or frequency, changing to another monoclonal antibody TNFi is conditionally recommended over a biologic in another category.*

Recommendations 13 and 14 assume that uveitis activity or severity guides therapy in the patient, irrespective of joint disease activity. The Voting Panel did not make a recommendation regarding preference between adalimumab and infliximab as a first-line TNFi or use of above-standard TNFi dosing at treatment initiation.

For children treated with a monoclonal antibody TNFi at standard dosing for patients with JIA who have an inadequate response to therapy, the Voting Panel conditionally recommended escalating the dose and/or frequency to above-standard dosing used for arthritis prior to switching to another monoclonal antibody TNFi. Although consensus was not reached regarding a specific dose or frequency, doses as high as infliximab 20 mg/kg administered every 2 weeks and adalimumab weekly have been reported in observational studies in children with JIA and uveitis (37–39). If treatment with an increased dose/frequency of the initial monoclonal antibody TNFi fails, the recommendation was to change to another monoclonal antibody TNFi prior to changing to a biologic agent in another category. These recommendations were conditional due to the very low quality evidence.

Recommendation 15. *In children and adolescents with JIA and active CAU who have failed methotrexate and 2 monoclonal antibody TNFi at above-standard dose and/or frequency, the use of abatacept or tocilizumab as biologic DMARD options, and mycophenolate, leflunomide, or cyclosporine as alternative nonbiologic DMARD options is conditionally recommended.*

The quality of evidence for subsequent treatment in children who have failed methotrexate in combination with monoclonal antibody TNFi treatment is very low. Based on the current literature, recommended alternative nonbiologic options are mycophenolate mofetil (40), leflunomide (41), or cyclosporine (42), and recommended alternative biologic options are abatacept (43–45) or tocilizumab (46,47); however, evidence supporting preference for a specific nonbiologic or biologic DMARD, combination therapies, and timing of initiation beyond methotrexate, adalimumab, and infliximab is currently lacking. For clarity, several PICO questions were combined in this recommendation.

Recommendations for education about and treatment of acute anterior uveitis (Table 3)

Recommendation 16. *In children and adolescents with spondyloarthritis, strongly recommend education regarding the warning signs of AAU for the purpose of decreasing delay in treatment, duration of symptoms, or complications of iritis.*

AAU is generally a manifestation in a subset of children who are HLA–B27 positive with enthesitis-related arthritis and in some cases of psoriatic arthritis. Although the quality of evidence was very low (no studies addressing these topics were identified), the Voting Panel strongly agreed, based on experience, that HLA–B27–positive patients with enthesitis-related arthritis or psoriatic arthritis and their families should be educated regarding warning signs of AAU, for the purpose of decreasing delay in treatment, duration of symptoms, or ocular complications. Signs include eye pain, redness, and photophobia. This recommendation was strong, because educating about a disease and warning signs is the standard of care.

Recommendation 17. *In children and adolescents with spondyloarthritis otherwise well controlled with systemic immunosuppressive therapy (DMARDs, biologics) who develop AAU, conditionally recommend against switching systemic immunosuppressive*

21514658, 2019, 6, Downloaded from https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.23871 by Cochrane Colombia, Wiley Online Library on [02/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

therapy immediately in favor of treating with topical glucocorticoids first.

Because AAU episodes are typically of short duration and may be easily controlled with topical glucocorticoids, the Voting Panel conditionally recommended continuing the same systemic immunosuppressive therapy and treating with topical glucocorticoids at the initial development of AAU (48). During an isolated short-lived episode of AAU, an immediate escalation or change in underlying systemic therapy may not be necessary without trying a course of topical glucocorticoids first. This recommendation was conditional, because there is a lack of supporting data. Furthermore, frequent recurrent episodes of AAU may prompt a change from a non–monoclonal antibody TNFi to a monoclonal antibody TNFi, or there may be ocular complications from use of topical glucocorticoids that require prompt adjustment of systemic treatment, to decrease exposure to glucocorticoid therapy.

Recommendations for tapering therapy for uveitis (Table 3)

Recommendation 18. *In children and adolescents with JIA and CAU that is controlled on systemic therapy but who remain on 1–2 drops/day of prednisolone acetate 1% (or equivalent), tapering topical glucocorticoids first is strongly recommended over systemic therapy.*

There is very low quality of evidence for timing of tapering of topical glucocorticoids and systemic therapy (25,49,50). Some ophthalmologists feel that in selected cases, it is not possible to discontinue topical glucocorticoids altogether, despite attempts to do so, and the patients may continue to receive 1–2 drops/day for extended periods of time. Despite the very low quality of evidence, the Voting Panel strongly recommended attempting to taper topical glucocorticoids prior to tapering systemic therapy because of the secondary complications that can occur with prolonged and frequent use of glucocorticoids (29,30). Tapering of systemic therapy first may lead to the need for increased frequency of topical glucocorticoids for uveitis flares.

Recommendation 19. *In children and adolescents with uveitis that is well controlled on DMARD and biologic systemic therapy only, conditionally recommend that there be at least 2 years of well-controlled disease before tapering therapy.*

The Voting Panel conditionally recommends attempted tapering of DMARD and biologic systemic therapy only after uveitis has been well controlled for at least 2 years. Relapse-free survival after withdrawal of methotrexate was significantly longer in patients treated with methotrexate for more than 3 years and who had controlled uveitis for more than 2 years before the withdrawal (50). Duration of systemic therapy may be longer than 2 years, because tapering should not begin until at least 2 years of uveitis control. Decisions to taper systemic therapy should also take into consideration other JIA manifestations, including arthritis activity.

DISCUSSION

This 2019 ACR guideline provides direction on the screening of children with JIA at risk of CAU, monitoring of children diagnosed with CAU, treatment with glucocorticoids, nonbiologic DMARDs, and biologic DMARDs for CAU, and education and treatment of children with or at risk of AAU. Few uveitis practice guidelines have a scope this broad (51–54). Although the quality of evidence was very low, and most recommendations were therefore conditional, this guideline fills an important clinical gap in the care of children with JIA-associated uveitis and may be updated as better evidence becomes available.

Optimal care of children with uveitis requires careful and close collaboration among subspecialists, because, in most cases, ophthalmologists assess uveitis activity and ocular complications and provide topical therapy, and rheumatologists manage systemic treatment. Thus, the Voting Panel consisted of both pediatric rheumatologists and ophthalmologists with expertise in uveitis evaluation and management. We acknowledge that there were more pediatric rheumatologists than ophthalmologists on the Voting Panel. However, both ophthalmologists were active in the voting process and in all discussions that led to the final recommendations.

A major limitation is the lack of good-quality evidence in children with JIA and uveitis. Only 1 well-conducted RCT on the use of adalimumab and methotrexate in children with JIA-associated uveitis was identified (11). This highlights the necessity for further studies in this population. We limited our recommendations to biologic DMARDs for which there were sufficient observational data and experience. Thus, biologics such as rituximab, golimumab, certolizumab, TNFi biosimilars, and the nonbiologic drug tofacitinib were not considered. These agents may be included in future guidelines. Although we based our recommendations on studies that focused on the treatment of uveitis specifically, it is difficult to separate treatment of arthritis and CAU in studies. Also, cost was not formally taken into consideration in the guideline. There was heavy reliance on 1 high-quality RCT for the guideline (11), and due to the lack of controlled trial data, most recommendations relied on expert opinion. There is an urgent need for RCTs in children with JIA-associated uveitis, which will better inform treatment decisions in this population. In addition, further investigations are needed on the role of antidrug antibodies, long-term ophthalmic screening in children with JIA, and drug tapering in children with refractory uveitis. As more evidence becomes available, these can inform future guidelines.

In summary, these recommendations provide guidance on the evaluation and management of children at risk of and those with JIA-associated uveitis by rheumatology and ophthalmology

21514658, 2019, 6, Downloaded from https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.23871 by Cochrane Colombia, Wiley Online Library on [02/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

experts, current literature, and patient and parent preferences and values, using state-of-the-art GRADE methodology. Persistent uncontrolled uveitis leads to sight-threatening ocular complications and permanent vision loss. The ultimate goal is to maintain optimal vision and ocular health in children with uveitis by limiting the duration of ocular inflammation, minimizing exposure to long-term topical glucocorticoids through the expedited use of systemic medications, and preventing secondary ocular sequelae.

ACKNOWLEDGMENTS

We thank Alexei Grom, MD, Ron Laxer, MD, FRCP, Mindy Lo, MD, PhD, Sampath Prahalad, MD, MSc, Meredith Riebschleger, MD, Angela Byun Robinson, MD, Grant Schulert, MD, PhD, Heather Tory, MD, and Richard Vehe, MD, for serving on the Expert Panel. We thank Suzanne Schrandt with the Arthritis Foundation for her involvement throughout the guideline development process. We thank our patient representative for adding valuable perspectives. We thank Liana Fraenkel, MD, MPH, for leading the Patient Panel meeting, as well as the patients and parents who participated in this guideline project: Linda Aguiar, Jake Anderson, Samantha Bell, Julianne Capron, Stephanie Dodunski, Holly Dwyer, Stephanie Kweicein, Carolina Mejia Pena, and Nikki Reitz, LCSW. We thank the American College of Rheumatology staff, including Regina Parker for assistance in organizing the face-to-face meetings and coordinating the administrative aspects of the project, and Robin Lane for assistance with manuscript preparation. We thank Janet Waters for help in developing the literature search strategy and performing the literature search and updates, and Janet Joyce for peer-reviewing the literature search strategy.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Angeles-Han had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Angeles-Han, Ringold, Beukelman, Lovell, Cuello, Holland, Nigrovic, Sen, Schneider, Halyabar, Turner, Reston.

Acquisition of data. Angeles-Han, Ringold, Beukelman, Lovell, Cuello, Becker, Colbert, Feldman, Holland, Ferguson, Gewanter, Guzman, Horonjeff, Nigrovic, Ombrello, Passo, Rabinovich, Sen, Schneider, Halyabar, Hays, Shah, Sullivan, Szymanski, Turgunbaev, Reston.

Analysis and interpretation of data. Angeles-Han, Ringold, Beukelman, Lovell, Cuello, Becker, Colbert, Feldman, Holland, Ferguson, Gewanter, Guzman, Horonjeff, Nigrovic, Ombrello, Passo, Stoll, Sen, Schneider, Halyabar, Hays, Shah, Sullivan, Turgunbaev, Reston.

REFERENCES

1. Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet 2007;369:767–78.
2. Holland GN, Denove CS, Yu F. Chronic anterior uveitis in children: clinical characteristics and complications. Am J Ophthalmol 2009;147:667–78.
3. Tay-Kearney ML, Schwam BL, Lowder C, Dunn JP, Meisler DM, Vitale S, et al. Clinical features and associated systemic diseases of HLA-B27 uveitis. Am J Ophthalmol 1996;121:47–56.
4. Rosenberg KD, Feuer WJ, Davis JL. Ocular complications of pediatric uveitis. Ophthalmology 2004;111:2299–306.
5. Thorne JE, Woreta F, Kedhar SR, Dunn JP, Jabs DA. Juvenile idiopathic arthritis-associated uveitis: incidence of ocular complications and visual acuity loss. Am J Ophthalmol 2007;143:840–6.
6. Smith JA, Mackensen F, Sen HN, Leigh JF, Watkins AS, Pyatetsky D, et al. Epidemiology and course of disease in childhood uveitis. Ophthalmology 2009;116:1544–51.
7. Gregory AC II, Kempen JH, Daniel E, Kacmaz RO, Foster CS, Jabs DA, et al. Risk factors for loss of visual acuity among patients with uveitis associated with juvenile idiopathic arthritis: the Systemic Immunosuppressive Therapy for Eye Diseases Study. Ophthalmology 2013;120:186–92.
8. Cassidy J, Kivlin J, Lindsley C, Nocton J, Section on Rheumatology, Section on Ophthalmology. Ophthalmologic examinations in children with juvenile rheumatoid arthritis. Pediatrics 2006;117:1843–5.
9. Heiligenhaus A, Niewerth M, Ganser G, Heinz C, Minden K, German Uveitis in Childhood Study Group. Prevalence and complications of uveitis in juvenile idiopathic arthritis in a population-based nation-wide study in Germany: suggested modification of the current screening guidelines. Rheumatology (Oxford) 2007;46:1015–9.
10. Henderson LA, Zurakowski D, Angeles-Han ST, Lasky A, Rabinovich CE, Lo MS, et al. Medication use in juvenile uveitis patients enrolled in the Childhood Arthritis and Rheumatology Research Alliance Registry. Pediatr Rheumatol Online J 2016;14:9.
11. Ramanan AV, Dick AD, Jones AP, McKay A, Williamson PR, Compeyrot-Lacassagne S, et al. Adalimumab plus methotrexate for uveitis in juvenile idiopathic arthritis. N Engl J Med 2017;376:1637–46.
12. Ringold S, Angeles-Han ST, Beukelman T, Lovell DJ, Cuello CA, Becker ML, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for non-systemic polyarthritis, sacroiliitis, and enthesitis. Arthritis Care Res 2019;71:717–34.
13. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–6.
14. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 2013;66:719–25.
15. Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation—determinants of a recommendation's direction and strength. J Clin Epidemiol 2013;66:726–35.
16. Jabs DA, Nussenblatt RB, Rosenbaum JT; Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data: results of the First International Workshop. Am J Ophthalmol 2005;140:509–16.
17. Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. J Clin Epidemiol 2011;64:395–400.
18. Jaeschke R, Guyatt GH, Dellinger P, Schunemann H, Levy MM, Kunz R, et al. Use of GRADE grid to reach decisions on clinical practice guidelines when consensus is elusive. BMJ 2008;337:a744.
19. Kodsi SR, Rubin SE, Milojevic D, Ilowite N, Gottlieb B. Time of onset of uveitis in children with juvenile rheumatoid arthritis. J AAPOS 2002;6:373–6.
20. Grassi A, Corona F, Casellato A, Carnelli V, Bardare M. Prevalence and outcome of juvenile idiopathic arthritis-associated uveitis and relation to articular disease. J Rheumatol 2007;34:1139–45.

21514658, 2019, 6, Downloaded from https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.23871 by Cochrane Colombia, Wiley Online Library on [02/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

21. Reininga JK, Los LI, Wulffraat NM, Armbrust W. The evaluation of uveitis in juvenile idiopathic arthritis (JIA) patients: are current ophthalmologic screening guidelines adequate? Clin Exp Rheumatol 2008;26:367–72.
22. Zannin ME, Buscain I, Vittadello F, Martini G, Alessio M, Orsoni JG, et al. Timing of uveitis onset in oligoarticular juvenile idiopathic arthritis (JIA) is the main predictor of severe course uveitis. Acta Ophthalmol 2012;90:91–5.
23. Papadopoulou M, Zetterberg M, Oskarsdottir S, Andersson Gronlund M. Assessment of the outcome of ophthalmological screening for uveitis in a cohort of Swedish children with juvenile idiopathic arthritis. Acta Ophthalmol 2017;95:741–7.
24. Chia A, Lee V, Graham EM, Edelsten C. Factors related to severe uveitis at diagnosis in children with juvenile idiopathic arthritis in a screening program. Am J Ophthalmol 2003;135:757–62.
25. Lerman MA, Lewen MD, Kempen JH, Mills MD. Uveitis reactivation in children treated with tumor necrosis factor α inhibitors. Am J Ophthalmol 2015;160:193–200.
26. Wolf MD, Lichter PR, Ragsdale CG. Prognostic factors in the uveitis of juvenile rheumatoid arthritis. Ophthalmology 1987;94:1242–8.
27. Musson DG, Bidgood AM, Olejnik O. An in vitro comparison of the permeability of prednisolone, prednisolone sodium phosphate, and prednisolone acetate across the NZW rabbit cornea. J Ocul Pharmacol 1992;8:139–50.
28. Slabaugh MA, Herlihy E, Ongchin S, van Gelder RN. Efficacy and potential complications of difluprednate use for pediatric uveitis. Am J Ophthalmol 2012;153:932–8.
29. Kothari S, Foster CS, Pistilli M, Liesegang TL, Daniel E, Sen HN, et al. The risk of intraocular pressure elevation in pediatric noninfectious uveitis. Ophthalmology 2015;122:1987–2001.
30. Thorne JE, Woreta FA, Dunn JP, Jabs DA. Risk of cataract development among children with juvenile idiopathic arthritis-related uveitis treated with topical corticosteroids. Ophthalmology 2010;117:1436–41.
31. Angeles-Han ST, Lo MS, Henderson LA, Lerman MA, Abramson L, Cooper AM, et al. Childhood Arthritis and Rheumatology Research Alliance consensus treatment plans for juvenile idiopathic arthritis–associated and idiopathic chronic anterior uveitis. Arthritis Care Res (Hoboken) 2019;71:482–91.
32. Tynjala P, Lindahl P, Honkanen V, Lahdenne P, Kotaniemi K. Infliximab and etanercept in the treatment of chronic uveitis associated with refractory juvenile idiopathic arthritis. Ann Rheum Dis 2007;66:548–50.
33. Foeldvari I, Becker I, Horneff G. Uveitis events during adalimumab, etanercept, and methotrexate therapy in juvenile idiopathic arthritis: data from the Biologics in Pediatric Rheumatology Registry. Arthritis Care Res (Hoboken) 2015;67:1529–35.
34. Saurenmann RK, Levin AV, Feldman BM, Laxer RM, Schneider R, Silverman ED. Risk of new-onset uveitis in patients with juvenile idiopathic arthritis treated with anti-TNFα agents. J Pediatr 2006;149:833–6.
35. Tappeiner C, Schenck S, Niewerth M, Heiligenhaus A, Minden K, Klotsche J. Impact of antiinflammatory treatment on the onset of uveitis in juvenile idiopathic arthritis: longitudinal analysis from a nationwide pediatric rheumatology database. Arthritis Care Res (Hoboken) 2016;68:46–54.
36. Klotsche J, Niewerth M, Haas JP, Huppertz HI, Zink A, Horneff G, et al. Long-term safety of etanercept and adalimumab compared to methotrexate in patients with juvenile idiopathic arthritis (JIA). Ann Rheum Dis 2016;75:855–61.
37. Kahn P, Weiss M, Imundo LF, Levy DM. Favorable response to high-dose infliximab for refractory childhood uveitis. Ophthalmology 2006;113:860–4.
38. Tambralli A, Beukelman T, Weiser P, Atkinson TP, Cron RQ, Stoll ML. High doses of infliximab in the management of juvenile idiopathic arthritis. J Rheumatol 2013;40:1749–55.
39. Correll CK, Bullock DR, Cafferty RM, Vehe RK. Safety of weekly adalimumab in the treatment of juvenile idiopathic arthritis and pediatric chronic uveitis. Clin Rheumatol 2018;37:549–53.
40. Sobrin L, Christen W, Foster CS. Mycophenolate mofetil after methotrexate failure or intolerance in the treatment of scleritis and uveitis. Ophthalmology 2008;115:1416–21.
41. Bichler J, Benseler SM, Krumrey-Langkammerer M, Haas JP, Hügle B. Leflunomide is associated with a higher flare rate compared to methotrexate in the treatment of chronic uveitis in juvenile idiopathic arthritis. Scand J Rheumatol 2015;44:280–3.
42. Kolomeyer AM, Tu Y, Miserocchi E, Ranjan M, Davidow A, Chu DS. Chronic non-infectious uveitis in patients with juvenile idiopathic arthritis. Ocul Immunol Inflamm 2016;24:377–85.
43. Tappeiner C, Miserocchi E, Bodaghi B, Kotaniemi K, Mackensen F, Gerloni V, et al. Abatacept in the treatment of severe, longstanding, and refractory uveitis associated with juvenile idiopathic arthritis. J Rheumatol 2015;42:706–11.
44. Birolo C, Zannin ME, Arsenyeva S, Cimaz R, Miserocchi E, Dubko M, et al. Comparable efficacy of abatacept used as first-line or second-line biological agent for severe juvenile idiopathic arthritis-related uveitis. J Rheumatol 2016;43:2068–73.
45. Zulian F, Balzarin M, Falcini F, Martini G, Alessio M, Cimaz R, et al. Abatacept for severe anti–tumor necrosis factor α refractory juvenile idiopathic arthritis–related uveitis. Arthritis Care Res (Hoboken) 2010;62:821–5.
46. Calvo-Rio V, Santos-Gomez M, Calvo I, Gonzalez-Fernandez MI, Lopez-Montesinos B, Mesquida M, et al. Anti–interleukin-6 receptor tocilizumab for severe juvenile idiopathic arthritis–associated uveitis refractory to anti–tumor necrosis factor therapy: a multicenter study of twenty-five patients. Arthritis Rheumatol 2017;69:668–75.
47. Tappeiner C, Mesquida M, Adan A, Anton J, Ramanan AV, Carreno E, et al. Evidence for tocilizumab as a treatment option in refractory uveitis associated with juvenile idiopathic arthritis. J Rheumatol 2016;43:2183–8.
48. Chang JH, McCluskey PJ, Wakefield D. Acute anterior uveitis and HLA-B27. Surv Ophthalmol 2005;50:364–88.
49. Breitbach M, Tappeiner C, Bohm MR, Zurek-Imhoff B, Heinz C, Thanos S, et al. Discontinuation of long-term adalimumab treatment in patients with juvenile idiopathic arthritis-associated uveitis. Graefes Arch Clin Exp Ophthalmol 2017;255:171–7.
50. Kalinina Ayuso V, van de Winkel EL, Rothova A, de Boer JH. Relapse rate of uveitis post-methotrexate treatment in juvenile idiopathic arthritis. Am J Ophthalmol 2011;151:217–22.
51. Bou R, Adan A, Borras F, Bravo B, Calvo I, De Inocencio J, et al. Clinical management algorithm of uveitis associated with juvenile idiopathic arthritis: interdisciplinary panel consensus. Rheumatol Int 2015;35:777–85.
52. Levy-Clarke G, Jabs DA, Read RW, Rosenbaum JT, Vitale A, van Gelder RN. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. Ophthalmology 2014;121:785–96.
53. Heiligenhaus A, Michels H, Schumacher C, Kopp I, Neudorf U, Niehues T, et al. Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis. Rheumatol Int 2012;32:1121–33.
54. Constantin T, Foeldvari I, Anton J, de Boer J, Czitrom-Guillaume S, Edelsten C, et al. Consensus-based recommendations for the management of uveitis associated with juvenile idiopathic arthritis: the SHARE initiative. Ann Rheum Dis 2018;77:1107–17.

21514658, 2019, 6, Downloaded from https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.23871 by Cochrane Colombia, Wiley Online Library on [02/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Rheumatol Int (2012) 32:1121–1133
DOI 10.1007/s00296-011-2126-1

REVIEW ARTICLE

Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis

A. Heiligenhaus · H. Michels · C. Schumacher · I. Kopp · U. Neudorf · T. Niehues · H. Baus · M. Becker · B. Bertram · G. Dannecker · C. Deuter · I. Foeldvari · M. Frosch · G. Ganser · M. Gaubitz · G. Gerdes · G. Horneff · A. Illhardt · F. Mackensen · K. Minden · U. Pleyer · M. Schneider · N. Wagner · M. Zierhut

Received: 11 April 2011 / Accepted: 22 August 2011 / Published online: 15 November 2011
© Springer-Verlag 2011

Abstract Uveitis in juvenile idiopathic arthritis (JIA) is frequently associated with the development of complications and visual loss. Topical corticosteroids are the first-choice therapy, and immunosuppression is commonly used. However, treatment has not been standardized. Representatives from the German Ophthalmological Society, Society for Childhood and Adolescent Rheumatology, and the German Society for Rheumatology reached consensus on a standardized treatment strategy according to disease severity in the individual patient. The recommendations were based on a systematic literature analysis in MEDLINE and consensus expert meetings. Evidence and recommendations were graded, and an algorithm for anti-inflammatory treatment and final statements confirmed in a Delphi method. An interdisciplinary, evidence-based treatment guideline for JIA uveitis is presented.

Guidelines of the German Ophthalmological Society (DOG) and the Society for Childhood and Adolescent Rheumatology (GKJR) in collaboration with the following professional societies: Working group of the Scientific Medical Specialty Societies (AWMF), Professional Association of Ophthalmologists (BVA), German Society for Rheumatology (DGRh), Parents' Association for Children with Uveitis and Their Families.

A. Heiligenhaus (✉) · C. Schumacher
Department of Ophthalmology, St. Franziskus Hospital, Hohenzollernring 74, 48145 Muenster, Germany
e-mail: arnd.heiligenhaus@uveitis-zentrum.de

A. Heiligenhaus · C. Schumacher
German Ophthalmological Society, Augenabteilung, Uveitiszentrum, St. Franziskus Hospital, Mu¨nster, Germany

H. Michels
Society for Childhood and Adolescent Rheumatology, Deutsches Zentrum fu¨r Kinder- und Jugendrheumatologie, Garmisch Partenkirchen, Germany

I. Kopp
Working group of the Scientific Medical Specialty Societies, Marburg, Germany

U. Neudorf
Society for Childhood and Adolescent Rheumatology, Universita¨ts Kinderklinik, Essen, Germany

T. Niehues
Society for Childhood and Adolescent Rheumatology, HELIOS Klinikum Krefeld, Zentrum fu¨r Kinder- und Jugendmedizin, Krefeld, Germany

H. Baus
Parents' Association for Children with Uveitis and Their Families, Frankfurt, Germany

M. Becker
German Ophthalmological Society, Stadtspital Triemli, Augenklinik, Zu¨rich, Switzerland

B. Bertram
Professional Association of Ophthalmologists, Augenarztpraxis, Aachen, Germany

G. Dannecker
Society for Childhood and Adolescent Rheumatology, Olgahospital, Klinik fu¨r Kinder- und Jugendmedizin, Pa¨diatrie, Stuttgart, Germany

C. Deuter · M. Zierhut
German Ophthalmological Society, Universita¨ts-Augenklinik, Tu¨bingen, Germany

I. Foeldvari
Society for Childhood and Adolescent Rheumatology, Hamburger Zentrum fu¨r Kinder- und Jugendrheumatologie, Klinikum Eilbeck, Hamburg, Germany

Keywords Adolescence · Children · Consensus · Evidence-based medicine · Juvenile idiopathic arthritis · Rheumatic diseases · Therapy · Uveitis

Preliminary comments

Uveitis in childhood can develop in conjunction with various inflammatory rheumatic diseases, and in particular with juvenile idiopathic arthritis (JIA). Indeed, chronic forms of these diseases are frequently associated with visual deterioration. In previous patient cohorts, the rate of blindness was high (up to 30%); however, this can be significantly reduced if screening is adequate and all currently available forms of treatment are exhausted [1, 2]. Nonetheless, compared to forms of uveitis that develop in adulthood, the risk of irreparable damage and the associated reduction in quality of life is still very high for children with JIA-associated uveitis. Thus, it is particularly important that these patients receive adequate treatment early on before permanent damage has developed.

Currently available studies of uveitis in patients with childhood arthritis have established certain clinical and laboratory parameters as prognostic factors. Long-term complications and a poor visual course were found particularly frequently if vision was poor at first presentation (\20/60), inflammatory activity was high at first diagnosis of uveitis, cataracts had formed, uveitis onset before arthritis had developed, interval between the onset of arthritis and uveitis was short (\6 months), early onset of disease, long duration of uveitis, macular edema, dense vitreous opacity, ocular hypotony, and glaucoma [1, 3–18].

The presence of complications at initial diagnosis represents an important prognostic criterion for further complications to develop [19], and a long period of chronic inflammation seems to be particularly critical. Even a low number of cells in the anterior chamber ([0.5+) is then associated with an increased risk of loss in visual acuity [16].

According to these studies, early diagnosis is highly important for long-term prognosis (evidence and recommendation level IIIA). Therefore, close screening should be commenced directly after arthritis has appeared. The screening intervals recommended to date in these studies are oriented on the incidence of uveitis for the various arthritis subtypes, presence of antinuclear antibodies (ANA), duration of arthritis, and the typical signs of uveitis (symptoms, red and painful versus no symptoms on the external white of the eye [19, 20]. Although no controlled studies have been conducted, the findings published prior to the screening era and before immunosuppressive drugs were used suggest that for a severe course of disease, the long-term prognosis can be improved by appropriate screening and the use of these substances.

Aims/goals

The treatment of uveitis in patients with JIA has not been standardized; therefore, the aim of the present guideline is

M. Frosch
Society for Childhood and Adolescent Rheumatology, Universita¨tskinderklinik Mu¨nster, Klinik und Poliklinik fu¨r Kinder- und Jugendmedizin, Mu¨nster, Germany

G. Ganser
Society for Childhood and Adolescent Rheumatology, St.-Josefs-Stift, Sendenhorst, Kinder- und Jugendrheumatologie, Sendenhorst, Germany

M. Gaubitz
German Society for Rheumatology, Akademie fu¨r Manuelle Therapie, Mu¨nster, Germany

G. Gerdes
Parents' Association for Children with Uveitis and Their Families, Mu¨nster, Germany

G. Horneff
Society for Childhood and Adolescent Rheumatology, Asklepios Klinik St. Augustin, Zentrum fu¨r Kinder- und Jugendmedizin, Sankt Augustin, Germany

A. Illhardt
Psychologischer Dienst, St. Josef-Stift, Sendenhorst, Kinder- und Jugendrheumatologie, Sendenhorst, Germany

F. Mackensen
German Ophthalmological Society, Universita¨ts-Augenklinik, Heidelberg, Germany

K. Minden
Society for Childhood and Adolescent Rheumatology, Deutsches Rheumaforschungszentrum, Berlin, Germany

U. Pleyer
German Ophthalmological Society, Universita¨tsaugenklinik, Charite, Berlin, Germany

M. Schneider
German Society for Rheumatology, Heinrich-Heine-Universita¨t, Klinik, und Poliklinik fu¨r Rheumatologie, Du¨sseldorf, Germany

N. Wagner
Society for Childhood and Adolescent Rheumatology, Rheinisch-Westfa¨lische Technische Hochschule, Kinder- und Jugendmedizin, Aachen, Germany

to develop a standardized, state-of-the-art, and qualitatively high treatment strategy according to disease severity in the individual patient that is based on the current literature and expert consensus. To that end, we defined the following goals: improve patient care, implement the current status of evidence-based medicine on the subject of uveitis, establish reasonable diagnostic and screening intervals, and develop a treatment algorithm that includes a flow diagram and facilitates patient care in interdisciplinary networks.

Methods

These guidelines were based on the consensus statements for the treatment of JIA-associated uveitis from 2004 [21] and for ''rheumatic uveitis'' from 2007 [22] and the treatment of JIA [23]. Representatives from the specialty societies DOG, GKJR, and DGRh and from patient groups joined forces to develop these guidelines. The methodological concept followed the German Instrument for Methodological Guideline Appraisal (DELBI [24, 25]).

The guidelines coordinators (AH, TN, and CS) conducted a systematic search of the literature on the subject of ''anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis''.

German and English were taken as publication languages. For the MEDLINE search, we employed the terms ''juvenile idiopathic arthritis'' (including the ACR und EULAR classifications) und ''uveitis and therapy''. During the last years, numerous classifications for rheumatic diseases of childhood were employed; therefore, we included the International League of Associations for Rheumatology [26] classification, American College of Rheumatology [27], and European League Against Rheumatism [28, 29] classifications and extended the search terms to incorporate juvenile rheumatoid arthritis (ACR) and juvenile chronic arthritis (EULAR). Furthermore, the term iridocyclitis, which was frequently used before the current standardization of uveitis nomenclature [30] of anterior uveitis was implemented, was added to the search terms. Owing to the insufficient body of evidence on the subject, we considered publications from the past 15 years.

On the reference date 15 November 2009, 305 publications were found (Table 1). Restricting the search to ''humans'' reduced the number of publications to 198. The results were assessed for plausibility and completeness.

The primary literature was then graded concerning evidence and recommendations (Tables 2, 3). For the various treatment measures, evidence tables were created (Tables 4, 5, 6, 7). Using an algorithm of frequently used courses of therapy as orientation, we developed key recommendations with graded levels of evidence and recommendation and drafted corresponding texts and guideline synopses for clinical questions that had been adequately addressed. These were distributed to all conference participants beforehand.

The 1-day consensus conference took place on 5 February 2010 in Muenster, Germany, headed by Prof. I. Kopp (AWMF) and Prof. A. Heiligenhaus with a 92% participation. After thorough discussion during the conference, the key statements were reworked and a consensus formulated. By subsequently employing a Delphi procedure,

Table 1 Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis

Key words	Publications (*N*)
Juvenile idiopathic (rheumatoid and chronic) arthritis and uveitis (iridocyclitis) and therapy	305
Limits: humans, published in the last 15 years	198
Limits: corticosteroids	32
Limits: nonsteroidal anti-inflammatory drugs	21
Limits: cyclophospamide	3
Limits: chlorambucil	3
Limits: methotrexate	41
Limits: cyclosporine	14
Limits: azathioprine	7
Limits: TNF-alpha inhibitors	33

PUBMED literature search (www.ncbi.nlm.nih.gov). ''Manually'' excluded: diagnostic studies, juvenile idiopathic arthritis, surgery, extraocular manifestations, and intermediate and posterior uveitis

Table 2 Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis

Level	Evidence
I	[1 randomized, controlled study (RCT) of good quality
II	Single RCT, [1 controlled, but nonrandomized study or [1 RCT of poorer quality
	Cohort or case–control study preferred from more than one research group or from more than one center
	Observations showing a very clear effect in noncontrolled studies
III	Expert opinion, clinical experience, or descriptive studies, cohort- or case–control studies of poorer quality

Table 3 Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis

Level	Recommendation
A	Strong recommendation
B	Recommendation
0	Open

Table 4 Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis (nonsteroidal antiphlogistics)

Drug	Dosage	Comment	Level of evidence and recommendation	Reference
Topical			IB	
Indomethacin	2–3×	Low efficacy compared to corticosteroids		[38–40]
Diclofenac	2–3×	Low efficacy compared to corticosteroids		[41]
Ketorolac trometamole	2–3×	Low efficacy compared to corticosteroids		
Tolmetine				[34, 39]
Systemic[#]			III0	
Diclofenac	2–3 mg/kg body weight/day in 3 doses; 1 single dose possible	The long half-life of the retard drugs is beneficial. Low efficacy compared to corticosteroids		[40]
Ibuprofen	20–40 mg/kg body weight/day in 3–4 doses	Availability as suspension is beneficial. Low efficacy compared to corticosteroids		
Indomethacin	1–3 mg/kg body weight/day in 2–3 doses	Availability as suspension is beneficial. Low efficacy compared to corticosteroids		
Naproxen	10–15 mg/kg body weight/day in 2 doses	Low efficacy compared to corticosteroids		

[#] none of these drugs approved for this indication

the free text for the guidelines and the algorithms were discussed again and formally approved by a vote.

All individuals who were involved in developing the guidelines declared that they had no financial or other conflicts of interest that would systematically affect the content of the guidelines. The process for developing the guidelines was financially supported by DOG and GKJR.

Anti-inflammatory therapy

Treatment of patients with uveitis and inflammatory rheumatic diseases is not curative; these individuals can only receive symptomatic treatment to suppress the inflammation. Therefore, attempts to ''eradicate the disease focus'' such as by extracting teeth are superfluous unless the teeth actually require treatment because of specific findings (IIIA). The objectives of treatment are to manage acute episodes or complications, treat the systemic underlying disease, give prophylaxis for recurrence and complications, avoid undesirable drug effects, and preserve vision.

Basic treatment principles

Uveitis is treated with respect to inflammatory activity, complications, and risk factors for losing visual acuity. For medical treatment, the underlying inflammatory rheumatic disease must also be taken into consideration. ANA-positive patients with chronic anterior uveitis who have not previously shown any clinical signs of an inflammatory rheumatic disease should be treated like patients with JIA-associated uveitis as the two conditions are highly comparable (consensus group, evidence and recommendation level III0).

It is recommended that treatment comprises three phases (see Fig. 1). This is based on the evidence for or against a treatment according to the literature (Tables 2, 3) and on consensus from the guidelines group concerning preferred clinical treatment strategies. Information about the preferred therapy is presented. Key statements are listed in Table 8.

Diagnosis and treatment should best be jointly planned and monitored by the ophthalmologist and pediatrician (pediatric rheumatologist). The ophthalmologist is responsible for giving local treatment, recommending further systemic anti-inflammatory treatment of uveitis, and treating possible complications.

Patients with chronically active and severe uveitis should be referred to physicians who are competent in treating JIA-associated uveitis (in particular at uveitis centers with core expertise). If systemic immunosuppression is required, this should be given and monitored by an experienced pediatric rheumatologist upon the advice of an ophthamology specialist. For JIA therapy, we refer to the corresponding interdisciplinary S2 guidelines [23].

Managing a relapse of uveitis

Clearing uveitis with and without corticosteroid treatment

A prospective, randomized, double-blind study showed that a relapse of uveitis clears better by using local corticosteroids than placebo [31]. Thus, active uveitis should be

Table 5 Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis (Corticosteroids)

Drug	Dosage	Comment	Level of evidence and recommendation	Reference
Topical[#]			IA	
Prednisolone acetate 1%	1 × up to hourly	High efficacy, high risk of glaucoma		[39, 46]
Dexamethasone phosphate 0.1%	1 × up to hourly	High efficacy; high risk of glaucoma		
Rimexolone 1%	1 × up to 5×	Moderately effective		[45, 46]
Subconjunctival or orbital floor injections			IIIA	
Dexamethasone phosphate	2–4 mg	Effective 1–3 days		
Triamcinolone acetonide	20–40 mg	Effective 1–2 months		
Intravitreal injections			III0	
Triamcinolone acetonide	2–4 mg	Effective 1–2 months		[101–104]
Systemic[#]			IIIA	[35]
Oral high-dose therapy	≥1–2 mg/kg body weight/day prednisolone equivalent	For a treatment duration of several weeks, relevant side effects can always be expected with respect to the cumulative drug dose		
Oral medium-dose therapy	0.2 and \1.0 mg/kg body weight/day prednisolone equivalent	For a treatment duration of several weeks, relevant side effects can always be expected with respect to the cumulative drug dose		
Oral low-dose therapy	≤0.15 mg/kg body weight/day prednisolone equivalent	Long-term side effects low; individually different side effects, growth retardation rare		
Intravenous pulse therapy	Normally 20–30 mg/body weight intravenous methylprednisolone (max. 1 g/dose) for 1–3 days	At intervals of ≥4 weeks lower long-term risk of side effects than for oral medium-or high-dose therapy; possibly indicated for ocular hypotony, vitreous body opacity and macular edema		[43]

[#] approved treatment for this indication

treated accordingly (IA) and commenced as early as possible.

The relevant criteria for assessing the efficacy of anti-inflammatory treatment are presently the subject of controversial debate. According to the recommendations of the Multinational Interdisciplinary Working Group for Uveitis in Childhood (MIWGUC), it is important—in addition to determining cells in the anterior chamber—to assess structural complications in the eye.

Indications for anti-inflammatory treatment

The goal of treating typical JIA-associated anterior uveitis should be ''no cells in the anterior chamber.'' Treatment should be initiated when [0.5+ cells are present [16, 30].

Fibrin formation in the anterior chamber and keratocytic precipitates with corneal edema and loss of visual acuity also require treatment. The question of whether the presence of only endothelial precipitates or a positive Tyndall effect is important for therapeutic decision making is presently being controversially debated. Alone, however, they do not represent a clear indication for treatment. Increased flare values indicate a disorder in the blood-aqueous fluid barrier and correlate with presence of complications and a poor visual outcome [32].

Should prognostic factors for threatening loss of vision be confirmed, anti-inflammatory treatment should be intensified. According to comprehensive studies, these factors include poor initial vision, ocular hypotony, glaucoma, cataract, macular edema, and dense vitreous body opacification ([2+) [1–18, 33] (consensus group, IIIB).

Evidence of band keratopathy, synechiae, cataract, or glaucoma in inactive uveitis does not per se comprise an indication for anti-inflammatory therapy (consensus group, IIIA). Associated with persisting inflammation, however, these symptoms indicate severe disease and immunosuppression is recommended (consensus group, IIIA).

In contrast, macular edema, ocular hypotony, and rubeosis iridis require that anti-inflammatory treatment be initiated or intensified even if no cells are detected in the anterior chamber as these conditions are often associated with chronic inflammation of the affected tissue (consensus group, IIIA).

96

Table 6 Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis (immunosuppressive drugs)

Drug	Dosage	Comment	Level of evidence and recommendation	Reference
Methotrexate	10–15 mg/m^2 week	Oral or subcutaneous administration	IIIA	[48, 52–59]
Cyclosporine A	≤3 mg/kg body weight/day in 2 doses	Gel capsules or syrup	III0 for monotherapy	[67, 69]
			IIIB for combination therapy	[65, 66, 68, 71]
Azathioprine	2–3 mg/kg body weight/day	Thiopurine methyltransferase levels should be determined to prevent severe hematotoxicity	IIIB	[62–64]
Mycofenolate mofetil	500–2,000 mg/day in 2 doses		III0	[78–80]
Sulfasalazine	500–2,000 mg/day in 2 doses		II0 for HLA-B27-positive patients	[81–83]
Chlorambucil	1–1.5 mg/kg body weight/day	High rate of adverse effects, thus not recommended	IIIA	[76, 77]

[#] none of these drugs approved for this indication

Table 7 Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis (TNF-alpha inhibitors)

Drug	Dosage	Comment	Level of evidence and recommendation	Reference
Adalimumab	24 mg/m^2 at 4–13 years or ≥ 14 years 40 mg every 2 weeks	Subcutaneous injection; currently, preferred TNF-alpha inhibitor	IIIA	[74, 93, 105]
Infliximab	5–10 mg/kg body weight every 2–8 weeks	Intravenous administration; intensive care required because of possible reaction to the infusion. Currently, second-choice TNF-alpha inhibitor	IIA	[85–91, 95, 96, 105]
Etanercept	0.4 mg/kg body weight 2×/week or 0.8 mg/kg 1×/week	Subcutaneous injections; occasionally associated with first presentation or worsening of uveitis; thus, only limited recommendation	I0	[85, 90, 97, 99, 100]

[#] none of these drugs approved for this indication

Algorithm for anti-inflammatory treatment

Treatment step 1

Topical corticosteroids High-potency glucocorticoids are more efficacious than low-potency preparations [31–35]; therefore, the high-potency drugs, such as prednisolone acetate 1% or dexamethasone 0.1%, should be used and not the low-potency alternatives, such as rimoxolone (consensus group IIIA). To prevent amblyopia (children under the age of 7 are at high risk), drops should be instilled when the children are awake and ointment applied for the night (consensus group IIIA).

In the first 3 days of a relapse, the drops should be applied frequently during the waking hours. How often the drops are instilled should be adapted to the severity of the inflammation (anterior chamber cells, fibrin, new synechiae), every 2 h or even hourly. The dosage should then be reduced within 6 weeks, according to the degree of inflammation (consensus group IIIA).

Even children who are being treated with topical corticosteroids need to be monitored for possible systemic adverse effects (e.g., Cushing syndrome). This risk increases with bilateral and high dosages (e.g., hourly) of high-potency corticosteroids (e.g., prednisolone 1%), particularly in young children (under 4 years) [36, 37].

Nonsteroidal antiphlogistics Topical nonsteroidal antiphlogistics play only a minor role in treating uveitis. Two

97

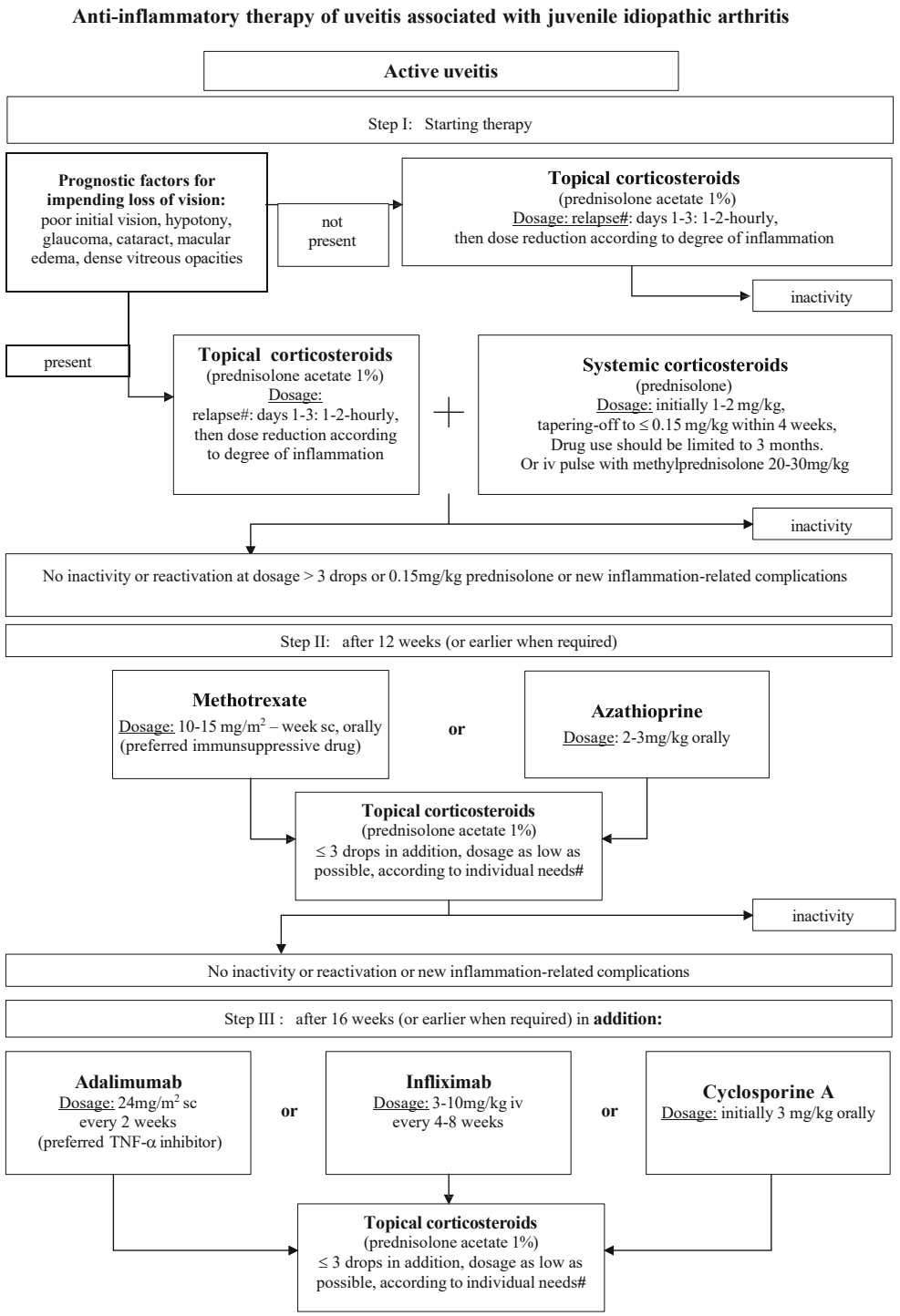


Fig. 1 Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis. Algorithm for anti-inflammatory treatment

randomized, controlled studies showed that *topical* treatment using nonsteroidal antiphlogistics was effective, but not as good as topical corticosteroids for treating mild, acute uveitis [34, 38, 39] (IB). Therefore, treating uveitis attacks with nonsteroidal antiphlogistics alone is not recommended (IB). *Systemic* nonsteroidal antiphlogistics were also reported to be less efficacious than high-potency topical corticosteroids [8, 40, 41] (III0). All these studies were conducted in adults and not in children with JIA uveitis. In summary, nonsteroidal antiphlogistics could only be recommended as adjuvant medication in cases of low numbers of cells (≤1+) in the anterior chamber.

98

Table 8 Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis (Key statements)

1.	Active uveitis must be treated (IA)
2.	Topical corticosteroids should be used initially to treat active anterior uveitis (IA)
3.	Topical and systemic nonsteroidal antiphlogistics should not be used alone to treat active anterior uveitis (IB)
4.	For severe, active uveitis presenting with prognostic factors indicating uveitis-related, impending loss of vision (poor vision at initial presentation, hypotony, glaucoma, cataract, macular edema, or dense vitreous body opacification), systemic corticosteroids should be considered for a limited period of a few weeks in addition to topical therapy (IIIA)
5.	For chronic anterior uveitis, the dosage of topical corticosteroids should be as low as possible, according to the needs of the individual patient. If inactivity is achieved by maintenance therapy ≤3 drops daily within 3 months, systemic immunosuppressive treatment is not required (IIIIA)
6.	Systemic immunosuppression should be initiated if inactivity cannot be achieved under topical corticosteroids ≤3 drops and/or within 3 months while under systemic maintenance corticosteroid therapy (0.15 mg kg/body weight/day prednisolone equivalent) or if undesired adverse effects of the corticosteroids or new inflammation-related complications of uveitis develop. For a very severe course of uveitis, a correspondingly shorter interval can be chosen (IIIA)
7.	If inactivity cannot be achieved in the eyes after a maximum of 16 weeks of treatment with one immunosuppressive drug and topical corticosteroid therapy ≤3 drops daily or if new inflammation-related complications of uveitis develop, another immunosuppressive drug (e.g., cyclosporin A) or a biological (e.g., adalimumab) should be added to the regimen. For a very severe course of uveitis, a correspondingly shorter interval can be chosen (IIA)
8.	If immunosuppressive drugs are administered, the physician should have experience in administering and monitoring treatment with the respective drug (IIIA)
9.	For severe uni- or bilaterally active uveitis associated with prognostic factors indicating uveitis-related, impending loss of vision (hypotony, macular edema, or dense vitreous body opacification), corticosteroid injections to the eye can be considered as ''rescue therapy'' (III0)
10.	To prevent or treat posterior synechiae associated with active anterior uveitis, cycloplegics should be administered (IIIA)

Systemic corticosteroids Oral administration of corticosteroids is generally less effective in reducing the number of anterior chamber cells than frequently instilling eye drops ([8,42], consensus group) (see Table 8). Oral treatment with corticosteroids such as prednisolone is normally initially administered at a dose of 1–2 mg/kg body weight (consensus group, IIIA). Alternatively, high-dose intravenous administration of methylprednisolone (dosage 20–30 mg/kg for 3 days) can be considered [35, 43] (IIIA).

When children receive systemic corticosteroid treatment, not only do the numerous known complications need to be taken into consideration (e.g., increase in intraocular pressure, cataracts, weight increase, and diabetic metabolism situation) but also growth retardation. Therefore, the dose should be tapered to under 0.15 mg/kg body weight within 4 weeks and drug use be limited to 3 months. The development of intraocular pressure is dose dependent under systemic corticosteroid treatment, and secondary development of cataract is subject to individual propensity for this condition [17, 35, 44].

Treatment of chronic or chronic, recurring uveitis

For chronic or chronic, recurring uveitis, treatment with higher-potency corticosteroid eye drops should be initiated (e.g., prednisolone acetate 1%; IA). After 4–6 weeks, the patient can be switched to less effective drugs (hence, drugs causing fewer adverse effects: e.g., rimexolone) [35, 45, 46] (IA). In individual cases, the lesser efficacy of the anti-inflammatory preparations needs to be weighed against the problems associated with more frequent application and compliance.

In many children, chronic irritation can often be stabilized with topical corticosteroids alone. Frequently, however, long-term treatment over several years is required [3, 42] (consensus group IIIA).

If high-dose treatment with eye drops is given for several months, the risk of typical adverse effects increases. The individual propensity for this, however, varies highly. Currently, it is presumed that three doses of drug (e.g., prednisolone acetate 1% or dexamethasone 0.1%) daily over several months per year are associated with an increased risk of cataract and glaucoma [47]. Therefore, we should strive to give the lowest possible dose. During periods with inactivity, it may be sufficient to give the drops once daily on alternating days. Corticosteroid treatment should not be ended abruptly in order to avoid a rebound effect.

In cases of aphakia or pseudophakia, it may be possible, or even necessary, to give more generous dosages of topical corticosteroids (e.g., to decrease the number of giant cells on the intraocular lens) as long as the intraocular pressure does not increase.

Rimexolone may be effective in cases of steroid-induced ocular hypertension, but compared to prednisolone acetate 1% and dexamethasone 0.1%, it shows a lower anti-inflammatory effect [35, 45] (IA).

99

The course of the inflammation decides whether low-dose maintenance treatment is needed. The dosage and choice of corticosteroid should be based on the individual circumstances. If inactivity can be achieved, further steps are not required for the time being.

Treatment step II

If the inflammation in the eyes has not resolved within 12 weeks (even sooner after clinical judgement) under treatment with topical corticosteroids maximally 3 times daily or in cases of recurring uveitis under a systemic corticosteroid dosage of more than 0.15 mg/kg body weight or if new uveitis complications develop, the anti-inflammatory treatment needs to be intensified and immunosuppressives and/or biologicals added to the regimen.

Treatment with immunosuppressives and biologicals If uveitis persists after all the aforementioned drugs have been tried or if uveitis recurs under a high dose of corticosteroids and severe, undesired adverse effects of the drug develop, treatment with immunosuppressives should be initiated. According to current knowledge, biologicals should not be given before trying the classic immunosuppressives.

It has been repeatedly shown that immunosuppressives can clear uveitis and have a corticosteroid-sparing effect. Despite frequently expressed reservations, these drugs are associated with a low rate of adverse effects if used adequately and monitored [48–50]. By using immunosuppressive treatment, visual prognosis and rate of complications could be improved in JIA-associated uveitis [13, 51]. Although corticosteroids can be spared under immunosuppression, low-dose maintenance treatment with corticosteroid drops (≤3/day) often needs to be continued. Whether treating JIA with immunosuppression early on prevents uveitis from developing later is the subject of controversial debate.

A basic precondition for applying immunosuppressive drugs or biologicals to treat persisting uveitis activity is the threat of loss of vision or further deterioration, presuming that it is still possible to improve or save vision.

Malignant conditions or other underlying diseases that may contraindicate immunosuppression must be excluded and compliance and monitoring of the medication ensured. The treatment plan should be worked out together with the patients and their parents. Information sheets for the individual immunosuppressive drugs are available via internet (http://gkjr.de/aufklaerungsboegen.html).

No randomized, controlled, or comparative studies are available yet for using immunosuppression to treat children with JIA-associated uveitis, only observational reports and case studies exist. Hence, the recommendations for immunosuppressive treatment in the present guidelines stem mainly from a consensus reached in our guidelines group.

Methotrexate Methotrexate has been shown to be efficacious in treating JIA in prospective, randomized studies [48]. The positive effect of methotrexate on JIA-associated uveitis has been reported in numerous case series [52–59].

Although prospective, controlled studies are lacking, methotrexate is currently the first-choice immunosuppressive drug for treating JIA-associated uveitis. A low rate of adverse effects has been reported for methotrexate [48]. Up to a third of patients did develop gastrointestinal problems and an aversion to the drug, however. It can be administered orally once per week or subcutaneously, in particular for higher dosages. The preferred dosage is 15 mg/m^2/week [60]. Methotrexate should be administered to children according to the present recommendations [61] (IIIA).

Azathioprine Azathioprine represents another drug for the long-term treatment of juvenile arthritis [62, 63]. There are only few published reports of the drug's effect on JIA-associated uveitis. However, these publications suggest that, by using azathioprine, inactivity can be achieved and corticosteroids spared [49, 64]. In summary, we can recommend azathioprine for treating uveitis in children (IIIB).

Cyclosporine A The efficacy of cyclosporine A in treating uveitis has been studied intensively in adults and has been clearly demonstrated. However, only a few publications exist on its efficacy in treating JIA-associated uveitis [65–71]. Consensus was reached that cyclosporine A alone was only mildly effective and thus should not be employed as the primary immunosuppressive to treat JIA-associated uveitis (IIIA). As it was more effective for treating patients who did not respond to previously administered immunosuppressive drugs, cyclosporine A can be administered as a combination drug if methotrexate or azathioprine treatment, for example, has failed (IIIB).

Cyclophosphamide and chlorambucil In a few individual case reports, uveitis improved under treatment with cyclophosphamide [72–74] or chlorambucil [75–77]. However, very severe side effects developed in the patients (e.g., infertility, leukopenia, thrombocytopenia, zoster infection, and others) and thus insofar as possible these drugs should not be used to treat childhood uveitis (IIIA).

Mycophenolate mofetil In recent years, mycophenolate mofetil has been applied as an immunosuppressive and corticosteroid-sparing drug. Although the substance is well tolerated and is associated with only few adverse effects, its significance for treating chronic JIA-associated uveitis has not been elucidated [78–80] (III0).

Sulfasalazine In a controlled study, sulfasalazine reduced the number of attacks of HLA-B27-associated acute

100

anterior uveitis in adults [81]. Another randomized, controlled study in 22 adults with ankylosing spondylitis demonstrated that sulfasalazine significantly reduced the number of uveitis attacks over a 3-year period [41, 82]. The data published on arthritic children with uveitis were in part positive [83]. However, the guidelines group assessed the efficacy as being low.

Choice and dosage of immunosuppressive drugs A drug should be chosen according to the personal experience of the physician, be based on the current guidelines, and depend on individual factors of the patient being treated [50, 51, 60, 84]. The dosages recommended in Fig. 1 should serve as orientation and must always be adapted to the individual patient. Under immunosuppressive treatment, corticosteroid eye drops should be reduced to the lowest possible dosage and in the intermediate term not exceed more than three daily applications. If uveitis inactivity can be achieved, further treatment is not required for the time being.

Treatment step III

If uveitis persists in the affected eyes or recurs under a maximum of 3 times daily topical corticosteroids or a systemic corticosteroid dosage of [0.15 mg/kg body weight or new complications of uveitis develop while under immunosuppressive treatment, the anti-inflammatory treatment should be intensified. In addition to the previous treatment with one immunosuppressive drug, a TNF-alpha inhibitor or cyclosporin A should be administered. The dosage of corticosteroid eye drops should be reduced to a minimum and in the intermediate term not be given any more than three times daily.

Infliximab (IIA) and adalimumab (IIIA) are highly effective and can thus be recommended [53, 74, 85–93]. Adalimumab is a completely humanized antibody that can effectively treat severe JIA/polyarthritis [94] and has been approved for treating children over 4 years of age. In this step of treating uveitis, adalimumab is currently the preferred TNF-alpha inhibitor.

In contrast, etanercept is less effective. Occasionally, even first or recurring severe attacks of uveitis have been reported under treatment with this drug [85, 92, 95–100] (I0).

Corticosteroid injections to the eye In the acute phase of severe uveitis associated with dense infiltration of the vitreous body, ocular hypotony, or macular edema, the physician may consider additional subconjunctival or orbital floor injections of methylprednisolone or dexamethasone (2–4 mg) if the topical corticosteroids are not effective. The injections act rapidly but are only effective for a short period [35]. The significant advantage of injections over oral administration is the lower rate of systemic side effects. Disadvantages include the possibly increased risk of development of cataract and more frequent increases in intraocular pressure with possible glaucoma damage. Short-term anesthesia for the injection is also often required.

If the goal of treatment is highly effective intraocular levels of drug over several weeks and a delay in treatment effect is acceptable, orbital floor injections (20–40 mg) or intraocular injections (2–4 mg) of a crystal suspension of triamcinolone acetonide can be considered to treat uni- or bilateral uveitis associated with dense vitreous body infiltration, hypotony, or macular edema (when topical corticosteroids are not effective) [101–104] (IIIA). Not enough data are available concerning the efficacy of surgically implanting biodegrable dexamethasone device into the eyes of children with anterior uveitis associated with inflammatory rheumatic diseases (III0).

Steroids injections should not be given to patients known to develop steroid-induced increases in intraocular pressure in order to prevent uncontrolled and long-term pressure increases.

For the treatment of JIA-associated uveitis, the guidelines group only considers intravitreal triamcinolone injections suitable in individual cases when the course of disease is particularly severe (impending loss of vision, for example, due to hypotony, macular edema, or dense infiltration of the vitreous body) and if the patient has not responded adequately to topical or systemic corticosteroids and immunosuppressives and biologicals (so-called rescue therapy) (III0).

Additional treatments Cycloplegics. Anti-inflammatory treatment of active anterior uveitis should be combined with cycloplegics to avoid posterior synechiae from developing or for their lysis. During acute attacks, the pupils should be dilated with scopolamine (IIIA).

Fresh synechiae should be treated as soon as possible. Cycloplegics can be administered alone (atropine, scopolamine, cyclopentolate, neosynephrine, or tropicamine), or initially possibly combined with each other as drops or given as a one-time subconjunctival injection (IIIA).

To treat chronic disease course, tropicamide should be applied during the night as a synechiae prophylaxis (IIIA). When using cycloplegics, care should be taken that pupils dilated for several days do not develop synechiae as a result and induce amblyopia in younger children.

References

1. Kotaniemi K, Aho K, Kotaniemi A (2001) Uveitis as a cause of visual loss in arthritides and comparable conditions. J Rheumatol 28:309–312

2. Smith JA, Mackensen F, Sen HN, Leigh JF, Watkins AS, Pyatetsky D, Tessler HH, Nussenblatt RB, Rosenbaum JT, Reed GF, Vitale S, Smith JR, Goldstein DA (2009) Epidemiology and course of disease in childhood uveitis. Ophthalmology 116:1544–1551
3. Kanski JJ (1977) Anterior uveitis in juvenile rheumatoid arthritis. Arch Ophthalmol 95:1794–1797
4. Kanski JJ (1990) Juvenile arthritis and uveitis. Surv Ophthalmol 34:253–267
5. Cabral DA, Petty RE, Malleson PN, Ensworth S, McCormick AQ, Shroeder M-L (1994) Visual prognosis in children with chronic anterior uveitis and arthritis. J Rheumatol 21:2370–2375
6. Carvounis PE, Herman DC, Cha S, Burke JP (2006) Incidence and outcomes of uveitis in juvenile rheumatoid arthritis, a synthesis of the literature. Graefe´s Arch Clin Exp Ophthalmol 244:281–290
7. Chia A, Lee V, Graham EM et al (2003) Factors related to severe uveitis at diagnosis in children with juvenile idiopathic arthritis in a screening program. Am J Ophthalmol 35:757–762
8. Dana MR, Merayo-Lloves J, Schaumberg DA, Foster CS (1997) Visual outcomes prognosticators in juvenile rheumatoid arthritis-associated uveitis. Ophthalmology 104:236–244
9. De Boer J, Wulffraat N, Rothova A (2003) Visual loss in uveitis of childhood. Br J Ophthalmol 87:879–884
10. Edelsten C, Reddy A, Stanford MR et al (2003) Visual loss associated with paediatric uveitis in English primary and referral centers. Am J Ophthalmol 135:676–680
11. Holland GN, Denove CS, Yu F (2009) Chronic anterior uveitis in children: clinical characteristics and complications. Am J Ophthalmol 147:667–678
12. Kotaniemi K, Kautiainen H, Karma A, Aho K (2001) Occurrence of uveitis in recently diagnosed juvenile chronic arthritis. A prospective study. Ophthalmology 108:2071–2075
13. Petty RE, Smith JR, Rosenbaum JT (2003) Arthritis and uveitis in children. A pediatric rheumatology perspective. Am J Ophthalmol 135:879–884
14. Mingels A, Hudde T, Heinz C et al (2005) Vision threatening complications in uveitis in childhood. Ophthalmologe 105:477–484
15. Minden K, Mingels A, Niewerth M, Heiligenhaus A, Ganser G (2007) Juvenile idiopathische Arthritis und Uveitis: Epidemiologie einschließlich der Daten aus der Kerndokumentation. Klin Monatsbl Augenheilk 224:469–472
16. Thorne JE, Woreta F, Kedhar SR et al (2007) Juvenile idiopathic arthritis-associated uveitis: incidence of ocular complications and visual acuity loss. Am J Ophthalmol 143:840–846
17. Wolf MD, Lichter PR, Ragsdale CG (1987) Prognostic factors in the uveitis of juvenile rheumatoid arthritis. Ophthalmology 94:1242–1248
18. Zulian F, Martini G, Falcini F, Gerloni V, Zannin ME, Pinello L, Fantini F, Facchin P (2002) Early predictors of severe course of uveitis in oligoarticular juvenile idiopathic arthritis. J Rheumatol 29:2446–2453
19. Heiligenhaus A, Niewerth M, Ganser G et al (2007) Prevalence and complications of uveitis in juvenile idiopahic arthritis in a population-based nation-wide study in Germany: suggested modification of the current screening guidelines. Rheumatology 46:1015–1019
20. Cassidy J, Kivlin J, Lindsley C, Nocton J, The Section on Rheumatology and the Section on Ophthalmology (2006) Ophthalmic examinations in children with juvenile rheumatoid arthritis. Pediatrics 117:1843–1845
21. Neudorf U, Heiligenhaus A (2004) Konsensus-Statement fu¨r die Behandlung der Uveitis bei juveniler idiopathischer Arthritis. Monatsschrift Kinderheilk 152:1240–1248
22. Michels H, Heiligenhaus A, Neudorf U et al (2005) Rheumatische Uveitis. Leitlinien Pa¨diatrie. Elsevier, Urban & Fischer
23. Guellac N, Niehues T (2008) Interdisciplinary and evidenz-based treatment guideline for juvenile idiopathic arthritis. Klin Pa¨diatr 220:392–402
24. Encke A, Kopp I, Selbmann HK, Hoppe J, Ko¨hler A, Ollenschla¨ger G (2005) Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF), A¨rztliches Zentrum fu¨r Qualita¨t in der Medizin (A¨ZQ), and (Hrsg). Deutsches Instrument zur methodischen Bewertung von Leitlinien: DELBI. Dt.A¨rztebl 102:1912–1913
25. A¨rztliches Zentrum fu¨r Qualita¨t in der Medizin (A¨ZQ) AdWMFA (2005) Deutsches Instrument zur methodischen Leitlinien-Bewertung (DELBI) Fassung 2005/2006. Z A¨rztl Fortbild Qualita¨tssich 99:468–519
26. Petty RE, Southwood TR, Manners P et al (2004) International League of Associations for rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton 2001. J Rheumatol 31:390–392
27. Brewer EJ Jr, Bass J, Baum J, Cassidy JT, Fink C, Jacobs J, Hanson V, Levinson JE, Schaller J, Stillman JS (1977) Current proposed revision of JRA criteria. JRA criteria subcommittee of the diagnostic and therapeutic criteria committee of the American rheumatism section of the arthritis foundation. Arthritis Rheum 20:195–199
28. Fantini F (1977) Rheumatoid arthritis in children and related forms. Updating of nomenclature, nosography, clinical manifestations and therapy, with reference to the EULAR/WHO workshop on the care of rheumatic children, Oslo, March 1977. Reumatismo 29:7–32
29. Wood P (1978) Special meeting on: nomenclature and classification of arthritis in children. In: Munthe E (ed) The care of rheumatic children. EULAR Publishers, Basle, pp 47–50
30. Jabs DA, Nussenblatt RB, Rosenbaum JT (2005) Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop. Am J Ophthalmol 140:509–516
31. Dunne JA, Travers JP (1979) Double-blind clinical trial of topical steroids in anterior uveitis. Br J Ophthalmol 63:762–767
32. Davis JL, Davis JL, Dacanay LM, Holland GN et al (2003) Laser flare photometry and complications of chronic uveitis in children. Am J Ophthalmol 135:763–771
33. Nussenblatt RB, Palestine AG, Chan CC, Roberge F (1985) Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. Ophthalmology 1992:467–471
34. Dunne JA, Jacobs N, Morrison A, Gilbert DJ (1985) Efficacy in anterior uveitis of two known steroids and topical tolmetin. Br J Ophthalmol 69:120–125
35. Gaudio PA (2004) A review of evidence guiding the use of corticosteroids in the treatment of intraocular inflammation. Ocul Immunol Inflamm 12:169–192
36. Ozerdem U, Levi L, Cheng L, Song MK, Scher C, Freeman WR (2000) Systemic toxicity of topical and periocular corticosteroid therapy in an 11-year-old male with posterior uveitis. Am J Ophthalmol 130:240–241
37. Kroger L, Kotaniemi K, Jaaskelainen J (2009) Topical treatment of uveitis resulting in adrenal insufficiency. Acta Paediatr 98:584–585
38. Sand BB, Krogh E (1991) Topical indometacin, a prostaglandin inhibitor, in acute anterior uveitis. A controlled clinical trial of non-steroid versus steroid anti-inflammatory treatment. Acta Ophthalmol (Copenh) 69:145–148
39. Young BJ, Cunningham WF, Akingbehin T (1982) Double-masked controlled clinical trial of 5% tolmetin versus 0.5% prednisolone versus 0.9% saline in acute endogenous nongranulomatous anterior uveitis. Br J Ophthalmol 66:389–391
40. Olson NY, Lindsley CB, Godfrey WA (1988) Nonsteroidal anti-inflammatory drug therapy in chronic childhood iridocyclitis. Am J Dis Child 142:1289–1292

41. Giordano M (1983) Dauerprophylaxe der rezidivierenden spondylitischen Iridozyklitis durch Antimalarika und nichtsteroidale Antiphogistika. Z Rheumatol 41:105–106
42. Chylack LT Jr, Bienfang DC, Bellows AR, Stillman JS (1975) Ocular manifestations of juvenile rheumatoid arthritis. Am J Ophthalmol 79:1026–1033
43. Wakefield D, McCluskey P, Penny R (1986) Intravenous pulse methylprednisolone therapy in severe inflammatory eye disease. Arch Ophthalmol 104:847–851
44. Thurau SR, Frosch M, Zierhut M, Gumbel H, Heiligenhaus A (2007) Topical and systemic corticosteroid therapy for uveitis in childhood. Klin Monatsbl Augenheilkd 224:516–519
45. Fan DS, Yu CB, Chiu TY, Wong CY, Ng JS, Pang CP, Lam DS (2003) Ocular-hypertensive and anti-inflammatory response to rimexolone therapy in children. Arch Ophthalmol 121:1716–1721
46. Foster CS, Alter G, DeBarge LR, Raizman MB, Crabb JL, Santos CI, Feiler LS, Friedlaender MH (1996) Efficacy and safety of rimexolone 1% ophthalmic suspension vs 1% prednisolone acetate in the treatment of uveitis. Am J Ophthalmol 122:171–182
47. Thorne JE, Woreta FA, Dunn JP, Jabs DA (2010) Risk of cataract development among children with juvenile idiopathic arthritis-related uveitis treated with topical corticosteroids. Ophthalmology 117:1436–1441
48. Giannini EH, Brewer EJ, Kuzmina N, Shaikov A, Maximov A, Vorontsov I, Fink CW, Newman AJ, Cassidy JT, Zemel LS (1992) Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. N Engl J Med 326:1043–1049
49. Hemady R, Tauber J, Foster CS (1991) Immunosuppressive drugs in immune and inflammatory ocular disease. Surv Ophthalmol 35:369–385
50. Kempen JH, Gangaputra S, Daniel E, Levy-Clarke GA, Nussenblatt RB, Rosenbaum JT, Suhler EB, Thorne JE, Foster CS, Jabs DA, Helzlsouer KJ (2008) Long-term risk of malignancy among patients treated with immunosuppressive agents for ocular inflammation: a critical assessment of the evidence. Am J Ophthalmol 146:802–812
51. Niehues T, Winterhalter S, Zierhut M, Michels H, Becker MD, Heiligenhaus A (2007) EBM analysis: classic DMARDs (disease-modifying antirheumatic drugs) and immunosuppressants in arthritis and uveitis. Klin Monatsbl Augenheilkd 224:520–525
52. Chan AY, Liu DT (2006) Methotrexate and chronic uveitis associated with juvenile idiopathic arthritis. J Rheumatol 33:198
53. Foeldvari I, Wierk A (2005) Methotrexate is an effective treatment for chronic uveitis associated with juvenile idiopathic arthritis. J Rheumatol 32:362–365
54. Heiligenhaus A, Mingels A, Heinz C, Ganser G (2007) Methotrexate for uveitis associated with juvenile idiopathic arthritis: value and requirement for additional anti-inflammatory medication. Eur J Ophthalmol 17:743–748
55. Lazar M, Weiner MJ, Leopold IH (1969) Treatment of uveitis with methotrexate. Am J Ophthalmol 67:383–387
56. Malik AR, Pavesio C (2005) The use of low dose methotrexate in children with chronic anterior and intermediate uveitis. Br J Ophthalmol 89:806–808
57. Samson CM, Waheed N, Baltatzis S, Foster CS (2001) Methotrexate therapy for chronic noninfectious uveitis: analysis of a case series of 160 patients. Ophthalmology 108:1134–1139
58. Shetty AK, Zganjar BE, Ellis GS Jr, Ludwig IH, Gedalia A (1999) Low-dose methotrexate in the treatment of severe juvenile rheumatoid arthritis and sarcoid iritis. J Pediatr Ophthalmol Strabismus 36:125–128
59. Weiss AH, Wallace CA, Sherry DD (1998) Methotrexate for resistant chronic uveitis in children with juvenile rheumatoid arthritis. J Pediatr 133:266–268
60. Ruperto N, Murray KJ, Gerloni V et al (2004) A randomized trial of parenteral methotrexate comparing an intermediate dose with a higher dose in children with juvenile idiopathic arthritis who failed to respond to standard doses of methotrexate. Arthritis Rheum 50:2191–2201
61. Niehues T, Horneff G, Michels H, Hock MS, Schuchmann L (2005) Evidence-based use of methotrexate in children with rheumatic diseases: a consensus statement of the Working Groups Pediatric Rheumatology Germany (AGKJR) and Pediatric Rheumatology Austria. Rheumatol Int 25:169–178
62. Kvien TK, Hoyeraal HM, Sandstad B (1986) Azathioprine versus placebo in patients with juvenile rheumatoid arthritis: a single center double blind comparative study. J Rheumatol 13:118–123
63. Savolainen HA, Kautiainen H, Isomaki H, Aho K, Verronen P (1997) Azathioprine in patients with juvenile chronic arthritis: a longterm followup study. J Rheumatol 24:2444–2450
64. Goebel J, Roesel M, Heinz C, Michels H, Ganser G, Heiligenhaus A (2011) Azathioprine as a treatment option for uveitis in patients with juvenile idiopathic arthritis. Br J Ophthalmol 95:209–213
65. Schlote T, Dannecker G, Thiel HJ, Zierhut M (1996) Cyclosporin A in therapy of chronic uveitis in childhood. Ophthalmologe 93:745–748
66. Kilmartin DJ, Forrester JV, Dick AD (1998) Cyclosporin A therapy in refractory non-infectious childhood uveitis. Br J Ophthalmol 82:737–742
67. Foeldvari I, Nielson S, Tzaribachev N, Quitsch J, Dressler F, Hilario M, Ku¨ster R, Borte M, Mazur-Zielinski H, Ja¨ger-Roman E, Wierk A (2006) Results of a multinational survey regarding the use of cyclosporine A in the treatment of juvenile idiopathic arthritis associated uveitis. EULAR abstract
68. Tappeiner C, Roesel M, Heinz C, Michels H, Ganser G, Heiligenhaus (2009) A Limited value of cyclosporine A for the treatment of patients with uveitis associated with juvenile idiopathic arthritis. Eye 23:1192–1198
69. Gerloni V, Cimaz R, Gattinara M, Arnoldi C, Pontikaki I, Fantini F (2001) Efficacy and safety profile of cyclosporin A in the treatment of juvenile chronic (idiopathic) arthritis. Results of a 10-year prospective study. Rheumatology (Oxford) 40:907–913
70. Kotaniemi K (1998) Late onset uveitis in juvenile-type chronic polyarthritis controlled with prednisolone, cyclosporin A and methotrexat. Clin Exp Rheumatol 16:469–471
71. Walton RC, Nussenblatt RB, Whitcup SM (1998) Cyclosporine therapy for severe sight-threatening uveitis in children and adolescents. Ophthalmology 105:2028–2034
72. Wittmer R (1987) Juvenile uveitis. Klin Monatsbl Augenheilk 191:332–333
73. Pras E, Neumann R, Zandman-Goddard G, Levy Y, Assai EL, Shoenfeld Y, Langevitz P (2004) Intraocular inflammation in autoimmune diseases. Semin Arthritis Rheum 34:602–609
74. Biester S, Deuter C, Michels H, Haefner R, Kuemmerle-Deschner J, Doycheva D, Zierhut M (2007) Adalimumab in the therapy of uveitis in childhood. Br J Ophthalmol 91:319–324
75. Godfrey WA, Epstein WV, O'Connor GR, Kimura SJ, Hogan MJ, Nozik RA (1974) The use of chlorambucil in intractable idiopathic uveitis. Am J Ophthalmol 78:415–428
76. Palmer RG, Kanski JJ, Ansell BM (1985) Chlorambucil in the treatment of intractable Uveitis associated with juvenile chronic arthritis. J Rheumatol 12:967–970
77. Miserocchi E, Baltatzis S, Ekong A, Roque M, Foster CS (2002) Efficacy and safety of chlorambucil in intractable noninfectious uveitis: the Massachusetts Eye and Ear Infirmary experience. Ophthalmology 109:137–142

78. Baltatzis S, Tufail F, Yu EN, Vredeveld CM, Foster CS (2003) Mycophenolate mofetil as an immunomodulatory agent in the treatment of chronic ocular inflammatory disorders. Ophthalmology 110:1061–1065
79. Doycheva D, Deuter C, Stuebiger N, Biester S, Zierhut M (2007) Mycophenolate mofetil in the treatment of uveitis in children. Br J Ophthalmol 91:180–184
80. Sobrin L, Christen W, Foster CS (2008) Mycophenolate mofetil after methotrexate failure or intolerance in the treatment of scleritis and uveitis. Ophthalmology 115:1416–1421
81. Munoz-Fernandez S, Hidalgo V, Fernandez-Melon J, Schlincker A, Bonillo G, Ruiz-Sancho D, Fonseca A, Gijon-Banos J, Martin-Mola E (2003) Sulfasalazine reduces the number of flares of acute anterior uvetiis over one year period. J Rheumatol 30:1277–1279
82. Beritez-Del-Castillo JM, Iradier T, Banares A (2000) Sulfasalazine in the prevention of anterior uveitis associated with ankylosing spondylitis. Eye 14:340–343
83. Huang JL, Hung IJ, Hsieh KH (1997) Sulphasalazine therapy in chronic uveitis of children with chronic arthritis. Asian Pac J Allergy Immunol 15:71–75
84. Heiligenhaus A, Horneff G, Greiner K, Mackensen F, Zierhut M, Foeldvari I, Michels H (2007) Inhibitors of tumour necrosis factor-alpha for the treatment of arthritis and uveitis in childhood. Klin Monatsbl Augenheilkd 224:526–531
85. Galor A, Perez VL, Hammel JP, Lowder CY (2006) Differential effectiveness of etanercept and infliximab in the treatment of ocular inflammation. Ophthalmology 113:2317–2323
86. Kahn P, Weiss M, Imundo LF, Levy DM (2006) Favorable response to high-dose infliximab for refractory childhood uveitis. Ophthalmology 113:860–864, e862
87. Mangge H, Heinzl B, Grubbauer HM, El-Shabrawi Y, Schauenstein K (2003) Therapeutic experience with infliximab in a patient with polyarticular juvenile idiopathic arthritis and uveitis. Rheumatol Int 23:258–261
88. Rajaraman RT, Kimura Y, Li S, Haines K, Chu DS (2006) Retrospective case review of pediatric patients with uveitis treated with infliximab. Ophthalmology 113:308–314
89. Richards JC, Tay-Kearney ML, Murray K, Manners P (2005) Infliximab for juvenile idiopathic arthritis-associated uveitis. Clin Experiment Ophthalmol 33:461–468
90. Saurenmann RK, Levin AV, Rose JB, Parker S, Rabinovitch T, Tyrrell PN, Feldman BM, Laxer RM, Schneider R, Silverman ED (2006) Tumour necrosis factor alpha inhibitors in the treatment of childhood uveitis. Rheumatology (Oxford) 45:982–989
91. Sharma SM, Ramanan AV, Riley P, Dick AD (2007) Use of infliximab in juvenile onset rheumatological disease-associated refractory uveitis: efficacy in joint and ocular disease. Ann Rheum Dis 66:840–841
92. Tynjala P, Lindahl P, Honkanen V, Lahdenne P, Kotaniemi K (2007) Infliximab and etanercept in the treatment of chronic uveitis associated with refractory juvenile idiopathic arthritis. Ann Rheum Dis 66:548–550
93. Vazquez-Cobian LB, Flynn T, Lehman TJ (2006) Adalimumab therapy for childhood uveitis. J Pediatr 149:572–575
94. Lovell DJ, Ruperto N, Goodman S et al (2008) Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med 359:810–820
95. Foeldvari I, Nielsen S, Kummerle-Deschner J, Espada G, Horneff G, Bica B, Olivieri AN, Wierk A, Saurenmann RK (2007) Tumor necrosis factor-alpha blocker in treatment of juvenile idiopathic arthritis-associated uveitis refractory to second-line agents: results of a multinational survey. J Rheumatol 34:1146–1150
96. Gallagher M, Quinones K, Cervantes-Castaneda RA, Yilmaz T, Foster CS (2007) Biological response modifier therapy for refractory childhood uveitis. Br J Ophthalmol 91:1341–1344
97. Reiff A, Takei S, Sadeghi S, Stout A, Shaham B, Bernstein B, Gallagher K, Stout T (2001) Etanercept therapy in children with treatment-resistant uveitis. Arthritis Rheum 44:1411–1415
98. Scrivo R, Spadaro A, Spinelli FR, Valesini G (2008) Uveitis following the use of tumor necrosis factor alpha inhibitors: comment on the article by Lim et al. Arthritis Rheum 58:1555–1556; author reply 1556–1557
99. Smith JA, Thompson DJ, Whitcup SM, Suhler E, Clarke G, Smith S, Robinson M, Kim J, Barron KS (2005) A randomized, placebo-controlled, double-masked clinical trial of etanercept for the treatment of uveitis associated with juvenile idiopathic arthritis. Arthritis Rheum 53:18–23
100. Tauber T, Daniel D, Barash J, Turetz J, Morad Y (2005) Optic neuritis associated with etanercept therapy in two patients with extended oligoarticular juvenile idiopathic arthritis. Rheumatology (Oxford) 44:405
101. Antcliff RJ, Spalton DJ, Stanford MR, Graham EM, Fytche TJ, Marshall J (2001) Intravitreal triamcinolone for uveitic cystoid macular edema: an optical coherence tomography study. Ophthalmology 108:765–772
102. Sallam A, Comer RM, Chang JH, Grigg JR, Andrews R, McCluskey PJ, Lightman S (2008) Short-term safety and efficacy of intravitreal triamcinolone acetonide for uveitic macular edema in children. Arch Ophthalmol 126:200–205
103. Roesel M, Gutfleisch M, Heinz C, Heimes B, Zurek-Imhoff B, Heiligenhaus A (2009) Orbital floor triamcinolone acetonide injections for the management of active non-infectious uveitis. Eye 23:910–914
104. Roesel M, Gutfleisch M, Heinz C, Heimes B, Zurek-Imhoff B, Heiligenhaus A (2009) Intravitreal and orbital floor triamcinolone acetonide injections in noninfectious uveitis: a comparative study. Ophthalmic Res 42:81–86
105. Tynja¨la¨ P, Kotaniemi K, Lindahl P, Latva K, Aalto K, Honkanen V, Lahdenne P (2008) Adalimumab in juvenile idiopathic arthritis-associated chronic anterior uveitis. Rheumatology (Oxford) 47:339–344

Ocular Immunology and Inflammation

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ioii20

Monitoring and Treatment of Juvenile Idiopathic Arthritis-associated Uveitis: Brazilian Evidence-based Practice Guidelines

LM Neves, LM Haefeli, LM Hopker, F Ejzenbaum, H Moraes do Nascimento, N Aikawa, MO Hilario, CS Magalhães, MT Terreri, F Sztajnbok, Professor CAA Silva & JD Rossetto

To cite this article: LM Neves, LM Haefeli, LM Hopker, F Ejzenbaum, H Moraes do Nascimento, N Aikawa, MO Hilario, CS Magalhães, MT Terreri, F Sztajnbok, Professor CAA Silva & JD Rossetto (2021): Monitoring and Treatment of Juvenile Idiopathic Arthritis-associated Uveitis: Brazilian Evidence-based Practice Guidelines, Ocular Immunology and Inflammation, DOI: 10.1080/09273948.2021.1876886

To link to this article: https://doi.org/10.1080/09273948.2021.1876886

Published online: 07 Apr 2021.

Submit your article to this journal

Article views: 42

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=ioii20

OCULAR IMMUNOLOGY AND INFLAMMATION
https://doi.org/10.1080/09273948.2021.1876886

Taylor & Francis
Taylor & Francis Group

ARTICLE

Check for updates

Monitoring and Treatment of Juvenile Idiopathic Arthritis-associated Uveitis: Brazilian Evidence-based Practice Guidelines

LM Neves, MD[a,b,c], LM Haefeli, MD[a,b,c], LM Hopker, MD[b,c,d,e], F Ejzenbaum, MD[b,c,e,f], H Moraes do Nascimento, MD[c,g], N Aikawa, MD[e,h,i], MO Hilario, MD[e,i,j], CS Magalhães, MD[e,i,k], MT Terreri, MD[e,i,l], F Sztajnbok, MD[e,i,m], Professor CAA Silva[e,h,i], and JD Rossetto, MD[b,c,e,g,m]

[a]Ophthalmology Department, Instituto Nacional De Saúde Da Mulher, Da Criança E Do Adolescente Fernandes Figueira- Fundação Oswaldo Cruz, Rio De Janeiro, RJ, Brazil; [b]Brazilian Society of Pediatric Ophthalmology (SBOP), Sao Paulo/SP, Brazil; [c]Brazilian Council of Ophthalmology (CBO), Sao Paulo/SP, Brazil; [d]Ophthalmology Department, Hospital De Olhos Do Paraná, Curitiba/PR, Brazil; [e]Brazilian Society of Pediatrics (SBP), Rio de Janeiro/RJ, Brazil; [f]Ophthalmology Department, Santa Casa De Misericórdia De São Paulo Sao Paulo/SP, Brazil; [g]Ophthalmology and Visual Science Department, Federal University of Sao Paulo – UNIFESP, São Paulo, SP, Brazil; [h]Pediatric Rheumatology Unit, Children's Institute, Hospital Das Clinicas HCFMUSP, Faculdade De Medicina, Universidade De Sao Paulo, SP, Brazil; [i]Brazilian Society of Rheumatology (SBR), Sao Paulo/SP, Brazil; [j]Pediatric Department, Santa Casa De Misericórdia De Porto Alegre, Porto Alegre/RS, Brazil; [k]Pediatric Rheumatology Division, São Paulo State University (UNESP), Botucatu/SP, Brazil; [l]Pediatric Rheumatology Unit, Federal University of São Paulo – UNIFESP, São Paulo/SP, Brazil; [m]Pediatric Department, Instituto De Puericultura E Pediatria Martagão Gesteira - IPPMG/Federal University of Rio De Janeiro - UFRJ - Rio De Janeiro/RJ, Brazil

ABSTRACT

Purpose: To present a national guideline for ophthalmologic care and surveillance of juvenile idiopathic arthritis-associated uveitis (JIA-uveitis).

Methods: Review article based on medical literature and the experience of an Expert Committee composed of members of the Brazilian Society of Pediatric Ophthalmology/Brazilian Council of Ophthalmology and the Brazilian Society of Pediatrics/Brazilian Society of Rheumatology. Studies with a high level of evidence were selected by searching the PubMed/Medline database. The final document was approved by the experts.

Results: The main recommendations are that children/adolescents with JIA should undergo screening according to their risk factors. Ophthalmological checkups should also consider ocular inflammation and therapy. Topical glucocorticoids should be the first line of therapy, with systemic glucocorticoids acting as bridge treatments in severe uveitis. Methotrexate should be the first-line systemic therapy and anti-tumor necrosis factor (anti-TNF alpha) the second for uncontrolled uveitis.

Conclusions: This evidence-based guideline for JIA-uveitis will be useful for both ophthalmology and rheumatology practice.

ARTICLE HISTORY
Received 21 October 2020
Revised 16 December 2020
Accepted 11 January 2021

KEYWORDS
Juvenile idiopathic arthritis; anterior uveitis; practice guideline; methotrexate; tumor necrosis factor-alpha; childhood

Juvenile idiopathic arthritis (JIA) is the most frequent chronic autoimmune rheumatic disease in children and adolescents.[1] It comprises a heterogeneous group of arthritis with an onset before 16 years of age and characterized by at least one joint inflammation lasting ≥ 6 weeks (Table 1). [4] JIA is also associated with uveitis, an inflammation of the uveal components of the eye, including the iris, ciliary body, and choroid. This JIA-associated uveitis (JIA-uveitis) is usually an iridocyclitis and is the commonest extra-articular manifestation.[1]

The pathogenesis of JIA-uveitis is unknown. Recently, a meta-analysis study pointed to a worldwide prevalence of 11.8%, with a decreasing incidence of uveitis related to early detection and appropriate surveillance and therapeutic protocols.[4] JIA-uveitis is usually asymptomatic; therefore, its diagnosis may be delayed, resulting in sight-threatening complications. One-third of JIA-uveitis cases may present with ocular complications by the time of diagnosis.[4] Ocular complication rates vary from 35.5–67% of affected children and adolescents. The complications can include synechia, keratopathy, cataract, glaucoma or ocular hypertension, macular fibrosis, and vision loss.[4] Diversely, uveitis associated with positive HLA-B27 and enthesitis-related arthritis, most commonly present with symptomatic acute anterior uveitis (AAU).

International guidelines have been developed, but no standardized national guideline has yet been established for screening, monitoring, and treating JIA-uveitis within our health system to target the silent disease associated with severe sight-threatening complications. Therefore, the aims of this document were to guide monitoring and treatment of JIA-uveitis in Brazil.

Material and methods

These guidelines were evidence-based for clinical applicability and clarity on communicating the recommendations. They were developed based on careful consideration of the medical literature and the clinical experience of the Expert Committee with the aim of defining the optimal ophthalmologic care for patients with JIA-uveitis. The literature review regarding the screening, diagnosis, treatment, and monitoring of JIA-uveitis was carried out through PubMed, from 2000 to 2019, and yielded 141 scientific studies within the following MeSH

CONTACT JD Rossetto juliadrossetto@gmail.com; julia_rossetto@hotmail.com Botucatu St, 822 - 2nd Floor, ZIP 04039-032, +55 11 5085-2010
© 2021 Taylor & Francis Group, LLC

Table 1. Definitions and prevalence of juvenile idiopathic arthritis (JIA) categories defined by ACR, EULAR, and ILAR classification.[2,3]

JIA category	Definition		Prevalence ACR	EULAR	ILAR
Oligoarthritis	Arthritis with 1–4 joints during the first 6 months of disease	Persistent: 1–4 joints	15.6%	17.6%	16.4%
		Extended: > 4 joints **after** the first 6 months of disease			
Polyarthritis	Arthritis with > 4 joints during the first 6 months of disease	RF negative	6.2%	8.1%	4.2%
		RF positive on at least two occasions more than 3 months apart	1.9%	1.7%	0.6%
Psoriatic arthritis	Arthritis and psoriasis or arthritis and at least **two** of: dactylitis; nail pitting or onycholysis; psoriasis in a first-degree relative		4.1%	1.1%	1.1%
Enthesitis-related arthritis	Arthritis and enthesitis or arthritis or enthesitis with at least **two** of: presence or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain; presence of HLA-B27 onset of arthritis in a male older than 6 years of age; acute symptomatic anterior uveitis; history of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome or acute anterior uveitis in a first-degree relative		13.8%	1.5%	3.1%
Systemic	Arthritis with or preceded by daily fever of at least 2 weeks' duration that is documented to be quotidian for at least 3 days and accompanied by one or more of: evanescent nonfixed erythematous rash; generalized lymph node enlargement; hepatomegaly and/or splenomegaly; serositis		6.4%	2.7%	2.4%
Undifferentiated	Arthritis that fulfills criteria in no category or in two or more of the above categories				2.7%

ACR: American College for Rheumatology. EULAR: European League Against Rheumatism. ILAR: International League of Associations for Rheumatology

terms: (anterior uveitis) AND (juvenile arthritis) NOT (rheumatoid arthritis) AND (incidence) OR (prevalence) OR (anterior uveitis) AND (iridocyclitis) AND (juvenile arthritis) NOT (rheumatoid arthritis) AND (signs and symptoms) OR (anterior uveitis) AND (juvenile arthritis) NOT (rheumatoid arthritis) AND (diagnosis) AND (GRADE approach) OR (anterior uveitis) AND (juvenile arthritis) NOT (rheumatoid arthritis) AND (therapeutics).

The data and selected scientific studies were retrieved and reviewed by six members of the Brazilian Society of Pediatric Ophthalmology (SBOP) and the Brazilian Council of Ophthalmology (CBO), as well as six members of the Brazilian Society of Pediatrics (SBP) or the Brazilian Society of Rheumatology (SBR). These studies consisted of meta-analyses and systematic reviews, as well as guidelines, panel consensus, case-control studies, observational studies, and case reports on JIA-uveitis to serve as the basis of the guideline recommendations. Studies with languages other than English or Portuguese were excluded.

The Expert Committee appraised the identified studies regarding their design and quality of execution. Studies qualified by the level of evidence and strength of recommendations were preferred and their classifications were uniformed, when applicable, based on Heiligenhaus et al. classification, as follows.[5]

Level of Evidence: Level I, based on two or more high-quality randomized clinical trials (RCTs); on studies with high evidence level by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE), or statements from SBP/SBR guideline with level A of evidence (Experimental or observational studies with higher consistency).[5–7] Level II, based on a small number of RCTs, more than one controlled but not a randomized study, or more than one RCT of lesser quality; on cohort or case-control studies, preferably from more than one research group or more than one center; on observations of clear-cut effects in non-controlled studies; on studies with moderate evidence level by GRADE, or statements from SBP/SBR guideline with level B of evidence (Experimental or observational studies with lower consistency).[5–7] Level III, based on expert opinion, clinical experience, on descriptive studies, cohort, or case-control studies of lower quality; on studies with low or very low evidence level by GRADE, or statements from SBP/SBR guideline with level C or D of evidence (case reports studies; or specialist opinion-based consensus).[5–7]

The strength of the recommendation was classified as Level A, meaning a strong recommendation ("shall") and when desirable effects outweighed undesirable effects by American College of Rheumatology/Arthritis Foundation (ACR/AF)[8]; Level B, a mitigated recommendation ("should"), including conditional recommendations (when desirable effects probably outweighed undesirable effects) by ACR/AF; and Level 0, an open recommendation ("can").[5,8]

All the society representatives involved approved the final guideline document. Ethics approval was waived because there was no human subject participation.

Results

Epidemiology, Pathogenesis, and disease markers

The JIA incidence varies from 1.6 to 23/100.000 and the prevalence from 3.8 to 400/100.000.[2] The pooled incidence and prevalence are higher for girls (10.0 [9.4–10.7]/100,000 and 19.4 [18.3–20.6]/100.000) than for boys (5.7 [5.3–6.2]/100,000 and 11.0 [10.2–11.9]/100,000).[2,9]

JIA-uveitis is the main extra-articular manifestation.[1] A recent meta-analysis estimated its pooled prevalence of 11.8% (95%CI 11.2 to 12.4%), with a decreasing incidence probably due to early detection and appropriate, preventive, and therapeutic protocols.[4] Uveitis in the pediatric population varies in different regions of the world. Globally, an inverse correlation is observed between a country's development level and both the frequency of the disease and the amount of disease-related and treatment-related damage.[10] The JIA-uveitis prevalence is higher in North America (31.5%) and in Northern (19.1%) and Southern (18.8%) Europe, but is lower in Latin America (6.4%), in Africa and the Middle East (5.9%), and in Southern Asia (5.0%).[10] In Brazil, the JIA-uveitis prevalence was reported as 6.4% at a tertiary hospital.[11]

The pathogenesis of JIA-uveitis is still unknown. JIA-uveitis is recognized as a multifactorial immune-mediated disease, thus composed of a complex genetic predisposition in association with environmental factors.[12] Histocompatibility allele profiles have been widely assessed, and the presence of the amino acid serine at position 11 in Human Leukocyte Antigen (HLA)-DRβ1 was associated with an increased risk of uveitis in JIA patients. Furthermore, association in the HLA-DRB1 genes was restricted to JIA in girls.[12]

The anti-histone antibodies (AHA) ≥ 15 U/mL were also reported as a significant predictor of uveitis only in girls.[9] An elevated erythrocyte sedimentation rate (≥ 20 mm/1st hour) at baseline was reported as an additional risk factor for uveitis development.[13,14] Additionally, the antigen presentation via major histocompatibility complex (MHC) class II was described as a critical disease mechanism for JIA-uveitis.[12,15]

Risk factors for JIA-uveitis

JIA-uveitis has several risk factors, including the age at arthritis onset, gender, JIA subtype, antinuclear antibody (ANA) positivity, and human leukocytes antigen (HLA)-B27 positivity.[1,4] Chronic anterior uveitis (CAU) is usually associated with a younger age at JIA onset (less than 6 years old), female gender, oligoarticular disease (four or fewer joints at disease onset), and ANA positivity.[1,16,17] Positive ANA occurs in 70 to 90% of JIA-uveitis cases.[4] Two large publications, a retrospective study of 1047 Canadian patients and a longitudinal cohort of 435 Nordic children, reported the significant age-dependent risk of developing uveitis only for girls.[9,18]

AAU is also associated with pre-teenaged and teenaged patients, male gender, enthesitis-related arthritis, and positive HLA-B27.[1,3] Uveitis can also be observed in patients with rheumatoid factor (RF)-negative polyarthritis, psoriatic arthritis, and, more rarely, in systemic-onset JIA.[3] In this regard, the polyarticular RF positivity subtype was revealed as protective for uveitis.[4]

The arthritis onset age was from 3.8–4.8 years in patients with uveitis and from 7.0–7.3 years in patients without uveitis.[17,19] The cumulative incidence of uveitis was 25–30% in an extended oligoarthritis course, followed by 16–18% in persistent oligoarthritis, 4–14% in rheumatoid-factor negative polyarthritis, and 10–12% in psoriatic arthritis.[3,17,20]

The effect of ethnicity is unclear, but risk factors for JIA-uveitis may differ among different ethnicities.[1,3,4] Some authors have suggested that JIA-uveitis may be more common in Caucasians, whereas Afro-American children and adolescents may present with JIA at a later onset, with a lower frequency of positive ANA and uveitis.[16,21–23]

Fifteen percent of Brazilian patients with JIA were Caucasians, with a slight male predominance (55.5%). The mean age at JIA onset was 5.1 years, and the mean age at uveitis onset was 9 years. In patients with CAU, 80% had oligoarticular JIA and 60% had positive ANA.[24]

Risk factors previously associated with JIA-uveitis poor prognosis include male sex, short duration between onset of arthritis and the development of uveitis, presence of synechiae, high anterior chamber cell grade, and poor visual acuity at uveitis diagnosis.[25–28]

Clinical presentation

JIA-uveitis is mostly anterior (iridocyclitis), non-granulomatous, bilateral, usually persistent (duration > 3 months), and rarely limited (duration ≤ 3 months).[29] The clinical course can be chronic (persistent uveitis with relapse in < 3 months after discontinued treatment), recurrent (repeated episodes separated by periods of inactivity without treatment lasting ≥ 3 months in duration), and acute (limited uveitis with sudden onset).

The arthritis typically precedes the uveitis, by a median of 4–5 months.[3,17,19] In 48% of patients, uveitis appears within 6 months of arthritis onset, and in 73%, uveitis occurs within 12 months.[17] In only 3–7% of patients does the uveitis precede the arthritis.[17,18,30–32]

CAU is the most frequent subtype, occurring in 68.3–90% of patients.[9,33] AAU occurs in 10–16.2% and is most often encountered in enthesitis-related arthritis. Recurrent anterior uveitis occurs in 12%,[9,33] whereas pan-uveitis has been rarely described, occurring in up to 3.5% of patients with JIA-uveitis.[33]

CAU is usually asymptomatic and leads to a high risk of sight-threatening complications due to delayed diagnosis. Ocular complications occur in 35.5–67% of affected children and adolescents, including synechiae (27–33%), band keratopathy (15.7–29%), cataract (8–31%), glaucoma or ocular hypertension (8–19%) and macular fibrosis (15.7–29%).[4] The cumulative incidence of visual impairment is 9.2% for JIA-uveitis.[34] Visual acuity estimates were less than 20/50 in 11–31% and less than 20/200 in 12%.[4] Legally blind status occurred in 5.6% of the affected eyes.[35] Importantly, one-third of the JIA-associated uveitis can present with ocular complications by the time of diagnosis.[4] Conversely, AAU presents as unilateral and episodic, with a sudden onset of ocular hyperemia, pain, and photophobia.[8]

JIA-uveitis diagnosis and screening

Ophthalmological screening of uveitis is recommended when JIA is suspected or diagnosed, within the first 6 weeks of diagnosis.[36] The ocular examination includes monocular age-appropriate visual acuity testing, intraocular pressure (IOP) measurement, slit-lamp examination, and dilated fundoscopy.

The slit-lamp examination identifies the anterior chamber inflammation by the presence of cells and flare, as well as ocular structural complications, including IOP abnormalities (hypotony, hypertension and/or glaucoma), synechiae formation, presence of cataract, band keratopathy, macular edema, epiretinal membrane, and/or vitreous inflammatory activity.[37] Intraocular inflammation should be graded following the Standardization of Uveitis Nomenclature (SUN) criteria for uveitis activity (Table 2).[29] The SUN classification also allows a comparison of the degree of inflammation between visits to assess the response to treatment and the disease activity during follow-up (Table 3). The anterior chamber reaction is the most sensitive response to treatment measures, as its control is associated with less functional damage and better health-related quality of life.[38]

Based on the British Society for Pediatric and Adolescent Rheumatology/Royal College of Ophthalmology (BSPAR/RCO) guidelines, patients diagnosed with JIA before the age of 11 should

Table 2. Standardization of uveitis nomenclature definitions.[29]

Category	Descriptor	Comment
Onset	Sudden	
	Insidious	
Duration	Limited	≤ 3 months duration
	Persistent	> 3 months duration
Course	Acute	Sudden onset and limited duration
	Recurrent	Repeated episodes separated by inactive periods without treatment for ≥ 3 months
	Chronic	Persistent uveitis with relapse in < 3 months after discontinuing treatment
Anterior chamber inflammation classification		
Cells per field[1]	Grade	Flare
< 1	0	None
1–5	0.5+	-
6–15	1+	Faint
16–25	2+	Moderate (iris and lens details clear)
26–50	3+	Marked (iris and lens details hazy)
> 50	4+	Intense (fibrin or plastic aqueous)
Field size[1]: 1 × 1 mm slit beam		

Table 3. Inflammation activity and disease control criteria by Standardization of Uveitis Nomenclature (SUN) and the American College of Rheumatology/Arthritis Foundation (ACR/AF) Guideline.[8,29]

Inflammation activity and disease control	
Active inflammation	≥ 0.5 + anterior chamber cells (ACR)
New uveitis activity	≥ 0.5 + anterior chamber cells with no history of prior uveitis
Additional signs of active inflammation	Fresh keratic precipitates, increased flare, and hypotony
Worsening activity	Two-step increase in the level of inflammation (anterior chamber cells) or increase from grade 3 to 4 (SUN)
Improved activity	Two-step decrease in the level of inflammation (anterior chamber cells) or decrease to grade 0 (SUN)
Controlled uveitis	Inactive (no cells) OR grade < 1+ anterior chamber cells without new complications due to active inflammation; absence of optic disc, macular edema, and vitreous haze (ACR)
Loss of control	Increase of anterior chamber cells to grade 1+ or more, or new signs of inflammation/complications of inflammation (ACR)
Remission	Inactive disease for 3 months after discontinuing all treatments for eye disease (SUN)
Complications	
Complications due to active inflammation	New development of synechiae, inflammatory membranes, or cystoid macular edema (ACR)
Complications representing cumulative damage	Cataract, glaucoma/elevated intraocular pressure, hypotony, or sequelae of keratic precipitates (ACR)

be monitored with the schedule described in Table 4, up to age 11 years.[39] For those diagnosed after the age of 11, ophthalmologic surveillance is recommended for one more year.[39]

According to the American College of Rheumatology/Arthritis Foundation (ACR/AF) guidelines, patients with JIA are classified as high, moderate, and low risk for developing uveitis.[8] High-risk patients are those with oligoarthritis, polyarthritis with negative RF, psoriatic arthritis, and undifferentiated arthritis, those with positive ANA, younger than 7 years age at JIA onset, **and** with a disease duration of less than 4 years. Low to moderate-risk patients are those with JIA in the aforementioned categories but with negative ANA, older than 7 years at JIA onset **or** with more than 4 years of disease duration, and those with systemic JIA, positive RF-polyarthritis, and enthesitis-related arthritis. The ACR/AF recommends screening every 3 months for children or adolescents with high-risk uveitis and every 6–12 months for low- to moderate-risk uveitis. Both have a level of evidence and strength of recommendation IIIB (Table 4).

According to the Brazilian Medical Association (AMB) and the Brazilian Society of Rheumatology (SBR) guidelines (level of evidence and strength of recommendation IIIB), ocular screening should start at the time of JIA diagnosis. Its frequency should be based on JIA subtype, age at the disease onset, disease duration, and positive ANA, as shown in Table 4.[6]

Recommendations

Assembling previous models, the proposed screening flow guidelines are shown in Figure 1.

JIA-uveitis treatment

Topical treatment

Topical glucocorticoids are the first-line treatment for acute and chronic uveitis, and prednisolone acetate 1% eye drops are recommended, based on good corneal penetration and low risk of glucocorticoid-induced IOP elevation (level of evidence and strength of recommendation IIIB).[1,8] The standard recommendation is one drop administered every 1 to 12 hours, according to inflammation severity, with a slow medication tapering with ophthalmological assessment at each step of regression. Moderate to severe anterior uveitis usually requires 1- to 2-hour dosing initially (level of evidence and strength of recommendation IIIB).[37,40] Recommended doses according to the inflammation in the

Table 4. Screening criteria for ophthalmological examination in juvenile idiopathic arthritis by the British Society for Pediatric and Adolescent Rheumatology/Royal College of Ophthalmology (BSPAR/RCO), the American College of Rheumatology/Arthritis Foundation (ACR/AF), and the Brazilian Society of Rheumatologic Pediatrician (BSRP) Guideline.[5,6,39]

	BSPAR/RCO (III B)	ACR/AF/ (III B)			BSRP (III B)
First exam	Before 6 weeks of diagnosis; If symptomatic: within a week of referral	No recommendations			At JIA diagnosis
Freq.	**Every 2 m for 6 m**	Oligoarthritis, polyarthritis and negative RF, psoriatic arthritis and undifferentiated arthritis		Systemic JIA, Polyarthritis and positive RF	JIA age of onset ≤ 6 y, disease duration ≤ 4 y, oligo/poly and ANA positive
	Followed by every 3–4 m for (see below):				**Every 3 m.**
	Oligoarticular JIA, psoriatic arthritis and enthesitis-related arthritis despite ANA status onset under 11 y:	PositiveANA JIA age of onset < 7 y **and** disease duration ≤ 4 y	NegativeANA, JIA age onset ≥7 y **or** disease duration > 4 y	Enthesitis-related arthritis	JIA age of onset ≤ 6 y, disease duration ≤ 4 y. Oligo/poly, negative ANA.
	< 3 y onset: 8 y				**or**
	3–4 y onset: 6 y				JIA age of onset ≤ 6 y disease duration > 4 y, oligo/polyarthritis, despite ANA status
	5–8 y onset: 3 y				**or**
	9–10 y onset: 1y				JIA age of onset > 6 y, disease duration ≤ 4 y, oligo/poly, despite ANA status
	Polyarticular, positive ANA, JIA onset less than 10 y				**Every 6 m**
	< 6 y onset: 5 y				Systemic JIA, polyarthritis with positive RF, and enthesitis-related arthritis
	6–9 y onset: 2 y				**or**
	Polyarticular, positive ANA JIA, JIA onset less than 7 y: 5 y	**Every 3 m**	**Every 6–12 m**		JIA age of onset ≤ 6 y, duration of JIA≥ 7 y oligo/polyarthritis, despite ANA status
					or
					JIA age of onset > 6 y, duration of JIA > 4 y, oligo/polyarthritis, despite ANA status
					Every 12 m.

Freq.: frequency. JIA: juvenile idiopathic arthritis. m: months. y: years. ANA: antinuclear antibody. RF: rheumatoid factor.

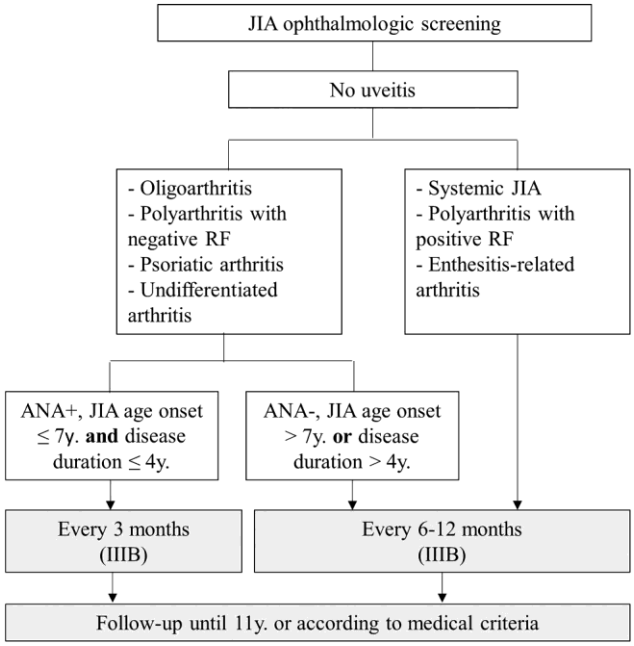


Figure 1. Ophthalmological screening recommendation in juvenile idiopathic arthritis combining the American College of Rheumatology/Arthritis Foundation and the British Society for Paediatric and Adolescent Rheumatology/Royal College of Ophthalmology guidelines.[6,39]
JIA = juvenile idiopathic arthritis; RF = rheumatoid factor; ANA = antinuclear antibody; y = years.

anterior chamber are one drop every 12 h for grade 0.5+, one drop every 8 h for grade 1+, one drop every 6 h for grade 2+, one drop every 4 h for grade 3+, and one drop every 1–2 h for grade 4 + . Topical treatment should be maintained as long as ≥ 0.5+ cells in the anterior chamber are present (level of evidence and strength of recommendation IIIB).[37,40]

In active CAU, increasing topical glucocorticoids for short-term control is recommended over adding systemic glucocorticoids (level of evidence and strength of recommendation IIIB).[8]

For patients still requiring one to two drops of topical glucocorticoids daily for uveitis control, particularly over 3 months, and who are not on systemic therapy, the recommendation is to add a systemic therapy, such as disease-modifying anti-rheumatic drugs (DMARDS), to allow tapering of the topical glucocorticoids (level of evidence and strength of recommendation IIIB).[1,8,41] Topical glucocorticoids at a dosage of one to two drops daily may be used as monotherapy in the absence of ocular complications (elevated IOP and cataracts) and with regular ocular checkups.[8]

For patients already on systemic therapy requiring one to two drops daily of topical glucocorticoids for uveitis control for over 3 months, the recommendation is to change or escalate systemic therapy (level of evidence and strength of recommendation IIIB).[8] Systemic therapy may be changed earlier than 3 months, depending on the ocular complications.[8]

Cycloplegic drops should be given to prevent or treat posterior synechiae in active uveitis. Cycloplegia is indicated in uveitis without synechiae or synechiae grades 1–2 however it is ineffective in grade 3. The recommended cycloplegic is tropicamide 10 mg/ml, one drop every 8 hours. Cycloplegics adverse events include somnolence, diminished accommodation (blurred vision, photophobia), and amblyopia.[37]

In unilateral or bilateral severe or refractory uveitis with sight-threatening risk factors, an ocular injection of glucocorticoids can be considered as a rescue therapy in selected cases (level of evidence and strength of recommendation III0).[5] These risk factors are initial decreased visual acuity, massive anterior chamber inflammation, hypotony, glaucoma, cataract, macular edema, or dense vitreous opacities.[5] Ocular injection has been recommended in patients with uveitis grades 3+ and 4+ without improvement after 2 weeks of treatment with oral corticosteroids, particularly in those with associated sight-threatening risk factors (level of evidence and strength of recommendation IIIB).[37] The location options for ocular injections of glucocorticoids are the subtenon or orbital floor (level of evidence and strength of recommendation III0) or intravitreal (level of evidence and strength of recommendation II0).[5] The subtenon or orbital floor injection dosage is 2–4 mg of dexamethasone phosphate or 20–40 mg of triamcinolone acetonide.[42–45] The intravitreal injection dosage is 700 mg of a dexamethasone phosphate implant and 2–4 mg of triamcinolone acetonide.[5,44,46–49] However, intraocular glucocorticoids are associated with cataract development and a risk of increased IOP, and IOP should be monitored every week (level of evidence and strength of recommendation IIIB).[37]

Topical and systemic nonsteroidal anti-inflammatory therapy should not be used as single therapy.[5]

Systemic treatment

The primary indication for systemic treatment is the failure of adequate control of inflammation after three months of topical treatment.[1,8,41] Systemic treatment may be started sooner, after

3 weeks without control, in the presence of sight-threatening risk factors such as initial decreased visual acuity, massive anterior chamber inflammation, hypotony, glaucoma, cataract, macular edema, or dense vitreous opacities (level of evidence and strength of recommendation IIIB).[37] Systemic treatment options for JIA-uveitis are divided into three subgroups: glucocorticoids, DMARDs (methotrexate, mycophenolate mofetil, cyclosporine A, and azathioprine), and biologic agents (anti-tumor necrosis factor [anti-TNF] blockers: adalimumab, infliximab, golimumab, etanercept; CTLA4-Ig: abatacept; and anti-IL6: tocilizumab). Each indication; mechanism of action; preferred dosage and administration route; ocular and systemic side effects; adverse events; and required laboratory routine tests are shown in Table 5.[1, 3, 50–57]

Both ophthalmologist and pediatric rheumatologist follow-ups are fundamental for indicating, monitoring, and guiding systemic treatment. Limited use of DMARDs due to adverse events should be assessed. Live and non-live virus vaccine schedules should be completed preferably within 4 weeks before treatment. Tuberculosis and latent tuberculosis infection screening should also be done before initiation of anti-TNF biologics. Drug adherence, contraception for adolescents, and rigorous monitoring for infections and malignancy should also be systematically evaluated.[5] Compliance with ophthalmologist and pediatric rheumatologist appointments should be also reinforced.

Topical glucocorticoid is more effective than systemic glucocorticoid in reducing anterior chamber cells.[5] However, the administration of systemic glucocorticoid as a bridge therapy should be considered in severe active uveitis with sight-threatening risk factors until a DMARD effect can be achieved.[5] Systemic glucocorticoids are usually given by the oral route. They can be used in oral high doses (1–2 mg/kg/day), intermediate doses (> 0.15 and < 1.0 mg/kg/day) or low doses (≤ 0.15 mg/kg/day) of prednisolone or equivalent (level of evidence and strength of recommendation III0).[5,42] Topical glucocorticoids should be tapered within 4 weeks to 0.15 mg/kg/day or less and limited to three months of use to avoid ocular and systemic complications (increased IOP, cataract, weight gain, diabetes mellitus, and growth retardation).[5] In very severe cases, intravenous treatment with methylprednisolone (pulse) can be used at 10–30 mg/kg/day in 2 h infusions for 3 days.[5,58]

The preferred initial systemic treatment for JIA-uveitis is the synthetic DMARD methotrexate (MTX), either oral or parenteral, with either subcutaneous, preferably, or and intramuscular route.[1,8] Laboratory routine should be performed every 1 to 3 months (Table 5), if transaminases increase up to 1 fold the upper limits, the MTX dose should be reversed; if transaminases increase more than 2 fold the upper limits, MTX should be suspended for 2–4 weeks and then restarted. Under normal transaminases status, treatment should be resumed otherwise its withdrawal is recommended. If no control of uveitis is observed or the disease worsens after 3–4 months on MTX, the prompt association with a biologic agent is recommended.[1] The ACR recommends monoclonal anti-TNF drugs, preferably adalimumab, infliximab, or golimumab (level of evidence and strength of recommendation IIIB).[8] Etanercept (a fusion protein receptor blocker) should not be considered for the treatment of JIA-associated uveitis.[59] For patients under one monoclonal anti-TNF at a standard dose and still with active CAU, a recommendation is to escalate the dose and/or frequency to above the standard before switching to another monoclonal anti-TNF (level of evidence and strength of recommendation IIIB).[8] In children and adolescents with active CAU who have failed the first monoclonal anti-TNF with proper dosage and/or frequency, changing to another monoclonal TNF inhibitor is recommended over switching to another biologic category.[8]

Patients with active CAU, despite MTX treatment plus monoclonal anti-TNF at the proper standard dosage, may switch to another biologic agent of different mechanism of action (abatacept or tocilizumab) or associated with immunomodulatory synthetic agents (mycophenolate, leflunomide, or cyclosporine). However, no evidence yet supports a specific drug, timing, or combination therapy.[8]

In patients with sight-threatening complications, the recommendation is an initial treatment with MTX combined with a monoclonal TNF inhibitor (level of evidence and strength of recommendation IIIB). The three-month threshold for adding or changing systemic therapy in children and adolescents who still require topical glucocorticoids to sustain uveitis control should be revised depending on the degree of ocular inflammation, the duration of topical and systemic therapy, and the presence of ocular complications.[8] The present committee suggests a one-month threshold for moderate to severe inflammatory conditions.

A recent systematic review evaluated the efficacy, response rates, and complications of DMARD treatment for JIA-uveitis.[4] The adalimumab pooled response rate estimates were 68% (95% CI: 66.4 to 70.6%) and drug-related side effects, including systemic complications (auto-immune diseases, local pain, anemia, depression, abscess, and sepsis) and ocular complications (cataracts and uveitis flares) occurred in 3 to 52% of the patients. The infliximab pooled response rate was 64.7% (95% CI: 59.8 to 69.3%). The most common side effects of both medications were reactivation of uveitis and infusion reaction in two-thirds, vitreous hemorrhage, and systemic infections. Of the synthetic DMARDs, only methotrexate was assessed, and its pooled response rate was 40.0% (95% CI: 36.0 to 44.2%). The heterogeneity of the response to MTX (33.9 to 85.7%) may have contributed to this result.[4]

Recommendations

Assembling the previously published recommendations, the treatment flow shown in Figure 2 is proposed.

Ocular complications of uveitis and its treatment

Ocular hypertension

IOP is defined as three successive measurements higher than 21 mmHg, or a single measurement higher than 30 mmHg.[60] IOP may occur due to several factors. For example, chronic inflammation may cause a dysfunctional trabecular meshwork and synechia formation, thereby leading to increased resistance outflow of aqueous humor. This can be further worsened by topical steroid use.[61]

Table 5. Drug names; mechanism of action; preferred dosage and route; ocular and systemic side effects; adverse events; and laboratory routine of synthetic and biological disease-modifying anti-rheumatic drugs (DMARDs) for juvenile idiopathic arthritis-associated uveitis.[1,5,50–57]

Drug name (level of evidence/ grade of recommendation)	Mechanism	Preferred dosage and route	Ocular and systemic side effects	Laboratory routine
Synthetic DMARDs				
Methotrexate (IIB)	Cellular adenosine release	10–15 mg/m^2 BS PO or SC weekly. Adjust dose gradually to achieve an optimal response.	GI discomfort, nausea, diarrhea, photosensitivity, rash, increased AST or ALT, cytopenias.	Baseline: Complete blood and platelet count. Renal function. Liver function. Chest X-ray. Monitoring: Hemogram, renal and liver function tests every 1–3 month.
Mycophenolate mofetil (III0)	Inhibitor of inosine-5-monophosphate dehydrogenase	300 mg/m^2 bd, increasing to 600 mg/m^2 bd	GI discomfort, leukopenia, pure red cell aplasia, hair loss, lymphoma and malignancy (particularly of the skin)	Complete blood cell counts weekly during the first month, twice monthly for the second and third months and then monthly
Cyclosporine A (III0)	Calcineurin inhibitor blocking T-cell proliferation	2.5–5 mg/kg/day in 2 doses	GI disturbance, hypertension, renal and liver dysfunctions, lipid abnormalities, hirsutism, gum hypertrophy.	Renal and liver functions, serum lipids, magnesium and potassium. Cyclosporine blood concentration adjusted to 100 mcg/dl
Azathioprine (III0)	Purine nucleoside analogue, inhibits DNA replication	1 to 3 mg/kg/day	Myelotoxicity and hepatotoxicity.	Complete blood and platelet count, liver function tests every 1–3 months.
Biological DMARDs				
Adalimumab (IIA)	Anti-TNF alfa/human monoclonal antibody	Body weight 10–15 kg: 10 mg SC every other week 15–30 kg: 20 mg SC every other week ≥ 30 kg: 40 mg SC every other week	Opportunistic infections by *Legionella, Listeria*, tuberculosis, and invasive fungal infections. Hepatitis B virus reactivation.	Check for latent infection. Avoid live vaccines during treatment or offer live vaccines prior to treatment. Complete blood count.
Infliximab (IIB)	Anti-TNF alfa/chimeric (mouse-human monoclonal antibody)	Initially 6 mg/kg/dose IV 3–10 mg/kg/dose IV at 2 weeks, then every 4–8 weeks, adjusted according to response	Infusion reaction. Hepatotoxicity (infliximab and tocilizumab). Heart failure. Hypersensitivity and anaphylaxis. Risk of cancer (invasive cervical cancer, hepatosplenic T-cell lymphoma). Cytopenias. Lupus-like syndrome. Demyelinating disease. Gastrointestinal perforation (tocilizumab). Vitreous hemorrhage (adalimumab and infliximab)	Hepatic function (infliximab and tocilizumab).
Tocilizumab (IIIB)	Anti-IL-6/humanized monoclonal antibody	Body weight < 30 kg: 10 mg/kg IV[8] body weight > 30 kg: 8 mg/kg IV[8] every 4 weeks		
Abatacept (III0)	Inhibition of lymphocyte co-stimulation (CTLA4)/human fusion protein	10 mg/kg IV At weeks 0, 2, 4 and every 4 weeks		

PO: by mouth. SC: subcutaneous. GI: gastro-intestinal. Bd: twice daily. Anti-TNF: Anti-tumor necrosis factor. IV: intravenous. IL interleukin. CTLA4: cytotoxic T-lymphocyte-associated protein 4.

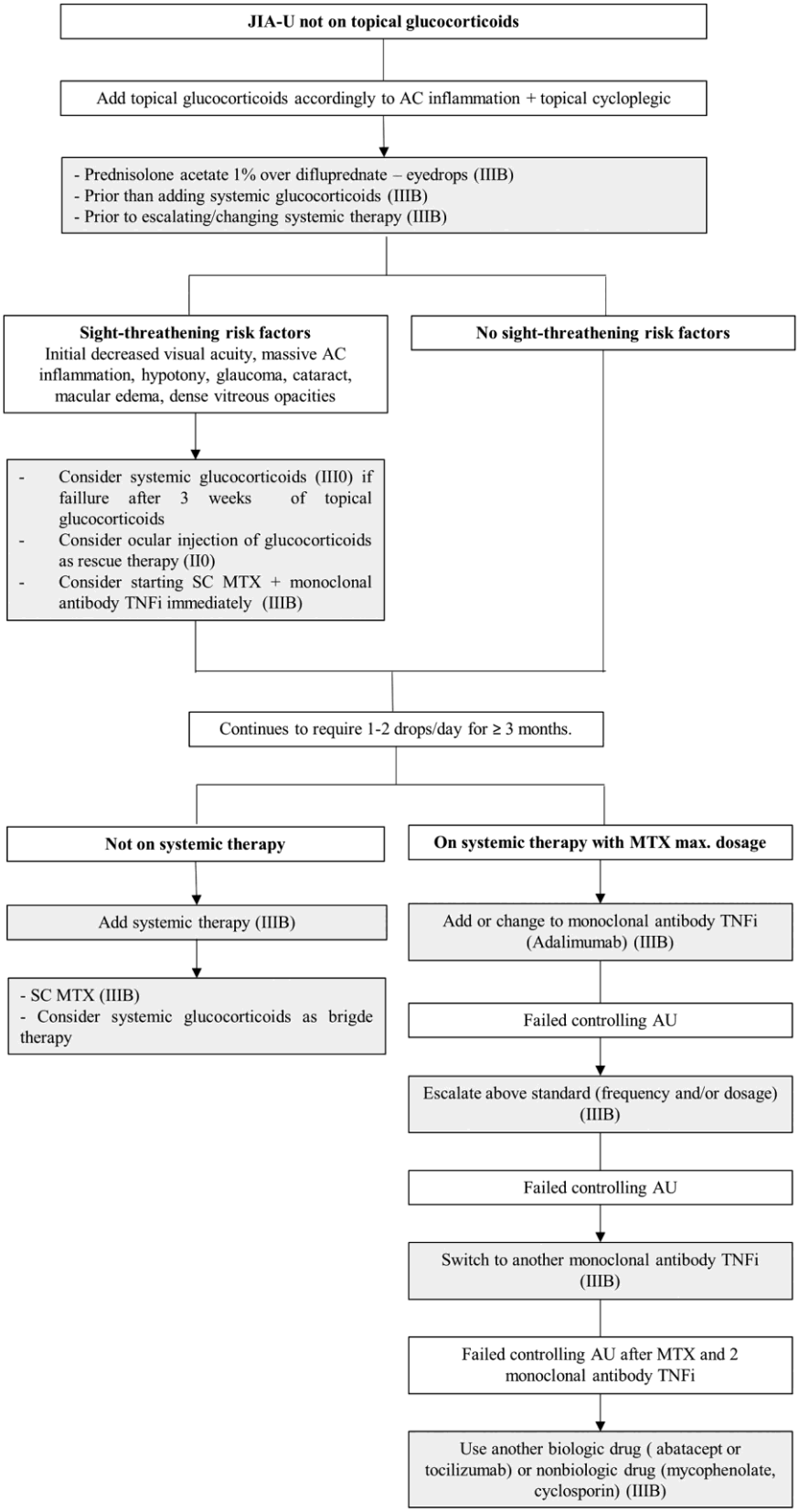


Figure 2. Treatment algorithm for chronic anterior uveitis (CAU) related to juvenile idiopathic arthritis (JIA-U) according to the American College of Rheumatology/ Arthritis Foundation (ACR/AF).[6]
Systemic therapy is defined as disease-modifying antirheumatic drugs and biologics. AC: anterior chamber; AU: anterior uveitis; SC: subcutaneous; MTX: methotrexate; TNFi: anti-TNF alpha.

Despite being the first line of treatment for JIA-uveitis, topical glucocorticoid drops, such as prednisolone and dexamethasone, are commonly associated with ocular complications in the lens and trabecular meshwork. The use of three drops of topical glucocorticoids daily over 4 years is associated with an increased risk of developing cataracts.[62] In patients using 0.1% dexamethasone four times daily over 8 weeks, an increased IOP (> 21 mmHg) occurred in approximately 60–70% of patients.[62]

IOP should be measured at every visit by applanation tonometry or tonopen.[63] Sedation for IOP measurement should be avoided if possible, and rebound tonometry can be considered for screening even though it overestimates the IOP.[60]

The increased IOP should be managed promptly with topical antihypertensives. If ocular hypertension persists, glaucoma-filtering surgery or goniotomy may be considered.[64,65] Although transscleral diode cyclophotocoagulation (TD-CPC) has already been reported as an effective surgical technique in the control of IOP in refractory secondary glaucoma, it does not show good results in controlling IOP as a primary surgical treatment in patients with JIA.[66,67]

By contrast, goniotomy was confirmed as an effective technique for first-line surgical treatment for medically uncontrolled glaucoma secondary to chronic childhood uveitis, in addition to being a safe and low-risk technique.[68,69] One consideration, however, is that its results may be limited in older patients or in patients with peripheral anterior synechiae, prior surgeries, and aphakia due to structural changes in the meshwork.[68,70] For these cases, as well as those in whom goniotomy surgery failed, the implantation of glaucoma drainage devices must be considered.

Although glaucoma drainage device implantation is the standard treatment for adult uveitic glaucoma, its results in juvenile uveitic glaucoma are still uncertain due to a lack of evidence reports.[71–74] Nevertheless, in many children with chronic uveitis, drainage device implantation (such as the Molteno or Ahmed devices) can be a safe and effective procedure for treating pediatric uveitic glaucoma.[72,75] Short-term and long-term complications of the implantation include endothelial cell loss, corneal decompensation, and tube erosion through the conjunctiva.[72] The trabeculotomy, another filtering surgery, can also be performed as an alternative to drainage devices, and it has the benefit of causing less inflammatory response after the surgical procedure.[76,77]

Regardless of the surgical procedure chosen, however, a point to remember is that the inflammatory response in the postoperative period is often exacerbated and complicates the control of both uveitis and IOP.[71] Furthermore, the need for a second intervention and associated glaucoma medications in the postoperative period is a frequent management step required to obtain long-term control of the IOP.[69,72,76]

Cataracts

Surgical treatment is indicated for patients with visually significant cataracts. The surgical procedures include lensectomy and vitrectomy via the pars plana or phacoemulsification with or without intraocular lens (IOL) implantation. The selection of the surgical procedure should consider the patient's age, the synechia pattern, the vision prognosis, and the surgeon's experience. The IOL implantation remains controversial due to a more aggressive inflammatory response in the postoperative period and a greater chance of complications.[21,78,79]

However, recent studies have suggested that IOLs may improve visual outcomes in patients with JIA-uveitis under good control.[80–82] In addition, in young children requiring unilateral surgery, the IOL implantation seems to be more advantageous compared to contact lens correction, particularly because JIA is associated with a high prevalence of dry eye, which can hinder the use of the contact lenses.[83] If IOL implantation is indicated, hydrophobic acrylic IOLs are the most suitable for the procedure.[80,84,85]

For the surgery to be performed safely, both eyes should ideally be free of inflammation (less than 1+ cells in the anterior chamber) for 3 months before the procedure. Furthermore, maintaining control of inflammation during and after surgery is also essential.[21] Preoperative anti-inflammatory medications, such as topical (prednisolone 1%) and systemic glucocorticoid (prednisone or methylprednisolone), are advised to avoid ocular inflammation triggered by the surgical procedure.[21,86,87] After the surgery, topical steroids use should be continued, with eventual tapering and discontinuation, based on each patient baseline usage.[78,86] Systemic steroids used for more than 14 days may also need tapering.[86,88] A recent study also suggests intraoperative intravitreal dexamethasone implantation to avoid the need to increase oral glucocorticoids in the preoperative period to prevent postoperative inflammation.

Macular edema and refractory inflammation

Factors that may be associated with macular edema are microvascular changes (for example, those caused by diabetes mellitus), inflammatory stress (related to uveitis duration), cataract surgery, and hypotony.[89,90]

The initial treatment for inflammatory edema is systemic therapy for uveitis control. In most severe uveitis cases that are refractory to MTX associated with TNF-α inhibitors, the use of the anti-interleukin-6 receptor antibody tocilizumab (TCZ) showed good results for resolution of macular edema.[91] Intravitreal therapies should be considered if systemic therapies are insufficient.[92] Recently, intraocular injectable implants of biodegradable dexamethasone have been used to treat macular edema and refractory inflammation. They provide slow local release of steroids, with good results in controlling inflammation but with a high rate of ocular hypertension. More studies are still needed to confirm their safety and benefits in these patients.[93]

Uveitis treatment monitoring

Every ophthalmologic exam must use age-appropriate visual acuity tests, classify the anterior chamber cell grade at the slit lamp by the SUN criteria, and quantify structural complications.[29] Furthermore, recording the duration of active inflammation and detailing the treatment response are also important.[21]

The recommendations for ophthalmological exams in children and adolescents once JIA-uveitis is diagnosed should be performed accordingly to the anterior chamber degree of inflammation (Table 2), as follows (level of evidence and strength of recommendation IIIB)[37]:

- In grades 3+ or 4+: weekly until improvement;
- In grades 1+ or 2+ (stable in two successive visits): every 2 weeks (or at least in less than 6 weeks);
- In grade 0.5+ (stable in two successive visits): every 6 weeks (or at least in less than 3 months).

* Follow-up may be individualized and agreed upon by the care team also according to the frequency of topical glucocorticoid administration, the IOP, and the presence of ocular complications.[8]

The recommendations for ophthalmological monitoring in children and adolescents with controlled JIA-uveitis were classified as Level A and should be performed as follows[8]:

- Monthly: if tapering or discontinuing topical glucocorticoids (III). The patient should be evaluated before each step of tapering.
- Within 2 months: if tapering or discontinuing systemic therapy* (III).
- Every 3 months: if on stable therapy, systemic or topical (III).

* In the suspension of systemic or immunomodulatory therapy, eye checkups should be performed every 2 months for 6 months.[94]

Tapering therapy in controlled JIA-uveitis

Tapering therapy in children and adolescents with controlled JIA-uveitis should be conducted as follows[8]:

- Patients on systemic therapy and 1–2 drops/day of prednisolone acetate 1% (or equivalent): it is recommended tapering topical steroids before tapering systemic therapy (level of evidence and strength of recommendation IIIA). Another recommended step is ophthalmic monitoring within one month after each change in topical glucocorticoids (level of evidence and strength of recommendation IIIA).
- Patients on systemic therapy only (synthetic DMARD and biologic therapy): tapering is recommended for systemic therapy only if the disease is controlled for at least 2 years (level of evidence and strength of recommendation IIIB).* A further recommended step is ophthalmic monitoring within 2 months after each change in systemic therapy (level of evidence and strength of recommendation IIIA).

* For tapering systemic therapy, other JIA manifestations, including arthritis activity, should be considered.

** Periodic clinical and laboratory evaluations should be performed after systemic medication withdrawal. We suggest the frequency of at least monthly evaluations in the first 3 months, followed by 2 visits at 2-month intervals and quarterly thereafter.

Recommendations

Assembling previous models, the proposed monitoring and tapering flow guidelines are shown in Figure 3.

Discussion

A Brazilian JIA epidemiological profile analysis is challenging due to the scarce database and the marked differences within its territory of continental dimensions. Two studies, investigating local populations, found that JIA prevalence among children under 16 years old ranged from 34 to 196/100,000, which is within the estimated global prevalence (3.8 to 400/100,000).-[2,95,96] One of those reports also analyzed JIA-uveitis and estimated its prevalence as 5.6%, which is below the global pooled prevalence (11.8%).[2,97] The oligoarticular subtype had a higher prevalence, following the international data.[2,97–99] However with only a slight difference in the prevalences of oligoarticular and systemic forms of the disease in one of the series.[97] Furthermore, there was no sex predominance,[97,99] diverging from global evidence,[2] but similar to African, Asian, and African-Americans populations.[20,100] Despite this epidemiological information, the treatment for JIA-uveitis has not undergone any local adaptation, so this therapeutic proposition can be used worldwide.

A delay in the diagnosis of JIA-uveitis can result in irreversible vision damage. According to the current data, one-third of patients with JIA-uveitis present with ocular complications at the time of diagnosis.[4] The ocular complication incidence rates can be as high as 67% of the JIA-affected children.[4]

In this context, efficient screening works as a secondary prevention, as it is essential for avoiding vision impairment and improving the health-related quality of life of JIA patients. A further consideration is that this is a population with chronic disease and members of a future workforce. Vision impairment could impact both education and employment.

JIA-uveitis treatment may be challenging due to frequent ophthalmologic consultations and systemic treatment conducted by an expert team of pediatric rheumatologists and ophthalmologists. Therefore, a formal recommendation for conducting its treatment and monitoring is essential and should include the available biological and synthetic drugs within the health system demands in different regions of the country. The drug compliance and adherence for ophthalmologist and pediatric rheumatologist appointments should also be periodically reinforced, particularly for JIA teenagers.

The current treatment guidelines for JIA-uveitis were developed by groups of rheumatologists, and their format and language are challenging for the ophthalmological community.[4–6,8] Thus, compiling the information and adjusting it to the daily practice of ophthalmologists are further requirements. Other forms of anterior uveitis in childhood occur less frequently but have treatments as challenging as that of JIA-uveitis. These also could be

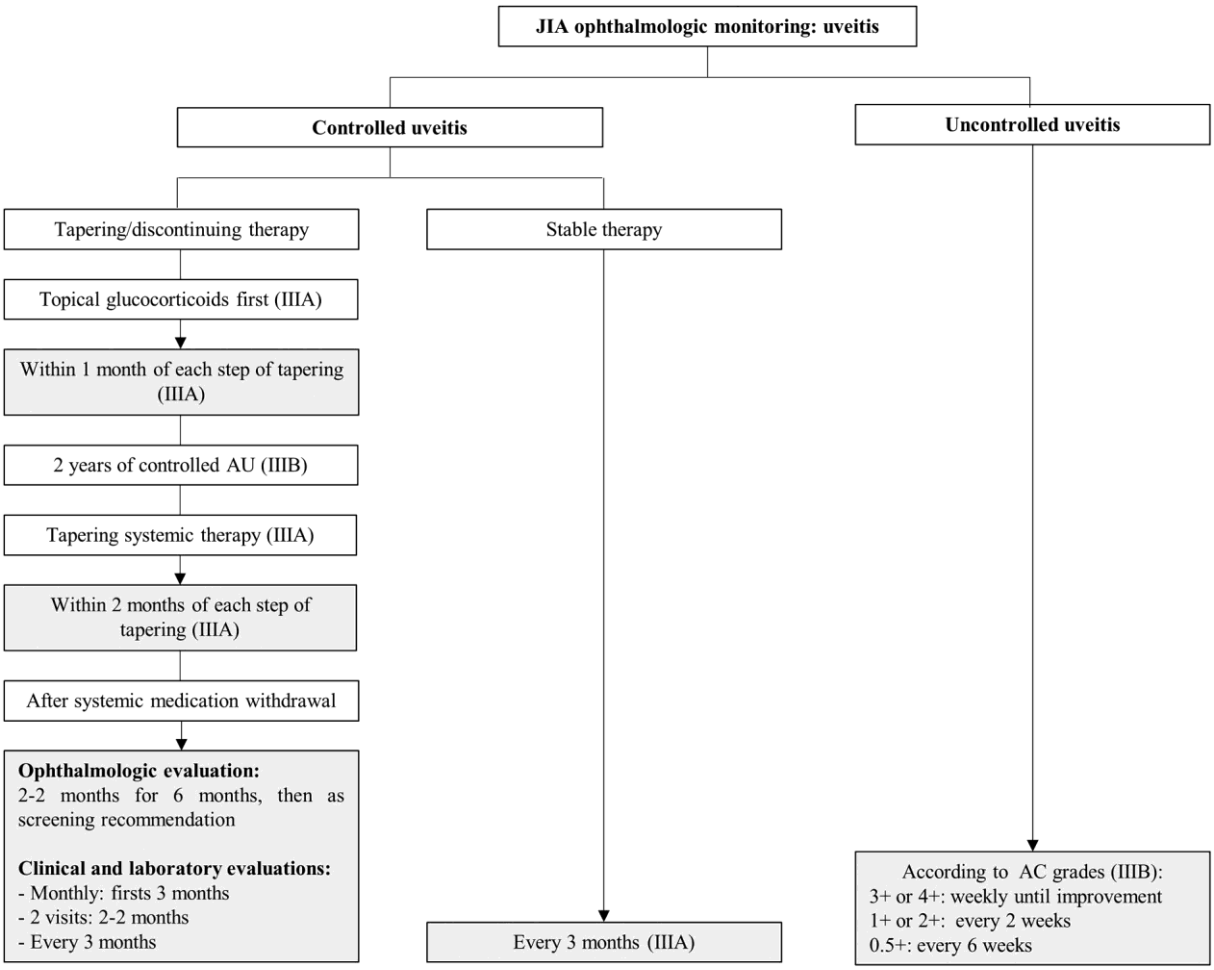


Figure 3. Ophthalmologic monitoring examinations and tapering therapy in juvenile idiopathic arthritis-related uveitis (JIA-uveitis).[6] Examinations can occur at 2–6-week intervals and can be tailored to the frequency of topical glucocorticoid administration, intraocular pressure, degree of inflammation, and presence of complications, as agreed on by the treatment team. JIA: juvenile idiopathic arthritis; AC: anterior chamber; AU: anterior uveitis.

addressed in the present guideline. Those include uveitis associated with Pediatric Granulomatous Arthritis (AGP, also known as Blau's Syndrome) and with juvenile ankylosing spondylitis. AGP is a monogenic autoinflammatory and granulomatous disease resulting from *NOD2* mutations; it presents with arthritis, dermatitis, and uveitis. The patient usually presents a chronic bilateral granulomatous panuveitis with multifocal chorioretinal lesions. Active anterior and posterior uveitis may persist in more than half of the patients, despite combined topical and systemic therapy. AGP uveitis is associated with high rates of ocular complications and moderate to severe vision impairment.[101] Juvenile ankylosing spondylitis is a chronic spine arthropathy predominant in males with positive HLA-B27 in 91% of patients.[102] The characteristic ocular involvement is a severe symptomatic unilateral AAU. The uveitis seen in 10–15% of these patients can be recurrent, alternating between the eyes.[102]

Therefore, after a comprehensive scientific review of JIA-uveitis, the aim of the Brazilian Pediatric Ophthalmology Society (SBOP) was to provide consensus-based and evidence-based guidelines for the routine practice of screening, diagnosing, treating, and monitoring JIA-uveitis from the joint perspectives of experts in ophthalmology and rheumatology nationwide.

Acknowledgments

Luciana Silva, MD, Ph.D. from the Federal University of Bahia and president of the Brazilian Society of Pediatrics.

Dirceu Solé, MD, Ph.D. from the Federal University of Sao Paulo and Scientific Committee Chief of the Brazilian Society of Pediatrics.

José Roberto Provenza, MD, Ph.D. from the Pontifical Catholic University of Campinas and president of the Brazilian Society of Rheumatology.

Eduardo dos Santos Paiva, MD, Ph.D. from the Federal University of Paraná and Scientific Committee Chief of the Brazilian Society of Rheumatology.

Disclosure of interests

There were no financial support to this sudy and the authors report no conflict of interest.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

ORCID

H Moraes do Nascimento MD http://orcid.org/0000-0003-0315-1317

References

1. Sen ES, Ramanan AV. Juvenile idiopathic arthritis-associated uveitis. *Best Pract Res Clin Rheumatol*. 2017;31(4):517–534. doi:10.1016/j.berh.2018.01.002.
2. Thierry S, Fautrel B, Lemelle I, Guillemin F. Prevalence and incidence of juvenile idiopathic arthritis: a systematic review. *Joint Bone Spine*. 2014;81(2):112–117. doi:10.1016/j.jbspin.2013.09.003.
3. Heiligenhaus A, Heinz C, Edelsten C, Kotaniemi K, Minden K. Review for disease of the year: epidemiology of juvenile idiopathic arthritis and its associated uveitis: the probable risk factors. *Ocul Immunol Inflamm*. 2013;21(3):180–191. doi:10.3109/09273948.2013.791701.
4. Jari M, Shiari R, Salehpour O, Rahmani K. Epidemiological and advanced therapeutic approaches to treatment of uveitis in pediatric rheumatic diseases: a systematic review and meta-analysis. *Orphanet J Rare Dis*. 2020;15(1):41. doi:10.1186/s13023-020-1324-x.
5. Heiligenhaus A, Minden K, Tappeiner C, et al. Update of the evidence based, interdisciplinary guideline for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis. *Semin Arthritis Rheum*. 2019;49:43–55. doi:10.1016/j.semarthrit.2018.11.004.
6. de Moraes AJPVA, Bica BERG, Len C, et al. Projeto Diretrizes; Artrite Idiopática Juvenil: diagnóstico. In: *Reumatologia SBdPeSBd*. ed. Sao Paulo, Brazil: AMB; 2012:1–16.
7. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924–926. doi:10.1136/bmj.39489.470347.AD.
8. Angeles-Han ST, Ringold S, Beukelman T, et al. American College of Rheumatology/Arthritis Foundation Guideline for the Screening, Monitoring, and Treatment of Juvenile Idiopathic Arthritis-Associated Uveitis. *Arthritis Care Res (Hoboken)*. 2019;2019(71):703–716. doi:10.1002/acr.23871.
9. Nordal E, Rypdal V, Christoffersen T, et al. Incidence and predictors of Uveitis in juvenile idiopathic arthritis in a Nordic long-term cohort study. *Pediatr Rheumatol Online J*. 2017;15(1):66. doi:10.1186/s12969-017-0195-8.
10. Consolaro A, Giancane G, Alongi A, et al. Phenotypic variability and disparities in treatment and outcomes of childhood arthritis throughout the world: an observational cohort study. *Lancet Child Adolesc Health*. 2019;3(4):255–263. doi:10.1016/S2352-4642(19)30027-6.
11. Fernandez DGNH, Nascimento C, Muccioli C, Belfort Jr RM. Uveitis in São Paulo, Brazil: 1053 New Patients in 15 Months. *Ocul Immunol Inflamm*. 2017;25:382–387. doi:10.3109/09273948.2015.1132741.
12. Haasnoot AJWKJ, Boer JH. Predicting uveitis in juvenile idiopathic arthritis: from biomarkers to clinical practice. *Expert Rev Clin Immunol*. 2019;15:657–666. doi:10.1080/1744666X.2019.1593139.
13. Tappeiner C, Klotsche J, Sengler C, et al. Risk Factors and biomarkers for the occurrence of uveitis in juvenile idiopathic arthritis: data from the inception cohort of newly diagnosed patients with juvenile idiopathic arthritis study. *Arthritis Rheumatol*. 2018;70:1685–1694. doi:10.1002/art.40544.
14. Pelegrín L, Casaroli-Marano R, Jordi Antón J, et al. Predictive value of selected biomarkers, polymorphisms, and clinical features for oligoarticular juvenile idiopathic arthritis-associated uveitis. *Ocul Immunol Inflamm*. 2014;22:208–212. doi:10.3109/09273948.2013.841495.
15. Haasnoot AJW, Schilham MW, Kamphuis S, et al. Identification of an amino acid motif in HLA-DRβ1 that distinguishes uveitis in patients with juvenile idiopathic arthritis. *Arthritis Rheumatol*. 2018;70:1155–1165. doi:10.1002/art.40484.
16. Lambert SR, Lyons CJ. *Taylor and Hoyt's Pediatric Ophthalmology and Strabismus*. 5th. Amsterdam: Elsevier; 2016.
17. Heiligenhaus A, Niewerth M, Ganser G, Heinz C, Minden K, German Uveitis in Childhood Study G. Prevalence and complications of uveitis in juvenile idiopathic arthritis in a population-based nation-wide study in Germany: suggested modification of the current screening guidelines. *Rheumatology (Oxford)*. 2007;46(6):1015–1019. doi:10.1093/rheumatology/kem053.
18. Saurenmann RK, Levin AV, Feldman BM, Laxer RM, Schneider R, Silverman ED. Risk factors for development of uveitis differ between girls and boys with juvenile idiopathic arthritis. *Arthritis Rheum*. 2010;62(6):1824–1828. doi:10.1002/art.27416.
19. Kotaniemi K. Occurrence of uveitis in recently diagnosed juvenile chronic arthritis A prospective study. *Ophthalmology*. 2001;108(11):2071–2075. doi:10.1016/S0161-6420(01)00773-4.
20. Saurenmann RK, Rose JB, Tyrrell P, et al. Epidemiology of juvenile idiopathic arthritis in a multiethnic cohort: ethnicity as a risk factor. *Arthritis Rheum*. 2007;56(6):1974–1984. doi:10.1002/art.22709.
21. Hawkins MJ, Dick AD, Lee RJ, et al. Managing juvenile idiopathic arthritis-associated uveitis. *Surv Ophthalmol*. 2016;61:197–210. doi:10.1016/j.survophthal.2015.10.005.
22. Schwartz MM, Simpson P, Kerr KL, Jarvis JN. Juvenile rheumatoid arthritis in African Americans. *J Rheumatol*. 1997;24:1826–1829.
23. Saurenmann RK, Levin AV, Feldman BM, et al. Prevalence, risk factors, and outcome of uveitis in juvenile idiopathic arthritis: a long-term followup study. *Arthritis Rheum*. 2007;56(2):647–657. doi:10.1002/art.22381.
24. Roberto AM, Terreri MT, Len C, Muccioli C, Hilario MO. [Uveitis in juvenile idiopathic arthritis]. *J Pediatr (Rio J)*. 2002;78:62–66. doi:10.2223/JPED.667.
25. Heiligenhaus A, Klotsche J, Tappeiner C, et al. Predictive factors and biomarkers for the 2-year outcome of uveitis in juvenile idiopathic arthritis: data from the Inception Cohort of Newly diagnosed patients with Juvenile Idiopathic Arthritis (ICON-JIA) study. *Rheumatology (Oxford)*. 2019;58:975–986. doi:10.1093/rheumatol-ogy/key406.
26. Angeles-Han ST, Yeh S, Vogler LB. Updates on the risk markers and outcomes of severe juvenile idiopathic arthritis-associated uveitis. *Int J Clin Rheumtol*. 2013;8(1):10.2217/ijr.12.83. doi:10.2217/ijr.12.83.
27. Chia A, Lee V, Graham EM, Edelsten C. Factors related to severe uveitis at diagnosis in children with juvenile idiopathic arthritis in a screening program. *Am J Ophthalmol*. 2003;135:757–762. doi:10.1016/S0002-9394(03)00225-3.
28. Edelsten C1, Lee V, Bentley CR, Kanski JJ, Graham EM. An evaluation of baseline risk factors predicting severity in juvenile idiopathic arthritis associated uveitis and other chronic anterior uveitis in early childhood. *Br J Ophthalmol*. 2002;86:51–56.
29. Jabs DA, Nussenblatt RB, Rosenbaum JT; Standardization of Uveitis Nomenclature Working G. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol*. 2005;140:509–516.
30. Chylack LT Jr. The ocular manifestations of juvenile rheumatoid arthritis. *Arthritis Rheum*. 1977;20:217–223.
31. Dana MR, Merayo-Lloves J, Schaumberg DA, Foster CS. Visual outcomes prognosticators in juvenile rheumatoid arthritis-associated uveitis. *Ophthalmology*. 1997;104(2):236–244. doi:10.1016/S0161-6420(97)30329-7.
32. Kanski JJ. Anterior uveitis in juvenile rheumatoid arthritis. *Arch Ophthalmol*. 1977;95:1794–1797. doi:10.1001/archopht.1977.04450100096010.
33. Sabri K, Saurenmann RK, Silverman ED, Levin AV. Course, complications, and outcome of juvenile arthritis-related uveitis. *J Aapos*. 2008;12:539–545. doi:10.1016/j.jaapos.2008.03.007.
34. Carvounis PE, Herman DC, Cha S, Burke JP. Incidence and outcomes of uveitis in juvenile rheumatoid arthritis, a synthesis of the literature. *Graefes Arch Clin Exp Ophthalmol*. 2006;244 (3):281–290. doi:10.1007/s00417-005-0087-3.
35. Bolt IB, Cannizzaro E, Seger R, Saurenmann RK. Risk factors and longterm outcome of juvenile idiopathic arthritis-associated uveitis in Switzerland. *J Rheumatol*. 2008;35:703–706.
36. Davies K, Cleary G, Foster H, et al. BSPAR Standards of Care for children and young people with juvenile idiopathic arthritis. *Rheumatology (Oxford)*. 2010;49:1406–1408. doi:10.1093/rheumatology/kep460.

37. Bou R, Adan A, Borrás F, et al. Clinical management algorithm of uveitis associated with juvenile idiopathic arthritis: interdisciplinary panel consensus. Rheumatol Int. 2015;35:777–785. doi:10.1007/s00296-015-3231-3.
38. Foeldvari I, Klotsche J, Simonini G, et al. Proposal for a definition for response to treatment, inactive disease and damage for JIA associated uveitis based on the validation of a uveitis related JIA outcome measures from the Multinational Interdisciplinary Working Group for Uveitis in Childhood (MIWGUC). *Pediatr Rheumatol Online J*. 2019;17:66.
39. The Royal College of Ophthalmologists. *British Society of Paediatric and Adolescent Rheumatology Guidelines for Screening for Uveitis in Juvenile Idiopathic Arthritis.* London; 2006.
40. Rhee DJ, Pyfer MF. The Wills eye manual: office and emergency room diagnosis and treatment of eye disease Wills eye hospital. In: *Anterior Uveitis (Iritis/iridocyclitis)*. Chapter 12; 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 1999.
41. Heiligenhaus A, Michels H, Schumacher C, et al. Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis. *Rheumatol Int*. 2012;32(5):1121–1133. doi:10.1007/s00296-011-2126-1.
42. Gaudio PA. A review of evidence guiding the use of corticosteroids in the treatment of intraocular inflammation. *Ocul Immunol Inflamm*. 2004;12(3):169–192. doi:10.1080/092739490500192.
43. Kanski JJ. Juvenile arthritis and uveitis. *Surv Ophthalmol*. 1990;34(4):253–267. doi:10.1016/0039-6257(90)90026-R.
44. Roesel M, Gutfleisch M, Heinz C, Heimes B, Zurek-Imhoff B, Heiligenhaus A. Intravitreal and orbital floor triamcinolone acetonide injections in noninfectious uveitis: a comparative study. *Ophthalmic Res*. 2009;42(2):81–86. doi:10.1159/000220600.
45. Roesel M, Gutfleisch M, Heinz C, Heimes B, Zurek-Imhoff B, Heiligenhaus A. Orbital floor triamcinolone acetonide injections for the management of active non-infectious uveitis. *Eye (Lond)*. 2009;23(4):910–914. doi:10.1038/eye.2008.114.
46. Antcliff RJ, Spalton DJ, Stanford MR, Graham EM, Ffytche TJ, Marshall J. Intravitreal triamcinolone for uveitic cystoid macular edema: an optical coherence tomography study. *Ophthalmology*. 2001;108(4):765–772. doi:10.1016/S0161-6420(00)00658-8.
47. Heiligenhaus A, Bertram B, Heinz C, et al. Statement of the German Ophthalmological Society, the Retina Society and the Professional Association of German Ophthalmologists for intravitreal treatment of macular edema in uveitis: date: 02/07/2014. *Ophthalmologe*. 2014;111:740–748. doi:10.1007/s00347-014-3130-0.
48. Pleyer U, Klamann M, Laurent TJ, et al. Fast and Successful Management of Intraocular Inflammation with a Single Intravitreal Dexamethasone Implant. *Ophthalmologica*. 2014. doi:10.1159/000368987.
49. Sallam A, Comer RM, Chang JH, et al. Short-term safety and efficacy of intravitreal triamcinolone acetonide for uveitic macular edema in children. *Arch Ophthalmol*. 2008;126(2):200–205. doi:10.1001/archophthalmol.2007.59.
50. Simonini G, Druce K, Cimaz R, Macfarlane GJ, Jones GT. Current Evidence of Anti-Tumor Necrosis Factor α Treatment Efficacy in Childhood Chronic Uveitis: a Systematic Review and Meta-Analysis Approach of Individual Drugs. *Arthritis Care Res (Hoboken)*. 2014;66(7):1073–1084. doi:10.1002/acr.22214.
51. US Food and Drug Administration (FDA). Abatacept. Reference ID: 3428402, 2013.
52. US Food and Drug Administration (FDA). Adalimumab. Reference ID: 4359269, 2018.
53. US Food and Drug Administration (FDA). Cyclosporin. Reference ID: 3303454
54. US Food and Drug Administration (FDA). Infliximab. Reference ID: 4608934. Maryland; 2020.
55. US Food and Drug Administration (FDA). Mycophenolate mofetil. Reference ID: 4310726 2018.
56. US Food and Drug Administration (FDA). Methotrexate. Reference ID: 4526395 2019.
57. US Food and Drug Administration (FDA). Tocilizumab. Reference ID: 3393637. 2013.
58. Wakefield D, McCluskey P, Penny R. Intravenous pulse methylprednisolone therapy in severe inflammatory eye disease. *Arch Ophthalmol*. 1986;104(6):847–851. doi:10.1001/archopht.1986.01050180081035.
59. Constantin T, Foeldvari I, Anton J, et al. Consensus-based recommendations for the management of uveitis associated with juvenile idiopathic arthritis: the SHARE initiative.. *Ann Rheum Dis*. 2018;77(8):1107–1117. doi:10.1136/annrheumdis-2018-213131.
60. Esmael A, Ismail YM, Elhusseiny AM, Fayed AE, Elhilali HM. Agreement profiles for rebound and applanation tonometry in normal and glaucomatous children. *Eur J Ophthalmol*. 2019;29(4):379–385. doi:10.1177/1120672118795060.
61. Rolim-de-moura CFNC, Esporcatte BLB. *Glaucoma Na Infância*. 1st ed. Sao Paulo: Cultura Medica; 2019.
62. Choi J, Hawley DP, Ashworth J, Edelsten C, Bossuyt A. An update on the modern management of paediatric uveitis. *Br J Ophthalmol*. 2019;103:1685–1689. doi:10.1136/bjophthalmol-2019-314212.
63. Sijssens KM, Rothova A, Berendschot TT, de Boer JH. Ocular hypertension and secondary glaucoma in children with uveitis. *Ophthalmology*. 2006;113:853–9 e2. doi:10.1016/j.ophtha.2006.01.043.
64. Bohnsack BL, Freedman SF. Surgical outcomes in childhood uveitic glaucoma. *Am J Ophthalmol*. 2013;155(1):134–142. doi:10.1016/j.ajo.2012.07.008.
65. Foster CS, Havrlikova K, Baltatzis S, Christen WG, Merayo-Lloves J. Secondary glaucoma in patients with juvenile rheumatoid arthritis-associated iridocyclitis. *Acta Ophthalmol Scand*. 2000;78(5):576–579. doi:10.1034/j.1600-0420.2000.078005576.x.
66. Frezzotti P, Mittica V, Martone G, et al. Longterm follow-up of diode laser transscleral cyclophotocoagulation in the treatment of refractory glaucoma. *Acta Ophthalmol.* 2010;88:150–155. doi:10.1111/j.1755-3768.2008.01354.x.
67. Dastiridou AIAS, Praidou A, Brazitikos P, Brozou CG, Tsironi EE. Transscleral diode laser cyclophotocoagulation for refractory glaucoma secondary to juvenile idiopathic arthritis: a short term follow-up.. *Int Ophthalmol*. 2013;33:409–413. doi:10.1007/s10792-012-9672-8.
68. Ho CLWE. Goniosurgery for glaucoma complicating chronic childhood uveitis. *Arch Ophthalmol*. 2004;122(6):838–844. doi:10.1001/archopht.122.6.838.
69. Freedman SF-R-R-R, Rojas MC, Enyedi LB. Goniotomy for glaucoma secondary to chronic childhood uveitis. *Am J Ophthalmol*. 2002;133:617–662. doi:10.1016/S0002-9394(02)01344-2.
70. Ho CLWD. Goniosurgery for glaucoma secondary to chronic anterior uveitis: prognostic factors and surgical technique. *J Glaucoma*. 2004;13:445–449. doi:10.1097/01.ijg.0000141368.96950.3c.
71. Carreno EVS, Portero A, Herraras JM, Maquet JA, Calonge M. Surgical outcomes of uveitic glaucoma. *J Ophthalmol Inflamm Infect*. 2011;1:43–53. doi:10.1007/s12348-010-0012-8.
72. Papadaki TGZI, Pasquale LR, Christen WB, Netland PA, Foster CS. Long-term results of Ahmed glaucoma valve implantation for uveitic glaucoma. *Am J Ophthalmol*. 2007;144:62–69. doi:10.1016/j.ajo.2007.03.013.
73. Rolim de Moura CF-BS, Stout A, Labree L, Nilfours M, Varma R. Experience with the Baerveldt glaucoma implant in the management of pediatric glaucoma. *Am J Ophthalmol*. 2005;139:847–854. doi:10.1016/j.ajo.2004.12.028.
74. Kafkala CHA, Choi J, Topalkara A, Foster CS. Ahmed valve implantation for uncontrolled pediatric uveitic glaucoma. *J Aapos*. 2005;9:336–340. doi:10.1016/j.jaapos.2005.04.006.
75. Kotaniemi -KS-K-K. Occurrence and management of ocular hypertension and secondary glaucoma in juvenile idiopathic arthritis-associated uveitis: an observational series of 104 patients. *Clin Ophthalmol*. 2007;1:455–459.
76. Wang QWJ, Fortin E, Hamel P. Trabeculotomy in the Treatment of Pediatric Uveitic Glaucoma. *J Glaucoma*. 2016;25:744–749. doi:10.1097/IJG.0000000000000516.
77. Wiese CHA, Heinz C. Changes in Inflammatory Activity after Glaucoma Filtration Surgery in Children with Chronic Anterior Uveitis. *Ocul Immunol Inflamm*. 2016;24:397–401. doi:10.3109/09273948.2015.1088041.

78. Acevedo S, Quinones K, Rao V, Cervantes-Castaneda RA, Foster CS. Cataract surgery in children with juvenile idiopathic arthritis associated uveitis. *Int Ophthalmol Clin*. 2008;48(2):1–7. doi:10.1097/IIO.0b013e3181695b80.
79. Phatak S, Lowder C, Pavesio C. Controversies in intraocular lens implantation in pediatric uveitis. *J Ophthalmic Inflamm Infect*. 2016;6(1):12. doi:10.1186/s12348-016-0079-y.
80. Grajewski RSZ-IB, Roesel M, Heinz C, Heiligenhaus A. Favourable outcome after cataract surgery with IOL implantation in uveitis associated with juvenile idiopathic arthritis. *Acta Ophthalmol*. 2012;90:657–662. doi:10.1111/j.1755-3768.2011.02110.x.
81. Terrada C, Julian K, Cassoux N, et al. Cataract surgery with primary intraocular lens implantation in children with uveitis: long-term outcomes. *J Cataract Refract Surg*. 2011;37:1977–1983. doi:10.1016/j.jcrs.2011.05.037.
82. Benezra DCE. Cataract surgery in children with chronic uveitis. *Ophthalmology*. 2000;107(7):1255–1260. doi:10.1016/S0161-6420(00)00160-3.
83. Akinci ACN, Uncu N, Kara N, Acaroglu G. Keratoconjunctivitis sicca in juvenile rheumatoid arthritis. *Cornea*. 2007;26:941–944. doi:10.1097/ICO.0b013e3180de1f34.
84. Magli AFR, Rombetto L, Alessio M. Cataract management in juvenile idiopathic arthritis: simultaneous versus secondary intraocularlens implantation. *Ocul Immunol Inflamm*. 2014;22:133–137. doi:10.3109/09273948.2013.834062.
85. Kotaniemi K, Penttila H. Intraocular lens implantation in patients with juvenile idiopathic arthritis associated uveitis. *Ophthalmic Res*. 2006;38:318–323. doi:10.1159/000096225.
86. Foster CS, Barrett F. Cataract development and cataract surgery in patients with juvenile rheumatoid arthritis-associated iridocyclitis. *Ophthalmology*. 1993;100(6):809–817. doi:10.1016/S0161-6420(93)31568-X.
87. Lundvall A. Cataract extraction and intraocular lens implantation in children with uveitis. *Br J Ophthalmol*. 2000;84(7):791–793. doi:10.1136/bjo.84.7.791.
88. Alves C, Robazzi TC, Mendonca M. Withdrawal from glucocorticosteroid therapy: clinical practice recommendations. *J Pediatr (Rio J)*. 2008;84:192–202. doi:10.2223/JPED.1773.
89. Paroli MPFC, Spinucci G, Abicca I, Sapia A, Spadea L. Severe macular edema in patients with juvenile idiopathic arthritis-related uveitis. *Case Rep Ophthalmol Med*. 2013;2013:803989.
90. Thorne JEWF, Kedhar SR, Dunn JP, Jabs DA. Juvenile idiopathic arthritis-associated uveitis: incidence of ocular complications and visual acuity loss. *Am J Ophthalmol*. 2007;143:840–846. doi:10.1016/j.ajo.2007.01.033.
91. Tappeiner C, Mesquida M, Adán A, et al. Evidence for tocilizumab as a treatment option in refractory uveitis associated with juvenile idiopathic arthritis. *J Rheumatol*. 2016;43:2183–2188. doi:10.3899/jrheum.160231.
92. Garweg JG. Macular Edema in Childhood Uveitis. *Klin Monbl Augenheilkd*. 2018;235:373–376. doi:10.1055/s-0043-123650.
93. Pichi F, Nucci P, Baynes K, Lowder CY, Srivastava SK. Sustained-release dexamethasone intravitreal implant in juvenile idiopathic arthritis-related uveitis. *Int Ophthalmol*. 2017;37(1):221–228. doi:10.1007/s10792-016-0265-9.
94. Ministerio da Saude. *Protocolo Clínico E Diretrizes Terapêuticas Da Artrite Reumatoide E Artrite Idiopática Juvenil*. Brasilia: Conitec; 2020.
95. Schinzel V, Silva SGL, Terreri MT, Len CA. Prevalence of juvenile idiopathic arthritis in school children from the city of São Paulo, the largest city in Latin America. *Adv Rheumatol*. 2019;59:32. doi:10.1186/s42358-019-0078-4.
96. Yamashita E, Terreri MT, Hilário MO, Len CA. Prevalence of juvenile idiopathic arthritis in children aged 6 to 12 years in Embu das Artes, state of Sao Paulo, Brazil. *Rev Bras Reumatol*. 2013;53:542–545. doi:10.1016/j.rbr.2013.04.005.
97. Santos FPST, Carvalho MAP, Pinto JA, ea. *Juvenile Idiopathic Arthritis in a Department of Rheumatology: Belo Horizonte*. Minas Gerais: Rev Med Minas Gerais; 2010:20.
98. Palman JS-WS, Hyrich K, McDonagh JE. Update on the epidemiology, risk factors and disease outcomes of Juvenile idiopathic arthritis. *Best Practice & Research Clinical Rheumatology*. 2018;32:206–222. doi:10.1016/j.berh.2018.10.004.
99. Fernandes TAPCJ, Magalhães CS. Remission status follow-up in children with juvenile idiopathic arthritis. *J Pediatr*. 2007;83:141–148. doi:10.1590/S0021-75572007000200008.
100. Kulas DTSL. Juvenile idiopathic arthritis. *Review Curr Opin Rheumatol*. 2001;13:392–398. doi:10.1097/00002281-200109000-00009.
101. Sarens IL, Casteels I, Anton J, et al. Blau Syndrome-Associated Uveitis: preliminary Results From an International Prospective Interventional Case Series. *Am J Ophthalmol*. 2018;187:158–166. doi:10.1016/j.ajo.2017.08.017.
102. Schaller JG. Ankylosing spondylitis of childhood onset. *Arthritis Rheum*. 1977;20:398–401.

Henderson *et al. Pediatric Rheumatology* (2016) 14:9
DOI 10.1186/s12969-016-0069-5

Pediatric Rheumatology

RESEARCH ARTICLE Open Access

Medication use in juvenile uveitis patients enrolled in the Childhood Arthritis and Rheumatology Research Alliance Registry

Lauren A. Henderson[1*], David Zurakowski[2], Sheila T. Angeles-Han[3], Andrew Lasky[4], C. Egla Rabinovich[5], Mindy S. Lo[1] and for the CARRA Registry Investigators

Abstract

Background: There is not yet a commonly accepted, standardized approach in the treatment of juvenile idiopathic uveitis when initial steroid therapy is insufficient. We sought to assess current practice patterns within a large cohort of children with juvenile uveitis.

Methods: This is a cross-sectional cohort study of patients with uveitis enrolled in the Childhood Arthritis and Rheumatology Research Alliance (CARRAnet) registry. Clinical information including, demographic information, presenting features, disease complications, and medications were collected. Chi-square and Fisher's exact tests were used to assess for associations between medications and clinical characteristics.

Results: Ninety-two children with idiopathic and 656 with juvenile idiopathic arthritis (JIA)-associated uveitis were identified. Indication (arthritis or uveitis) for medication use was not available for JIA patients; therefore, detailed analysis was limited to children with idiopathic uveitis. In this group, 94 % had received systemic steroids. Methotrexate (MTX) was used in 76 % of patients, with oral and subcutaneous forms given at similar rates. In multivariable analysis, non-Caucasians were more likely to be treated initially with subcutaneous MTX ($P = 0.003$). Of the 53 % of patients treated with a biologic DMARD, all received a tumor necrosis factor (TNF) inhibitor. TNF inhibitor use was associated with a higher frequency of cataracts (52 % vs 21 %; $P = 0.001$) and antinuclear antibody positivity (49 % vs 29 %; $P = 0.04$), although overall complication rates were not higher in these patients.

Conclusion: Among idiopathic uveitis patients enrolled in the CARRAnet registry, MTX was the most commonly used DMARD, with subcutaneous and oral forms equally favored. Patients who received a TNF inhibitor were more likely to be ANA positive and have cataracts.

Keywords: Uveitis, Juvenile idiopathic arthritis (JIA), Idiopathic uveitis, DMARD, Infliximab, Adalimumab, Methotrexate

Background

Non-infectious juvenile uveitis is an inflammatory ocular disease that can lead to visual disability if not adequately controlled. Uveitis occurs as a primary disease (idiopathic uveitis) but can also be associated with systemic disease, typically juvenile idiopathic arthritis (JIA). In the pediatric population, uveitis remains a diagnostic challenge because children may not report symptoms until substantial visual damage has accrued. Rapid and effective control of the disease is essential because prolonged ocular inflammation is associated with higher rates of ocular complications and vision loss [1–3]. Unfortunately, there is no uniform approach to the evaluation and treatment of juvenile uveitis. In part, the lack of standardization is due to the limited number of clinical studies in this condition. Current treatment strategies for juvenile uveitis are mostly extrapolated from small, retrospective case series and there have been no randomized controlled trials in this patient population. In addition,

* Correspondence: Lauren.Henderson@childrens.harvard.edu
[1]Division of Immunology, Boston Children's Hospital, Boston, MA and Department of Pediatrics, Harvard Medical School, 1 Blackfan Circle, Karp Building, 10th Floor, Boston, MA 02115, USA
Full list of author information is available at the end of the article

BioMed Central

© 2016 Henderson et al. Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

few studies have examined treatment practice patterns in the care of juvenile uveitis, and these patterns may also vary between pediatric rheumatology and ophthalmology providers. Improved understanding of current practice may help inform future decisions regarding optimal care of these patients.

Glucocorticoids (oral and/or topical) are often the first step in treatment of anterior, non-infectious uveitis in children but long term use is discouraged due to side effects [4, 5]. Methotrexate is the most commonly prescribed steroid-sparing medication, and its therapeutic efficacy has been documented in several small case series [4, 6–10]. Methotrexate can be given either orally or subcutaneously. Subcutaneous administration has greater bioavailability compared to oral, which can be quite variable [11, 12]. However, for many patients, especially children, oral dosing is preferred. Other disease-modifying anti-rheumatic drugs (DMARDs) such as cyclosporine, tacrolimus, azathioprine, and mycophenolate mofetil are also used to treat uveitis, although most published reports have focused on adult, rather than pediatric, patients [13–23]. More recently, reports describe successful use of the TNF inhibitors infliximab and adalimumab in both JIA-associated and idiopathic uveitis [24–27]. In refractory cases of JIA associated uveitis, tociluzumab, abatacept, and rituximab have also been used [28–30].

Several groups have proposed guidelines for the treatment of JIA-associated uveitis based on literature review and expert opinion [31–33]. There is consensus among these treatment guidelines that topical steroids should be used first, followed by methotrexate for refractory disease. However, they differ in their recommendations on the use of systemic glucocorticoids, preferred route of methotrexate administration, and choice of second-line steroids sparing agents. Further, they have not yet been validated prospectively and it is unknown how closely providers adhere to these recommendations.

Comparative effectiveness research (CER) represents an alternative approach to the establishment of treatment guidelines by expert opinion. CER methodologies are well suited to study diseases such as juvenile uveitis that are relatively uncommon, making randomized controlled trials with large cohorts less feasible [34, 35]. Consensus Treatment Plans (CTPs), in which patients are treated according to one of several algorithms, are intended to help standardize care, while at the same time collecting information on outcomes that will allow comparison of different treatment practices. The implementation of CTPs and subsequent analysis of outcome data represent a form of CER. This approach has been trialed for multiple pediatric rheumatologic conditions, though not juvenile uveitis [36–39].

In this study, we examined data from CARRAnet, a large registry of North American pediatric rheumatology patients, in order to characterize current practice patterns in the treatment of juvenile uveitis. Better understanding of the factors influencing selection of steroid-sparing medications is necessary to inform the development of standardized treatment regimens and CTPs.

Methods

CARRAnet registry

CARRAnet was developed by the Childhood Arthritis and Rheumatology Research Alliance (CARRA) and is a multicenter registry of children with rare pediatric rheumatologic conditions ("CARRA registry" on https://clinicaltrials.gov). Over 50 pediatric rheumatology research centers in the United States and Canada have enrolled over 9000 children into the registry since its inception. Children were eligible to participate if they had 1 of 12 specified rheumatologic diseases that were being studied in the registry. The primary diagnosis at enrollment was determined by the child's treating rheumatologist. The registry opened with recruitment of children with JIA in May 2010; recruitment of children idiopathic uveitis began in February 2012, at which time collection of detailed information on uveitis presentation and treatment was also introduced to the registry. Demographic and clinical data, including information on prior medication use and disease complications, were gathered by family interview, medical record review, and/or provider recall and subsequently entered into a secure online database. Consent/assent was obtained from all study participants.

Uveitis data

After Institutional Review Board approval, we obtained de-identified enrollment data from children with JIA-associated and idiopathic uveitis who participated in the CARRA registry from June 2010 to September 2013. Although the registry was developed for prospective data collection, at the time of our inquiry, only data from a single, baseline registry enrollment visit was available for most patients. Data collected included uveitis type, number of affected eyes,duration of current episode (if active uveitis present), history of ocular complications, and current and prior medication use. Possible ocular complications listed included increased intraocular pressure, keratic precipitates, posterior synechiae, cataracts, macular edema, epiretinal membrane, snowbanks, snowballs, retinal vasculitis, macular atrophy, hypopyon, iris nodules, band keratopathy, and history of eye surgery. Information on topical therapies (steroid, mydriatic, and anti-glaucoma drops), systemic glucocorticoids, intra-ocular steroids, intravenous immunoglobulin, non-biologic disease-modifying antirheumatic drugs

(DMARDs), and biologic agents were included in the registry. Long-term steroid use was defined as a history of systemic glucocorticoid treatment for > 1 month. Drug use was categorized as "current," "past," "never," or "unknown." For this analysis, "ever drug use" was defined as past and/or current use. Information on medication dose and dates of drug initiation/cessation were not included in the registry. Thus, while some longitudinal information regarding treatment could be inferred based on current and past use of medications, details such as duration of therapy were not available. For JIA patients, the indication for a systemic medication (arthritis vs. uveitis) was not recorded. Finally, data collection also included "ANA status," where a positive response was defined as a history of testing positive for anti-nuclear antibody (ANA). Date of ANA testing was not included in the registry.

Statistical analysis

Demographic differences between JIA-associated and idiopathic uveitis groups were compared with Mann-Whitney U and chi-square tests. Univariate analysis was performed between first-use of oral MTX and subcutaneous MTX, and between biologic and non-biologic groups, using the Mann-Whitney U-test for median age and Fisher's exact test for percentages. Multivariable logistic regression (backward selection) was applied to identify predictive factors, with the likelihood ratio test used to assess significance of the independent predictors [40]. Odds ratios and 95 % confidence intervals (CI) were derived for significant multivariable predictors of route of MTX administration and for use of biologics.

In these univariate and multivariate analyses, Caucasian race included both Hispanic and non-Hispanic ethnicities. Due to the small number of subjects endorsing racial categories other than Caucasian/white and black/African American, racial categories were collapsed into Caucasian and non-Caucasian to allow sufficient patient numbers for statistical analysis. Statistical analysis was performed using IBM/SPSS Statistics (version 22.0, IBM, Armonk, NY). Two-tailed $P < 0.05$ were considered statistically significant.

Results

Patient characteristics

There were 92 children with idiopathic uveitis and 646 children with JIA uveitis identified in the CARRA registry (Table 1). Children with JIA uveitis were significantly younger at disease onset (median age 2.8 years) than children with idiopathic uveitis (median 8.5 years) ($P < 0.001$) (Table 1). Females were more frequently affected than males in both forms of the disease; however, patients with JIA uveitis were more likely to be female than those with idiopathic uveitis (78 % vs 55 %; $P < 0.001$) (Table 1). A greater percentage of patients with JIA uveitis (92 %) were Caucasian as compared to children with idiopathic uveitis (77 %) ($P < 0.001$) (Table 1).

Table 1 Subject characteristics

	Idiopathic Uveitis *N* = 92	JIA Uveitis *N* = 646
Age at onset, yrs	8.5	2.8
Median (IQR)	(5.3-10.9)	(1.7-5.2)
Gender (n, %)		
Female	51 (55 %)	504 (78 %)
Male	41 (45 %)	142 (22 %)
Disease duration, yrs		
Median (IQR)	2.9 (1.2-5.2)	6.1 (3.2-9.5)
Race* (n, %)		
Caucasian	71 (77 %)	596 (92 %)
Black	12 (13 %)	22 (3 %)
Asian	4 (1 %)	16 (2 %)
Other	3 (3 %)	19 (3 %)
Unknown	2 (2 %)	0 (0 %)
Ethnicity (n, %)		
Hispanic	12 (13 %)	61 (9 %)
Non-Hispanic	79 (86 %)	580 (90 %)
Unknown	1 (1 %)	5 (0.5 %)
ANA (n, %)		
Positive	30 (32 %)	385 (60 %)
Negative	45 (49 %)	184 (28 %)
Unknown	17 (18 %)	77 (12 %)

Characteristics of the idiopathic and JIA uveitis patients are listed in the table.
*Race was self-reported, and subjects could select more than one category
JIA juvenile idiopathic arthritis, *IQR* interquartile range

Uveitis characteristics

Information on uveitis disease characteristics and ocular complications was available for all patients with idiopathic uveitis but only 69 of 646 patients with JIA uveitis. Therefore, our evaluation of uveitis features was limited to patients with idiopathic uveitis. Anterior uveitis was the most common subtype of the disease (62 %), followed by panuveitis (21 %), intermediate uveitis (13 %), and posterior uveitis (4 %). Most children with idiopathic uveitis (77 %) had bilateral involvement. Ocular complications were common and noted in 71 (77 %) children with idiopathic uveitis: 35 had cataracts, 26 had undergone eye surgery, 13 had abnormal corrected vision, and 3 were blind in the affected eye (Fig. 1). Other frequently reported complications included posterior synechiae, band keratopathy, macular edema, and keratic precipitates. The majority of patients (64 children) reported having more than one complication. Among JIA uveitis patients for whom ocular complication data was

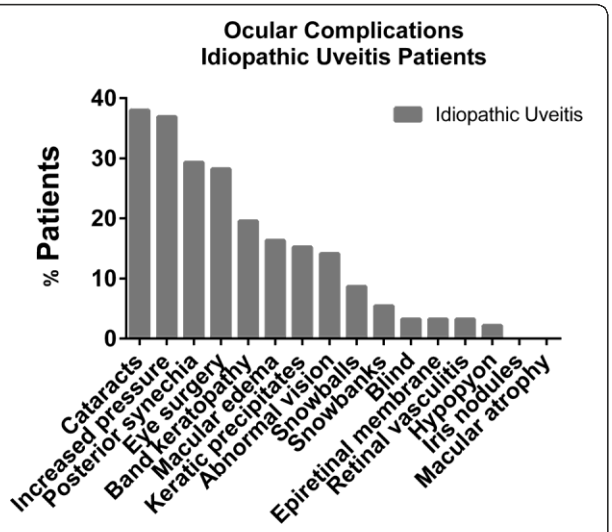


Fig. 1 Ocular Complications in Idiopathic Uveitis. The number of idiopathic uveitis patients with each ocular complication is depicted in the figure

known, cataracts again were the most common complication, although overall complication rate was lower (Additional file 1: Figure S1).

Medication use

Data on medications ever used was available on all idiopathic and almost all (643/646) JIA uveitis patients (Tables 2 and 3). Use of DMARDs and biologic agents was similar in both groups. A majority of patients received a DMARD (83 % of idiopathic and 88 % of JIA uveitis patients). At least one biologic agent was used in 53 % of children with idiopathic uveitis and 56 % of children with JIA-associated uveitis. In patients with JIA uveitis, the indication for medication use was not specified and could have been due to either arthritis or uveitis disease activity. Therefore, in order to evaluate medication use for uveitis specifically, we restricted the remaining medication analysis to patients with idiopathic disease.

Table 2 DMARD use in idiopathic and JIA uveitis

Drug	Idiopathic Uveitis *N* = 92 (%)	JIA Uveitis *N* = 643 (%)
Methotrexate	70 (76)	549 (85)
Oral	44 (48)	375 (58)
SQ	46 (50)	416 (65)
Mycophenolate mofetil	9 (10)	33 (5)
Cyclosporine	3 (3)	20 (3)
Sulfasalazine	1 (1)	47 (7)
Hydroxychloroquine	0 (0)	27 (4)
Leflunomide	0 (0)	20 (3)
Tacrolimus	0 (0)	8 (1)
Azathioprine	0 (0)	3 (0.4)
Cyclophosphamide	0 (0)	1 (0.2)

Data in this table represent "ever drug use" in patients with data available on DMARD drug exposure (92/92 patients with idiopathic uveitis and 643/646 patients with JIA uveitis)
JIA juvenile idiopathic arthritis, *SQ* subcutaneous

Table 3 Biologic agent use in idiopathic and JIA uveitis

Drug	Idiopathic Uveitis *N* = 92 (%)	JIA Uveitis *N* = 643 (%)
TNF inhibitor	49 (53)	353 (55)
Adalimumab	18 (20)	196 (30)
Certolizumab	0 (0)	1 (0.2)
Etanercept	0 (0)	159 (25)
Golimumab	1 (1)	3 (0.5)
Infliximab	36 (39)	174 (27)
Abatacept	0 (0)	23 (4)
Anti-IL-1	0 (0)	9 (1.5)
Anakinra	0 (0)	7 (0.2)
Rilonacept	0 (0)	1 (0.2)
Canakinumab	0 (0)	1 (0.2)
Rituximab	0 (0)	4 (0.5)
Tocilizumab	0 (0)	4 (0.5)

Data in this table represent "ever drug use" in patients with data available on biologic drug exposure (92/92 patients with idiopathic uveitis and 643/646 patients with JIA uveitis)
JIA juvenile idiopathic arthritis

Glucocorticoid use in idiopathic uveitis

Topical steroid drops were used in 90 % of idiopathic uveitis patients, with hourly dosing employed at some point in the disease course in 26 % (Table 4). Of the 5 children who did not receive topical steroid drops, 4 were treated with oral or IV glucocorticoids. None of the idiopathic uveitis patients received intra-ocular steroid injections. Almost all (94 %) of idiopathic uveitis patients had received systemic glucocorticoids. Further, 38 % of idiopathic uveitis patients had received long-term systemic glucocorticoids.

DMARD use in idiopathic uveitis

Of the 92 idiopathic uveitis patients, 70 (76 %) received methotrexate (MTX), making it the most frequently utilized steroid-sparing agent. Overall, the oral and subcutaneous (SQ) forms of MTX were used at similar rates (Table 2). In 96 % of patients who had received MTX, it was possible to determine the initial route of MTX administration prescribed to treat idiopathic uveitis. SQ MTX was used first in 54 % of children, while oral MTX was prescribed first in 46 %. A minority (29 %) of patients had been trialed on both formulations (SQ to oral in 10 patients; oral to SQ in 7 patients; in 3 subjects the order could not be determined). By univariate analysis,

Table 4 Steroid use in idiopathic uveitis

	Idiopathic Uveitis N (%)
Topical steroid drops	
Yes	83 (90)
No	5 (5)
Unknown	4 (4)
Max topical steroid drop freq	
Hourly	24 (26)
12x/day	10 (11)
6x/day	4 (4)
4x/day	16 (17)
3x/day	6 (7)
2x/day	3 (3)
Daily	3 (3)
Unknown	21 (23)
Intraocular steroids	
Yes	0 (0)
No	85 (92)
Unknown	7 (8)
Systemic steroids	
Yes	86 (94)
No	4 (4)
Unknown	2 (2)
IV pulse steroids	
Yes	4 (4)
No	82 (89)
Unknown	6 (7)
Long-term systemic steroids	
Yes	35 (38)
No	50 (54)
Unknown	7 (8)

Topical and systemic steroid use in idiopathic uveitis patients is depicted in the table. *Max* maximum, *freq* frequency

the initial use of the SQ MTX was associated only with non-Caucasian race (P = 0.046). This relationship persisted in the multivariable analysis with adjustment for age at disease onset, ethnicity, race, gender, uveitis type, and ocular complications (P = 0.003) (Table 5). DMARDs other than methotrexate that were less frequently used in idiopathic uveitis patients included cyclosporine (N = 3), mycophenolate mofetil (N = 9), and sulfasalazine (N = 1) (Table 2).

Biologic use in idiopathic uveitis

Among the 49 idiopathic uveitis patients treated with a biologic medication, all received a tumor necrosis factor (TNF) inhibitor: infliximab (n = 36), adalimumab (n = 18), or golimumab (n = 1) (Table 3). Of these, all but 2 had also received methotrexate. In univariate analysis, patients who had received a TNF inhibitor were more likely to have a history of a cataract compared to patients who had never been exposed to a biologic agent (53 % vs. 21 %; P = 0.002) (Table 6). This association remained in multivariable analysis adjusting for age at disease onset, ethnicity, race, gender, uveitis type, ANA status, and ocular complications (odds ratio = 5.6; P = 0.001). In addition, multivariate modeling also revealed that a positive ANA, defined as a history of testing positive for ANA, was significantly associated with TNF inhibitor use after adjusting for other disease and patient characteristics (P = 0.04) (Table 6).

Multiple biologic agent use in idiopathic uveitis

Six idiopathic uveitis patients were treated with multiple biologic agents. All of these patients had received both infliximab and adalimumab. In 5 of these patients, the order of TNF inhibitor use could be determined: 3 patients switched from adalimumab to infliximab, while 2 patients switched from infliximab to adalimumab.

Biologic use without preceding DMARD in idiopathic uveitis

Two patients included in the registry were treated with infliximab without a preceding DMARD. Neither of these patients had anterior uveitis, while both had ocular complications. The first patient was diagnosed with bilateral panuveitis and had developed snowballs and posterior synechiae. The second child had posterior uveitis complicated by retinal vasculitis and blindness in the affected eye.

Discussion

Optimization of care for children with uveitis remains a challenging goal without better comparative effectiveness studies. These types of studies are particularly challenging to conduct in children given the rarity of uveitis and the practical considerations regarding therapeutic trials in children. In this study, we sought to present a preliminary overview of current practice patterns in the treatment of pediatric uveitis, using a large North American patient registry. This analysis includes description of one of the largest cohorts of pediatric idiopathic uveitis patients published to date. A total of 26 contributing centers were represented within this cohort.

We first examined steroid use in these patients. Somewhat surprisingly, nearly all patients had been treated with systemic glucocorticoids; indeed, more patients reported using systemic glucocorticoids than topical steroids. About a third of patients reported long-term use of systemic glucocorticoids, and several patients had received intravenous glucocorticoid pulses. In contrast to the pattern of steroid use documented in our cohort of patients, published treatment

Table 5 Factors associated with initial route of MTX Administration in idiopathic uveitis

Variable	Oral MTX *N* = 31	SQ MTX *N* = 36	Univariate *P* value	Multivariable Logistic Regression		
				Odds Ratio	95 % CI	*P* value
Age at onset, yrs			0.06			0.61
Median (IQR)	9.4 (5.7-11.8)	7.1 (5.0-9.3)				
Gender			1.00			0.73
Female	13 (42 %)	15 (42 %)				
Male	18 (58 %)	21 (58 %)				
Ethnicity			1.00			0.72
Hispanic	2 (6 %)	2 (6 %)				
Non-Hispanic	29 (94 %)	34 (94 %)				
Race			0.046*	12.7	1.5-106.8	0.003*
Caucasian	27 (87 %)	22 (65 %)				
Non-Caucasian	4 (13 %)	12 (35 %)				
Uveitis type			0.65			0.51
Anterior	19 (61 %)	26 (72 %)				
Pan	4 (13 %)	5 (14 %)				
Intermediate	7 (23 %)	4 (11 %)				
Posterior	1 (3 %)	1 (3 %)				
ANA status			1.00			0.95
Positive	11 (44 %)	15 (44 %)				
Negative	14 (56 %)	19 (56 %)				
Complications**	25 (81 %)	28 (80 %)	1.00			0.73
Cataracts	15 (48 %)	16 (44 %)	0.81			0.94

Data in this table include subject characteristics associated with the route of methotrexate administration initially prescribed
IQR interquartile range, *SQ* subcutaneous, *CI* confidence interval, *ANA* antinuclear antibody
*Statistically significant, **Presence of at least one ocular complication

guidelines for JIA-associated uveitis reserve systemic glucocorticoids for patients with severe ocular inflammation (grades 3+ or 4+) or impending vision loss [31, 32]. The discrepancy between systemic glucocorticoid use in our cohort compared to the treatment guidelines may represent a point where current treatment practices deviate from expert opinion. It is possible that this deviation is due to differences in treatment approaches between idiopathic and JIA-associated uveitis. Alternatively, the high rate of systemic glucocorticoiduse in our cohort could be explained by higher disease severity, a possibility that is difficult to assess as the CARRAnet registry did not include information about grade of inflammation. However, the overall rate of ocular complications in our cohort (80 %) is within the range of prior reports in juvenile uveitis [1, 2, 41].

The use of steroid-sparing medications in idiopathic uveitis was then evaluated. Most patients had received methotrexate, in either oral or subcutaneous form. Subcutaneous methotrexate has higher bioavailability than oral dosing, but use of subcutaneous methotrexate for initial therapy is not clearly standard among providers. We found that idiopathic uveitis patients in our study were evenly divided between oral and subcutaneous dosing. Univariate and multivariate analysis demonstrated that subcutaneous administration was used more frequently for non-Caucasians than Caucasians. A possible explanation could be that non-Caucasians had, or were at least perceived to have, more severe disease. However, other characteristics such as complication rate, age of onset, gender, and ANA status were not different between patients who were treated with oral versus subcutaneous methotrexate. There is limited literature on the role of race and ethnicity in juvenile uveitis. In one study of JIA-associated uveitis, African-American children tended to have worse physician global assessment scores [42]. Another study has also suggested that African-American patients may have more severe disease [43]. In contrast, white race was a predictor of remission in one study of JIA-associated uveitis, but race was not a factor affecting development of complications [44]. Whether these findings are applicable to idiopathic uveitis patients is less clear. Other factors that may influence medication selection were not able

Table 6 Factors associated with biologic agent use in idiopathic uveitis

Variable	Biologics *N* = 49	No Biologics *N* = 43	Univariate *P* value	Multivariable Logistic Regression		
				Odds Ratio	95 % CI	*P* value
Age at onset, yrs			0.35			0.90
Median (IQR)	7.7 (5.1-10.2)	8.9 (6.8-11.4)				
Gender			0.21			0.07
Female	24 (49 %)	27 (63 %)				
Male	25 (51 %)	16 (37 %)				
Ethnicity			0.54			0.92
Hispanic	5 (10 %)	7 (16 %)				
Non-Hispanic	44 (90 %)	36 (84 %)				
Race			0.20			0.87
Caucasian	35 (73 %)	36 (86 %)				
Non-Caucasian	13 (27 %)	6 (14 %)				
Uveitis type			0.44			0.82
Anterior	27 (55 %)	30 (70 %)				
Pan	13 (27 %)	6 (14 %)				
Intermediate	7 (14 %)	5 (12 %)				
Posterior	2 (4 %)	2 (5 %)				
ANA status			0.07***			
Positive	20 (49 %)	10 (29 %)		3.0	1.0-8.6	0.04*
Negative	21 (51 %)	25 (71 %)		Reference		
Any complication	39 (81 %)	32 (74 %)	0.46			0.16
Cataracts	26 (53 %)	9 (21 %)	0.002*	5.6	1.8-17.2	0.001*

IQR interquartile range, *CI* confidence interval
*Statistically significant, ***Trend

to be captured in our study; these include patient preference, concerns about medication compliance, and regional availability of injectable methotrexate due to drug shortages [45].

More than half of our idiopathic uveitis cohort received biologic therapy, all in the form of TNF inhibitors. Infliximab was used twice as frequently as adalimumab, which was interesting given that recent literature seems to have favored adalimumab over infliximab in some analyses [46, 47]. One explanation for this may be the earlier availability of infliximab. However, our patients were first enrolled beginning in 2010; adalimumab use in juvenile uveitis was reported as early as 2006 [48]. There were no racial differences between patients who had or had not received TNF inhibitor therapy. However, patients treated with TNF inhibitors were more likely to be ANA positive and to have cataracts, again suggesting that these patients either had, or were perceived to have, more severe disease. Unfortunately, the design of the registry did not allow the ability to capture whether ANA positivity and cataract development preceded or followed TNF inhibitor administration. Several studies have identified ANA positivity as a risk factor for ocular complications and visual acuity loss in JIA-associated uveitis; however, other studies have not replicated this finding [2, 49–51]. There is, thus, no clear explanation of the association between ANA positivity and TNF inhibitor use in our cohort apart from the possible perception of increased disease severity.

Cataract development may be secondary to disease activity or chronic steroid use. In our cohort, patients with cataracts had higher frequencies of other ocular complications but similar rates of glucocorticoiduse compared to children without cataracts. Thus, differences in disease severity more likely explain the association between cataract development and the use of TNF inhibitors. Further understanding of this relationship is limited by the available data, which in this registry database did not specify the timing of TNF inhibitor initiation with regard to cataract formation.

Limitations

Although the size of our idiopathic uveitis pediatric cohort was relatively large, interpretation of the impact of

specific medications on patient outcome is limited by the lack of follow up. This was a relatively early cross-sectional look at enrollment data, but collection of data from follow up visits remains ongoing. We hope that over time, further analyses will allow more detailed examination of the factors that influence the selection of medications, as well as their efficacy.

The CARRAnet database did not include data on the indication for medication use in JIA uveitis patients. Therefore, it was not possible to determine if a medication was used for active arthritis and/or uveitis. Thus, we limited the majority of our analysis to idiopathic uveitis patients. It is unclear if our findings are applicable to JIA uveitis patients, given the differences in race, gender, and ANA status in both groups which may be associated with differences in disease severity, and subsequently medication use. The database also did not collect information on medication dosage, which can also vary greatly from provider to provider and also influence the decision for whether to move on to another agent. Future iterations of this database will hopefully allow more granular analysis of medication dosage.

Finally, our cohort may be influenced by selection bias, as these patients were all under the care of a pediatric rheumatologist. Patients with milder disease may be managed solely by ophthalmologists without coming to the attention of a rheumatology provider.

Conclusions

There is not yet a commonly accepted, standardized approach in the treatment of juvenile idiopathic uveitis. Analysis of a North American pediatric rheumatology data registry identified points of consensus and divergence in the current treatment practices for this disease. Compared to expert treatment guidelines, clinicians used systemic steroids more frequently and for prolonged courses. Steroid-sparing treatment strategies were generally similar for children with JIA-associated and idiopathic uveitis. Among patients with idiopathic uveitis, almost all were treated with methotrexate, although oral and subcutaneous forms of the medication were equally favored. Non-Caucasian patients were more likely to be prescribed subcutaneous rather than oral methotrexate. More than half of our idiopathic uveitis patients were also treated with a TNF inhibitor, and infliximab was used twice as often as adalimumab. TNF inhibitor use may reflect higher disease severity, or the perception of higher disease activity, as it was also associated with higher rates of ANA positivity and cataract formation.

Our findings on the treatment of juvenile uveitis in North America lay the foundation for future investigation into identified areas of treatment variability. Comparative effectiveness research, particularly CTPs, will be helpful in studying systemic steroid use and the efficiency of oral versus subcutaneous methotrexate, and the TNF inhibitors infliximab and adalimumab.

Additional file

Additional file 1: Figure S1. Ocular complications in JIA associated uveitis. (TIF 294 kb)

Abbreviations

CARRA: Childhood Arthritis and Rheumatology Research Alliance; CER: comparative effectiveness research; CTP: consensus treatment plans; DMARD: disease-modifying anti-rheumatic drug; JIA: Juvenile idiopathic arthritis; MTX: methotrexate; SQ: subcutaneous; TNF: tumor necrosis factor.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

LAH participated in conceptualization of the study, data organization, interpretation of results, and manuscript preparation. Statistical analysis was performed by DZ. The study design and manuscript preparation was overseen by MSL, with significant contributions and insight from SAH, CER, and AL. All authors read and approved the final manuscript.

Acknowledgements

We would also like to thank all participants and hospital sites that recruited patients for the CARRA Registry. The authors thank the following CARRA Registry site principal investigators and research coordinators: L. Abramson, E. Anderson, M. Andrew, N. Battle, M. Becker, H. Benham, T. Beukelman, J. Birmingham, P. Blier, A. Brown, H. Brunner, A. Cabrera, D. Canter, D. Carlton, B. Caruso, L. Ceracchio, E. Chalom, J. Chang, P. Charpentier, K. Clark, J. Dean, F. Dedeoglu, B. Feldman, P. Ferguson, M. Fox, K. Francis, M. Gervasini, D. Goldsmith, G. Gorton, B. Gottlieb, T. Graham, T. Griffin, H. Grosbein, S. Guppy, H. Haftel, D. Helfrich, G. Higgins, A. Hillard, J.R. Hollister, J. Hsu, A. Hudgins, C. Hung, A. Huttenlocher, N. Ilowite, A. Imlay, L. Imundo, C.J. Inman, J. Jaqith, R. Jerath, L. Jung, P. Kahn, A. Kapedani, D. Kingsbury, K. Klein, M. Klein-Gitelman, A. Kunkel, S. Lapidus, S. Layburn, T. Lehman, C. Lindsley, M. Macgregor-Hannah, M. Malloy, C. Mawhorter, D. McCurdy, K. Mims, N. Moorthy, D. Morus, E. Muscal, M. Natter, J. Olson, K. O'Neil, K. Onel, M. Orlando, J. Palmquist, M. Phillips, L. Ponder, S. Prahalad, M. Punaro, D. Puplava, S. Quinn, A. Quintero, C. Rabinovich, A. Reed, C. Reed, S. Ringold, M. Riordan, S. Roberson, A. Robinson, J. Rossette, D. Rothman, D. Russo, N. Ruth, K. Schikler, A. Sestak, B. Shaham, Y. Sherman, M. Simmons, N. Singer, S. Spalding, H. Stapp, R. Syed, E. Thomas, K. Torok, D. Trejo, J. Tress, W. Upton, R. Vehe, E. von Scheven, L. Walters, J. Weiss, P. Weiss, N. Welnick, A. White, J. Woo, J. Wootton, A. Yalcindag, C. Zapp, L. Zemel, and A. Zhu.

Funding

This project was funded by the National Eye Institute (US) (K23EY021760), Rheumatology Research Foundation (US) (Scientist Development Award), National Institute of Allergy and Infectious Diseases (US) (T32AI007512), National Institute of Arthritis and Musculoskeletal and Skin Diseases (US) (RC2AR058934), Arthritis Foundation (US), Friends of CARRA and the Duke Clinical Research Institute (US).

Author details

[1]Division of Immunology, Boston Children's Hospital, Boston, MA and Department of Pediatrics, Harvard Medical School, 1 Blackfan Circle, Karp Building, 10th Floor, Boston, MA 02115, USA. [2]Departments of Anesthesia and Surgery, Boston Children's Hospital and Harvard Medical School, Boston, MA, USA. [3]Department of Pediatrics and Ophthalmology, Emory University School of Medicine, Atlanta, GA, USA. [4]Department of Pediatric Rheumatology, Randall Children's Hospital at Legacy Emanuel, Portland, OR, USA. [5]Division of Rheumatology, Department of Pediatrics, Duke Children's, Durham, NC, USA.

Received: 14 July 2015 Accepted: 4 February 2016
Published online: 16 February 2016

References

1. Rosenberg KD, Feuer WJ, Davis JL. Ocular complications of pediatric uveitis. Ophthalmology. 2004;111(12):2299–306. doi:10.1016/j.ophtha.2004.06.014.
2. Thorne JE, Woreta F, Kedhar SR, Dunn JP, Jabs DA. Juvenile idiopathic arthritis-associated uveitis: incidence of ocular complications and visual acuity loss. Am J Ophthalmol. 2007;143(5):840–6. doi:10.1016/j.ajo.2007.01.033.
3. Gregory 2nd AC, Kempen JH, Daniel E, Kacmaz RO, Foster CS, Jabs DA, et al. Risk factors for loss of visual acuity among patients with uveitis associated with juvenile idiopathic arthritis: the Systemic Immunosuppressive Therapy for Eye Diseases Study. Ophthalmology. 2013;120(1):186–92. doi:10.1016/j.ophtha.2012.07.052.
4. Simonini G, Cantarini L, Bresci C, Lorusso M, Galeazzi M, Cimaz R. Current therapeutic approaches to autoimmune chronic uveitis in children. Autoimmun Rev. 2010;9(10):674–83. doi:10.1016/j.autrev.2010.05.017.
5. Thorne JE, Woreta FA, Dunn JP, Jabs DA. Risk of cataract development among children with juvenile idiopathic arthritis-related uveitis treated with topical corticosteroids. Ophthalmology. 2010;117(7):1436–41. doi:10.1016/j.ophtha.2009.12.003.
6. Chan AY, Liu DT. Methotrexate and chronic uveitis associated with juvenile idiopathic arthritis. J Rheumatol. 2006;33(1):198. author reply.
7. Foeldvari I, Wierk A. Methotrexate is an effective treatment for chronic uveitis associated with juvenile idiopathic arthritis. J Rheumatol. 2005;32(2):362–5.
8. Heiligenhaus A, Mingels A, Heinz C, Ganser G. Methotrexate for uveitis associated with juvenile idiopathic arthritis: value and requirement for additional anti-inflammatory medication. Eur J Ophthalmol. 2007;17(5):743–8.
9. Malik AR, Pavesio C. The use of low dose methotrexate in children with chronic anterior and intermediate uveitis. Br J Ophthalmol. 2005;89(7):806–8. doi:10.1136/bjo.2004.054239.
10. Weiss AH, Wallace CA, Sherry DD. Methotrexate for resistant chronic uveitis in children with juvenile rheumatoid arthritis. J Pediatr. 1998;133(2):266–8.
11. Herman RA, Veng-Pedersen P, Hoffman J, Koehnke R, Furst DE. Pharmacokinetics of low-dose methotrexate in rheumatoid arthritis patients. J Pharm Sci. 1989;78(2):165–71.
12. Hoekstra M, Haagsma C, Neef C, Proost J, Knuif A, van de Laar M. Bioavailability of higher dose methotrexate comparing oral and subcutaneous administration in patients with rheumatoid arthritis. J Rheumatol. 2004;31(4):645–8.
13. Esterberg E, Acharya NR. Corticosteroid-sparing therapy: practice patterns among uveitis specialists. J Ophthalmic Inflamm Infect. 2012;2(1):21–8. doi:10.1007/s12348-011-0047-5.
14. Chang PY, Giuliari GP, Shaikh M, Thakuria P, Makhoul D, Foster CS. Mycophenolate mofetil monotherapy in the management of paediatric uveitis. Eye. 2011;25(4):427–35. doi:10.1038/eye.2011.23.
15. Doycheva D, Deuter C, Stuebiger N, Biester S, Zierhut M. Mycophenolate mofetil in the treatment of uveitis in children. Br J Ophthalmol. 2007;91(2):180–4. doi:10.1136/bjo.2006.094698.
16. Lee SH, Chung H, Yu HG. Clinical outcomes of cyclosporine treatment for noninfectious uveitis. Korean J Ophthalmol. 2012;26(1):21–5. doi:10.3341/kjo.2012.26.1.21.
17. Molina C, Modesto C, Martin-Begue N, Arnal C. Leflunomide, a valid and safe drug for the treatment of chronic anterior uveitis associated with juvenile idiopathic arthritis. Clin Rheumatol. 2013;32(11):1673–5. doi:10.1007/s10067-013-2315-2.
18. Goebel JC, Roesel M, Heinz C, Michels H, Ganser G, Heiligenhaus A. Azathioprine as a treatment option for uveitis in patients with juvenile idiopathic arthritis. Br J Ophthalmol. 2011;95(2):209–13. doi:10.1136/bjo.2009.173542.
19. Daniel E, Thorne JE, Newcomb CW, Pujari SS, Kacmaz RO, Levy-Clarke GA, et al. Mycophenolate mofetil for ocular inflammation. Am J Ophthalmol. 2010;149(3):423–32. doi:10.1016/j.ajo.2009.09.026. e1-2.
20. Galor A, Jabs DA, Leder HA, Kedhar SR, Dunn JP, Peters 3rd GB, et al. Comparison of antimetabolite drugs as corticosteroid-sparing therapy for noninfectious ocular inflammation. Ophthalmology. 2008;115(10):1826–32. doi:10.1016/j.ophtha.2008.04.026.
21. Pasadhika S, Kempen JH, Newcomb CW, Liesegang TL, Pujari SS, Rosenbaum JT, et al. Azathioprine for ocular inflammatory diseases. Am J Ophthalmol. 2009;148(4):500–9. doi:10.1016/j.ajo.2009.05.008. e2.
22. Hogan AC, McAvoy CE, Dick AD, Lee RW. Long-term efficacy and tolerance of tacrolimus for the treatment of uveitis. Ophthalmology. 2007;114(5):1000–6. doi:10.1016/j.ophtha.2007.01.026.
23. Kilmartin DJ, Forrester JV, Dick AD. Cyclosporin A therapy in refractory non-infectious childhood uveitis. Br J Ophthalmol. 1998;82(7):737–42.
24. Dobner BC, Max R, Becker MD, Heinz C, Veltrup I, Heiligenhaus A, et al. A three-centre experience with adalimumab for the treatment of non-infectious uveitis. Br J Ophthalmol. 2013;97(2):134–8. doi:10.1136/bjophthalmol-2011-301401.
25. Lerman MA, Burnham JM, Chang PY, Daniel E, Foster CS, Hennessy S, et al. Response of pediatric uveitis to tumor necrosis factor-alpha inhibitors. J Rheumatol. 2013;40(8):1394–403. doi:10.3899/jrheum.121180.
26. Suhler EB, Lowder CY, Goldstein DA, Giles T, Lauer AK, Kurz PA, et al. Adalimumab therapy for refractory uveitis: results of a multicentre, open-label, prospective trial. Br J Ophthalmol. 2013;97(4):481–6. doi:10.1136/bjophthalmol-2012-302292.
27. Simonini G, Druce K, Cimaz R, Macfarlane GJ, Jones GT. Current evidence of anti-tumor necrosis factor alpha treatment efficacy in childhood chronic uveitis: a systematic review and meta-analysis approach of individual drugs. Arthritis Care Res (Hoboken). 2014;66(7):1073–84. doi:10.1002/acr.22214.
28. Heiligenhaus A, Miserocchi E, Heinz C, Gerloni V, Kotaniemi K. Treatment of severe uveitis associated with juvenile idiopathic arthritis with anti-CD20 monoclonal antibody (rituximab). Rheumatology. 2011;50(8):1390–4. doi:10.1093/rheumatology/ker107.
29. Tsang AC, Roth J, Gottlieb C. Tocilizumab for severe chronic anterior uveitis associated with juvenile idiopathic arthritis in a pediatric patient. Ocul Immunol Inflamm. 2014;22(2):155–7. doi:10.3109/09273948.2013.866254.
30. Zulian F, Balzarin M, Falcini F, Martini G, Alessio M, Cimaz R, et al. Abatacept for severe anti-tumor necrosis factor alpha refractory juvenile idiopathic arthritis-related uveitis. Arthritis Care Res. 2010;62(6):821–5. doi:10.1002/acr.20115.
31. Bou R, Adan A, Borras F, Bravo B, Calvo I, De Inocencio J, et al. Clinical management algorithm of uveitis associated with juvenile idiopathic arthritis: interdisciplinary panel consensus. Rheumatol Int. 2015. doi:10.1007/s00296-015-3231-3.
32. Heiligenhaus A, Michels H, Schumacher C, Kopp I, Neudorf U, Niehues T, et al. Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis. Rheumatol Int. 2012;32(5):1121–33. doi:10.1007/s00296-011-2126-1.
33. Levy-Clarke G, Jabs DA, Read RW, Rosenbaum JT, Vitale A, Van Gelder RN. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. Ophthalmology. 2014;121(3):785–96. doi:10.1016/j.ophtha.2013.09.048. e3.
34. Horn SD, Gassaway J. Practice-based evidence study design for comparative effectiveness research. Med Care. 2007;45(10 Supl 2):S50–7. doi:10.1097/MLR.0b013e318070c07b.
35. Sox HC, Goodman SN. The methods of comparative effectiveness research. Annu Rev Public Health. 2012;33:425–45. doi:10.1146/annurev-publhealth-031811-124610.
36. DeWitt EM, Kimura Y, Beukelman T, Nigrovic PA, Onel K, Prahalad S, et al. Consensus treatment plans for new-onset systemic juvenile idiopathic arthritis. Arthritis Care Res. 2012;64(7):1001–10. doi:10.1002/acr.21625.
37. Li SC, Torok KS, Pope E, Dedeoglu F, Hong S, Jacobe HT, et al. Development of consensus treatment plans for juvenile localized scleroderma: a roadmap toward comparative effectiveness studies in juvenile localized scleroderma. Arthritis Care Res. 2012;64(8):1175–85. doi:10.1002/acr.21687.
38. Mina R, von Scheven E, Ardoin SP, Eberhard BA, Punaro M, Ilowite N, et al. Consensus treatment plans for induction therapy of newly diagnosed proliferative lupus nephritis in juvenile systemic lupus erythematosus. Arthritis Care Res. 2012;64(3):375–83. doi:10.1002/acr.21558.
39. Ringold S, Weiss PF, Colbert RA, DeWitt EM, Lee T, Onel K, et al. Childhood arthritis and rheumatology research alliance consensus treatment plans for new-onset polyarticular juvenile idiopathic arthritis. Arthritis Care Res. 2014;66(7):1063–72. doi:10.1002/acr.22259.
40. Hosmer DW, Lemeshow S. Applied Logistic Regression. 2nd ed. New York: John Wiley and Sons; 2000.
41. Woreta F, Thorne JE, Jabs DA, Kedhar SR, Dunn JP. Risk factors for ocular complications and poor visual acuity at presentation among patients with uveitis associated with juvenile idiopathic arthritis. Am J Ophthalmol. 2007;143(4):647–55. doi:10.1016/j.ajo.2006.11.025.
42. Angeles-Han ST, Pelajo CF, Vogler LB, Rouster-Stevens K, Kennedy C, Ponder L, et al. Risk markers of juvenile idiopathic arthritis-associated uveitis in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry. J Rheumatol. 2013;40(12):2088–96. doi:10.3899/jrheum.130302.

43. Angeles-Han ST, McCracken C, Yeh S, Jenkins K, Stryker D, Rouster-Stevens K, et al. Characteristics of a cohort of children with Juvenile Idiopathic Arthritis and JIA-associated Uveitis. Pediatr Rheumatol Online J. 2015;13(1):19. doi:10.1186/s12969-015-0018-8.
44. Edelsten C, Lee V, Bentley CR, Kanski JJ, Graham EM. An evaluation of baseline risk factors predicting severity in juvenile idiopathic arthritis associated uveitis and other chronic anterior uveitis in early childhood. Br J Ophthalmol. 2002;86(1):51–6.
45. G Salazar E, Bernhardt MB, Li Y, Aplenc R, Adamson PC. The impact of chemotherapy shortages on COG and local clinical trials: a report from the Children's Oncology Group. Pediatr Blood Cancer. 2015;62(6):940–4. doi:10.1002/pbc.25445.
46. Simonini G, Taddio A, Cattalini M, Caputo R, De Libero C, Naviglio S, et al. Prevention of flare recurrences in childhood-refractory chronic uveitis: an open-label comparative study of adalimumab versus infliximab. Arthritis Care Res. 2011;63(4):612–8. doi:10.1002/acr.20404.
47. Zannin ME, Birolo C, Gerloni VM, Miserocchi E, Pontikaki I, Paroli MP, et al. Safety and efficacy of infliximab and adalimumab for refractory uveitis in juvenile idiopathic arthritis: 1-year followup data from the Italian Registry. J Rheumatol. 2013;40(1):74–9. doi:10.3899/jrheum.120583.
48. Vazquez-Cobian LB, Flynn T, Lehman TJ. Adalimumab therapy for childhood uveitis. J Pediatr. 2006;149(4):572–5. doi:10.1016/j.jpeds.2006.04.058.
49. Heiligenhaus A, Niewerth M, Ganser G, Heinz C, Minden K, German Uveitis in Childhood Study G. Prevalence and complications of uveitis in juvenile idiopathic arthritis in a population-based nation-wide study in Germany: suggested modification of the current screening guidelines. Rheumatology (Oxford). 2007;46(6):1015–9. doi:10.1093/rheumatology/kem053.
50. Paroli MP, Abbouda A, Restivo L, Sapia A, Abicca I, Pivetti Pezzi P. Juvenile idiopathic arthritis-associated uveitis at an Italian tertiary referral center: clinical features and complications. Ocul Immunol Inflamm. 2015;23(1):74–81. doi:10.3109/09273948.2013.855798.
51. Paroli MP, Spinucci G, Liverani M, Monte R, Pezzi PP. Uveitis in childhood: an Italian clinical and epidemiological study. Ocul Immunol Inflamm. 2009;17(4):238–42. doi:10.1080/09273940802702561.

Submit your next manuscript to BioMed Central and we will help you at every step:

- We accept pre-submission inquiries
- Our selector tool helps you to find the most relevant journal
- We provide round the clock customer support
- Convenient online submission
- Thorough peer review
- Inclusion in PubMed and all major indexing services
- Maximum visibility for your research

Submit your manuscript at
www.biomedcentral.com/submit

BioMed Central

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/survophthal

Review article

Update on the systemic management of noninfectious uveitis in children and adolescents

Inês Leal, MD, FEBO, PhD [a,b,*], *Laura R. Steeples, MBChB (Hons), FRCOphth* [c,d], *Shiao Wei Wong, FRCOphth* [c], *Chiara Giuffrè, MD, FEBO* [e,h], *Sasa Pockar, MD* [c], *Vinod Sharma, MBBS, MS, DipNB, FRCS Edin, FRCOphth* [c], *Elspeth K.Y. Green, MBBS, MRes, FRCOphth* [c], *Janine Payne* [c], *Nicholas P. Jones, FRCP* [f], *Alice Sieu Eng Chieng, MBCHB, RCPCH, MSC* [g], *Jane Ashworth, BMBCh, FRCOphth, PhD* [c,i]

[a] *Ophthalmology Department, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisboa, Portugal*

[b] *Visual Sciences Study Centre, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal*

[c] *Manchester Royal Eye Hospital, Manchester University Hospitals NHS Foundation Trust, Manchester, UK*

[d] *Academic Health Science Centre, Manchester, UK*

[e] *Centro Europeo di Oftalmologia, Palermo, Italy*

[f] *School of Biological Sciences, University of Manchester, Manchester, UK*

[g] *Manchester Children's Hospital, University of Manchester, Manchester, UK*

[h] *Ophthalmology Department, San Raffaele Scientific Institute, University Vita-Salute, Milan, Italy*

[i] *Division of Evolution & Genomic Sciences, University of Manchester, Manchester, UK*

ARTICLE INFO

Article history:
Received 21 July 2022
Revised 22 December 2022
Accepted 13 January 2023
Available online 19 January 2023

Keywords:
Non infectious uveitis
Multidisciplinary management
Systemic treatment
Children and adolescents

ABSTRACT

Noninfectious uveitis (NIU) in children and adolescents is a rare but treatable cause of visual impairment in children. Treatments for pediatric NIU and their side effects, along with the risks of vision loss and the need for long-term disease monitoring, pose significant challenges for young patients and their families. Treatment includes local and systemic approaches and this review will focus on systemic therapies that encompass corticosteroids, conventional synthetic disease-modifying antirheumatic drugs (csDMARD), and biological disease-modifying antirheumatic drugs (bDMARD). Treatment is generally planned in a stepwise approach. Methotrexate is well-established as the preferential csDMARD in pediatric NIU. Adalimumab, an antitumor necrosis factor (TNF) agent, is the only bDMARD formally approved for pediatric NIU and has a good safety and efficacy profile. Biosimilars are gaining increasing visibility in the treatment of pediatric NIU. Other bDMARD with some evidence in literature for the treatment of pediatric NIU include infliximab, tocilizumab, abatacept, rituximab and, more recently, Janus kinase inhibitors. Important

* Corresponding author. Inês Leal, Ophthalmology Department, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Av. Prof. Egas Moniz, 1649-035 Lisboa
E-mail address: ines.leal@chln.min-saude.pt (I. Leal).

0039-6257/© 2023 Published by Elsevier Inc.
https://doi.org/10.1016/j.survophthal.2023.01.002

aspects of managing children on these systemic therapies include vaccination issues, risk of infection, and psychological distress. Also, strategies need to address regarding primary nonresponse/secondary loss of response to anti-TNF treatment, biological switching, and monitoring regimens for these drugs. Optimal management of pediatric uveitis involves a multidisciplinary team, including specialist pediatric uveitis and rheumatology nurses, pediatric rheumatologists, psychological support, orthoptic and optometry support, and play specialists.

© 2023 Published by Elsevier Inc.

1. Introduction

Pediatric uveitis is a rare but treatable cause of visual impairment in children. Approximately 60% of children with uveitis will have associated systemic disease, most commonly rheumatological,[31] and therefore thorough investigation is required in a child without a prior diagnosis. The most common type of uveitis seen in children is juvenile idiopathic arthritis-associated uveitis (JIA-U), often picked up on screening of an asymptomatic child.[39] In this review, we will use the term *pediatric* to refer to children and adolescents up to 18 years old.

Children with uveitis are at risk of visual loss secondary to cataracts, macular edema, secondary glaucoma, and amblyopia. In contrast to adult uveitis, the majority of children with uveitis have minimal or no symptoms. As a result, children may have severe structural complications already present at the time of diagnosis; however, early initiation of treatment with immunosuppressive therapy , which currently includes conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and biological disease-modifying antirheumatic drugs (bDMARDs), prevents the development of such complications in the majority of children. There is high-quality evidence to support the use of adalimumab (ADA), alongside methotrexate (MTX), in pediatric noninfectious uveitis (NIU). Evidence to support other immunomodulatory treatments in pediatric NIU is more limited and current care is guided by this, alongside expert opinion and multidisciplinary panels.[10,31,80,180,201]

The treatments for pediatric NIU and their side-effects, alongside the risks of vision loss and need for long-term disease monitoring, are undoubtedly a significant burden for young patients and their families; compliance has been recognized as a major issue. It is important to recognize and consider the potential impact of these factors on education, physical and emotional well-being, child growth, and development alongside therapy in the delivery of pediatric uveitis care. We present a comprehensive review and practical approach for the systemic management of chronic pediatric NIU, with a focus on the use of noncorticosteroid systemic therapies, multidisciplinary care, and strategies for dealing with treatment challenges. Grading of available published evidence using Oxford Centre for Evidence criteria has been done, and for the reader's convenience, the table has been included in supplemental files (Supplemental Table 2).[152]

2. Investigation of pediatric uveitis

All children with NIU regardless of clinical features, laterality or severity, should be considered as having possible systemic disease; however, an expert panel did not reach a consensus on whether children without systemic symptoms should be referred to a pediatrician or rheumatologist.[187] (evidence level 5) A tailored work-up, including laboratory tests, radiological analysis, and multimodal ocular imaging, should be initiated based on the clinical profile of individual patients. It is of paramount importance to rule out certain infectious causes of uveitis. Investigations also serve as necessary baseline tests prior to systemic therapies, ensuring safety to proceed with immunomodulatory medications. In our practice, all children with new-onset uveitis are referred to a pediatrician or pediatric rheumatologist for systemic examination. Autoimmune, vasculitis, and infection screens are requested based on ocular inflammatory disease features and patient and family history.

3. Systemic management of NIU in children

A stepwise approach is typically applied to the management of NIU. Topical corticosteroids are generally used as first-line treatment and often started immediately, with escalation to systemic treatment if inadequate control or high-risk of vision loss to prevent the risk of complications.[39] For the reader's convenience, side effects are detailed in a specific section for the 2 most common drugs used in pediatric NIU, MTX and ADA.

3.1. Systemic corticosteroids

Systemic corticosteroids are used to gain rapid control of NIU, particularly if there is sight-threatening involvement, including posterior segment disease, severe anterior chamber inflammation, hypotony, dense vitreous opacities, and/or macular or optic nerve edema.[39,53,56,64,73,82,82,95] Typically, oral prednisolone (up to 1 mg/kg) is used, or sometimes intravenous methylprednisolone (30 mg/kg up to 3 doses daily/alternate days), and tapered rapidly according to clinical response.[92]

Systemic corticosteroids can result in serious systemic and ocular complications and should not form part of long-term strategy. Infections, weight gain, growth retardation,

Table 1 – Investigations before and while on systemic steroid treatment.

Key time points	Relevant investigations	Purpose
Prior to initiating therapy	Full blood count	Baseline status‡,¶,††
	Glucose	
	AST, ALT, creatinine, urea, urinalysis	
	Height	Baseline–monitor weight gain
	Weight	*,§, ¶,††
	Blood pressure	Identify hypertension †,#
	Chest X ray	Exclude previous chest infections including TB††
	Syphilis testing, IGRA, and TST testing	Exclude infection including TB††
During therapy	Full blood count	Identify hyponatremia, hyper or hypokalemia,
	Glucose	hyperglycemia ‡,††
	AST, ALT, creatinine, urea, urinalysis	
	Height and weight every 6 months	Identify growth retardation and weight gain ¶
	Blood pressure	Identify hypertension††
Prior to cessation of therapy	Synacthen testing	Identify adrenal supression‖,**

AST = aspartate transaminase; ALT = alanine transaminase; IGRA = interferon gamma release assay test; TB = Tuberculosis; TST = tuberculin skin test.

*Ahmet A, Mokashi A, Goldbloom EB, C. H, Jurencak R, P. K. Adrenal suppression from glucocorticoids: preventing an iatrogenic cause of morbidity and mortality in children.

†Boon LM, MacDonald DM, Mulliken JB. Complications of systemic corticosteroid therapy for problematic hemangioma. Plast Reconstr Surg 104(6):1616–23.

‡Buchman AL. Side effects of corticosteroid therapy. J Clin Gastroenterol 33(4):289–94. d

§Domecq JP, Prutsky G, Leppin A, et al. Clinical review: drugs commonly associated with weight change: a systematic review and meta-analysis. *J* Clin Endocrinol Metab Feb;100(2).

‖Health Professionals NHSGGCP. Adrenal suppression secondary to exogenous glucocorticoid - guidance for children on long term steroid therapy [Internet. In: *National Health Service Greater Glasgow and Cylde Guidelines*. https://www.clinicalguidelines.scot.nhs.uk/nhsggc-paediatric-clinical-guidelines/nhsggc-guidelines/endocrinology/adrenal-suppression-secondary-to-exogenous-glucocorticoid-guidance-for-children-on-long-term-steroid-therapy/.

¶Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy Asthma Clin Immunol* 2013;9(1).

#Panoulas VF, Douglas KM, Stavropoulos-Kalinoglou A, et al. Long-term exposure to medium-dose glucocorticoid therapy associates with hypertension in patients with rheumatoid arthritis. *Rheumatology* 47(1):72–5.

**S. WR, J. D, C. B, C.L. D, G. VV, N. A. a search for variables predicting cortisol response to low-dose corticotropin stimulation following supraphysiological doses of glucocorticoids. J Pediatr 163(2):484–488 1.

††Stanbury RM, Graham EM. Systemic corticosteroid therapy: side effects and their management. Br J Ophthalmol 82:704–8.

adrenal suppression, cushingoid habitus, hyperactivity, and osteoporosis are reported.[191] The psychological impact can be significant and distressing, including sleep disorders, mood disturbance, and rarely psychosis.[2,65] Investigations before and while on systemic corticosteroid treatment are presented in Table 1.

3.2. *Noncorticosteroid nonbiologic systemic therapies*

Escalation to csDMARD treatment is necessary for children with NIU refractory to 1-2 topical steroid drops/day and in those requiring systemic corticosteroid to maintain control.[11,57] The presence of complications (posterior synechiae, cataract, or glaucoma), steroid-related complications, and/or underlying systemic inflammation are also indications to start csDMARD, sometimes urgently.[23,59,164] MTX is well-established as the preferential csDMARD in pediatric NIU,[125] especially in JIA-associated uveitis, with a good safety profile. (evidence level 2) [63,83,181]

3.2.1. *MTX*

MTX was effective as a single immunosuppressive therapy agent in childhood chronic NIU with improvement in inflammation in almost 75% of patients in a systematic review (evidence level 2).[183] It is administered orally or via subcutaneous (sc) injection. Less variable bioavailability and less gastrointestinal upset, especially nausea, are suggested with s/c administration.[126] While higher doses of sc MTX treatment (≧ 15 mg/m^2/week) show no more side effects than a lower dose (<15 mg/m^2/day), higher doses are associated with more favorable vision outcomes and shorter times to uveitis disease remission.[206] A similar efficacy was however observed (67% success in uveitis control).[206] Our preference is to use sc MTX, 10–15 mg/m^2/week, with a maximum dose of 25 mg/week.

Escalation to a bDMARD is indicated in: (1) cases refractory to an adequate trial of MTX (3 months); (2) some high-risk cases (e.g., patients at first presentation with severe anterior and/ or intermediate inflammation, optic disc, or macular edema and/or sight-threatening complications such as significant synechiae, cataract, and/or glaucoma) before 3 months of MTX; and (3) MTX intolerance.[27,39] The addition of a second csDMARD has not been proven to improve uveitis control and carries a risk of significant adverse effects [116] The American College of Rheumatology (ACR)/Arthritis Foundation Guideline for JIA recommends that in children with

active uveitis despite 1–2 corticosteroid drops/day for at least 3 months plus systemic MTX; changing or escalating treatment is recommended over continuing current systemic therapy.[11] This approach is also applied to the management of most non-JIA chronic uveitis.[10]

3.2.2. *MTX side effects or toxicity in pediatric uveitis*

In patients experiencing MTX adverse effects, particularly abnormal liver function tests (LFTs) and anticipatory or drug-related nausea/vomiting, dose reduction (or drug cessation) may be necessary.[183] Dose reduction carries a potential risk of reactivation/worsening of uveitis control. Escalation to bDMARD therapy may then become necessary. The impact of MTX on disease should be reviewed after 6 weeks, although it may take 12 weeks to see the full effect. If MTX is not working after 12 weeks, treatment escalation with the addition of a bDMARD should be considered as per NICE guidance/NHS England pathway.[145] Embryotoxicity and teratogenicity have been reported with MTX and sexual health should be addressed before starting treatment; if a child is prepubescent at the time of initiating treatment, this issue should be revisited when appropriate.[135] If bDMARD therapy is contraindicated or poorly tolerated, patients can be transitioned to a different csDMARD (in class or a different class), such as from MTX to mycophenolate mofetil (MMF), although evidence to support switching csDMARD is limited. MMF is generally not effective for the control of arthritis in JIA.[150]

Children taking MTX are at increased risk of infection or reactivation of infection.[136] Intercurrent infections rather than MTX treatment itself may cause transient dips in white cells or neutrophil count or transient elevations of liver function enzymes, which usually settle without action.[135,165] Bone marrow toxicity is possible.[204] Photosensitivity, psoriatic skin lesions aggravated by UV radiation, gastrointestinal toxicity with stomatitis or diarrhea all have been described as early signs of toxicity, and pulmonary toxicity with pneumonitis has been reported.[133] Nephrotoxicity at high doses is also possible, and major toxicity with MTX can occur during intercurrent illness, particularly if there is impairment of renal function or sepsis. It is recommended that MTX be stopped temporarily during severe infection or when the infection is not responding to standard treatment, but can be restarted when the infection has cleared. It should be discontinued in patients who develop opportunistic infections.[204]

A systemic antiemetic (like ondansetron 100–150 μg/kg 30 minutes before MTX and can be repeated every 8–12 hours [maximum per dose 8 mg] as required). or cyclizine (0.5–1 mg/kg up to 3 times a day [maximum per dose 25 mg] for up to 11 years old and 50 mg for older children, taken 1 hour before MTX). Ondansetron can be given for children with nausea and vomiting, and we routinely give ondansetron to all patients in our service, pre- and post-MTX, to prevent physical and subsequent anticipatory nausea and psychological effects. Folic acid supplementation is given to all patients (5 mg once to a maximum 6 times/week) to prevent nausea, fatigue, mouth ulcers, and hair loss. For needle phobia and anticipatory anxiety successful strategies include (1) switch to oral MTX/other csDMARD or temporarily stop MTX for a defined period; (2) multidisciplinary, developmental-appropriate support for the patient and family including play therapy, and psychological support; and (3) sometimes temporary community/hospital nurse drug administration.

Young adults should be counseled about the risks associated with alcohol use while using MTX. Alcohol intake should be kept to a minimum, and binge drinking should be particularly avoided to reduce the risk of liver damage.[91,165]

3.2.3. *MMF and mycophenolate sodium*

There is limited evidence to support the use of MMF or mycophenolate sodium (MPS) in childhood uveitis. Moderate efficacy, steroid-sparing effect, safety, and tolerability have been demonstrated in JIA and non-JIA diseases (evidence level 2/3).[33,49,50] In 1 study, MPS demonstrated reactivation-free survival of 65% in children with non-JIA-U at 2 years.[50] Mycophenolate is used as a second line csDMARD in JIA-U, but arthritis may flare even if uveitis is under good control; therefore, it should be considered together with bDMARD.[190]

3.2.4. *Azathioprine*

There is limited evidence demonstrating the efficacy of azathioprine (AZA) in inflammation control and its steroid-sparing effect as a monotherapy or in combination with other csDMARD in JIA-U.[85] In chronic NIU, tolerability and favorable visual outcomes were reported.[71,176] We use a dose up to 2mg/kg/day with thiopurine S-methyltransferase (TMPT) enzyme testing prior to starting AZA.[94] Azathioprine has the overall reported toxicity-related discontinuation rate of 0.16/patient-years compared to MTX of 0.13/patient-years and MMF at 0.1/patient-years. The concern with rare homozygous deficiency of thiopurine methyltransferase (TPMT) with azathioprine usage does require initial measurement of TPMT level and close titration of azathioprine dose in the prevention of pancytopenia.[88,153]

3.2.5. *Cyclosporin*

There is a lack of evidence to support the use of cyclosporin as monotherapy in pediatric NIU. In 1 study, uveitis control was achieved with ciclosporin monotherapy in around a quarter of patients, but uveitis control and steroid-sparing effect were observed more often when used as combination therapy with MTX and other immunosuppressants such as ADA and ETA (evidence level 3).[194] Cyclosporin has a significant toxicity profile; adverse effects are common and with limited evidence of efficacy, its use in pediatric NIU is very uncommon and not recommended (level 3/4 evidence).[32]

3.2.6. *Leflunomide*

Although leflunomide is an alternative to MTX when the latter cannot be used, it is generally not considered for JIA-U treatment.[150] With very low evidence to support it, its role in the prevention of anti-TNF drugs antibodies formation has been acknowledged.[96,143]

3.3. *Biological disease-modifying antirheumatic drugs*

The use of ADA and infliximab (IFX) monoclonal antitumor necrosis factor (anti-TNF) therapies is supported with evidence of effective uveitis control, vision stability/improvement, and steroid-sparing effect.[121] There is high-quality evidence for ADA with MTX (evidence level 1)[19,157] for NIU

refractory to MTX monotherapy. Beyond these agents, there is a lack of good quality evidence for management approaches.

In 2019, ACR guidelines[10] for JIA chronic uveitis stated: (1) there is no recommendation or preference for ADA or IFX as the first line anti-TNF agent; (2) other systemic anti-TNF agents are recommended over etanercept (ETA), and (3) systemic tocilizumab (TCZ) and abatacept are recommended for patients failing both MTX alone and combined with 2 monoclonal anti-TNF agents (separately).[10] A recently-updated metaanalysis[121] demonstrated the efficacy of both ADA and IFX therapy in refractory chronic pediatric uveitis, for uveitis control and improvement or stabilization of vision. However, ADA showed superior results to IFX in this setting, with higher success in sustained disease control. Both ADA and IFX were significantly superior to ETA. Current evidence, therefore, supports the preferential use of ADA as the first line anti-TNF agent,[121] and ADA is the only licensed biologic for JIA-U worldwide.

3.3.1. Anti-TNF biologic therapies

3.3.1.1. ADA. Evidence for the efficacy and safety of ADA for the treatment of NIU in children is obtained from the SYCAMORE and ADJUVITE trials[18,80,90,157,162] and other retrospective data from clinical registries[209] or case series.[76] In these trials, ADA effectively controlled inflammation in children refractory to topical corticosteroids and MTX therapy. SYCAMORE was a randomized, multicenter, placebo-controlled, double-masked trial that showed a clear therapeutic benefit of ADA in JIA-U and has led to formal licensing of this drug for the treatment of JIA-U in Europe and for children 2 years of age or older in the USA (FDA approved in 2018). ADA was associated with a lower rate of treatment failure but with a much higher incidence of adverse events compared to placebo. The ADA arm showed a longer median duration of sustained disease control than placebo (179 weeks versus 14 weeks).[19] The ADJUVITE trial, (a double-blind, randomized, placebo-controlled trial of ADA in JIA-U during 2 months followed by an open-label period where all patients were followed up during ADA treatment for 10 months) demonstrated that ADA was effective in control of inflammation, with around half of patients achieving at least 30% reduction of inflammation assessed with laser flare photometry after 2 months of treatment, compared to 20% of those receiving placebo. There were no study drug-related adverse events.[157] In a single-center, 5-year follow up study of SYCAMORE study participants, drug-induced disease remission did not persist when ADA was discontinued after 1-2 years; ADA was well tolerated and achieved excellent visual outcomes.[90] The first phase 4 RCT assessing the feasibility of discontinuing ADA in patients with quiescent NIU (JIA-U or antinuclear antibodies (ANA)-positive chronic anterior uveitis) is currently recruiting (NCT03816397; ADJUST Trial (The ADA in JIA-U Trial)).[4]

ADA should be started with a loading dose of 40 mg for patients <30 kg and 80 mg for patients ≧30 kg, 1 week prior to the start of maintenance therapy: 20 mg fortnightly for patients <30 kg and 40 mg fortnightly for patients ≧30 kg. Monitoring of drug blood levels is not routinely performed but might be useful if disease control is lost. In some instances, ADA can be escalated to weekly dosing to achieve disease control, despite limited evidence to support it.[37,114,169]

The dose and any induction regime for ADA in pediatric uveitis is per local country approval. Our practice in the UK is to commence patients on a loading dose. Practice may vary in different health care settings due to constraints of licensing and insurance. The ADA label in some countries, such as in the US, does not include an induction regime.

ADA should not be stopped before ocular surgery because of the potential risk of flare-up of uveitis but should be stopped at least 2 weeks before elective nonocular surgery. For higher-risk procedures, stopping 3–5 half-lives (i.e., 70 days before surgery) should be considered.[72] In our experience, it is extremely difficult to be able to suspend ADA treatment in JIA more than 2 months to plan elective surgery, due to the risk of uveitis flare. Missing 2 doses of ADA is usually recommended in our practice, as an adaptation of this regime. ADA can be recommenced after surgery when there is evidence of safe wound healing (typically around 2 weeks), and there is no evidence of infection.[87]

3.3.1.2. ADA side-effects and toxicity in pediatric uveitis. Common side effects (affecting 1 in 10 people or more) include injection site reactions and other common reported side effects are respiratory tract infections, low white blood cell count, low red blood cell count, increased blood levels of lipids, headache, abdominal pain, nausea and vomiting, rash, musculoskeletal pain and increased plasma levels of liver enzyme.[5] In published literature on pediatric uveitis, however, few side-effects have been reported, as it is a well-tolerated medication.[25,123] Injection site reactions have been less often reported with the change in the Humira (ADA) formulation in 2016.[155]

One of the most common concerns, as shown in a study of ADA efficacy and safety in Japanese children and young people with JIA, was that 8% developed abnormal hepatic function.[93] In a study looking at patients on weekly ADA for JIA with and without associated uveitis, 2 out of 60 developed transaminitis.[40] In a study assessing the efficacy and safety of ADA in children and adolescents with active JIA-associated uveitis, up to 7% had increased levels of ALT and AST.[162]

A variety of less common side effects have been described with ADA use, such as agranulocytosis, aplastic anemia, pancytopenia, vasculitis, alopecia, anemia, and arrhythmias.[147] In the SYCAMORE trial, 5% of patients in the ADA group developed blood or lymphatic system disorders, 2% developed respiratory, thoracic or mediastinal disorders, and 3% gastrointestinal disorders.[162] In a study looking at 268 patients on weekly ADA (off-label use) for various indications, 1 developed autoimmune hepatitis, 2 developed transaminitis, and 3 developed anemia.[37] Munoz-Gallego et al studied 12 children with NIU, one of whom developed palmoplantar psoriasis during ADA therapy that improved after discontinuation of the drug.[142] Optic neuritis was reported in some studies.[36]

3.3.1.3. IFX. IFX) is a chimeric human-murine monoclonal antibody to TNF administered intravenously.[76,166] Evidence supports the efficacy of IFX for disease control, vision stability, and steroid-sparing in pediatric NIU.[15,159,200,209] There is limited evidence of moderate efficacy in NIU control in children refractory to ADA therapy. (evidence

level 3). [15,17,200,98,101,159,168,174,175,184,197] In our practice, the regimen for IFX is as follows: 6 mg/kg loading dose at week 0, week 2, week 6, and then 8 weekly for maintenance treatment. A starting low dose of IFX at 6 mg/kg is usually chosen, but we can increase this to 10 mg/kg if needed or alternatively increase the frequency to 4–8 weekly.[38,118]

Despite limited evidence and off-label use, IFX can be a valuable drug for children not responding to ADA or unable to cope with s/c treatment who need tracking of infusion administration. A response rate of 72% has been suggested in a metaanalysis of pediatric uveitis on IFX.[182] The practice in the US varies significantly from the practice in Europe, being the current standard dose intervals of 4 weeks after a loading dose at week 0 and week 2. This different pattern is relevant since outstanding response rates have been documented in the literature with IFX at intervals of 4 weeks in pediatric uveitis.[104,199]

3.3.1.4. Golimumab. Golimumab (GLM) is a fully-humanized anti-TNF monoclonal antibody approved for the treatment of polyarticular JIA. A few retrospective case series (evidence level 4) suggest its efficacy and safety as a therapeutic option in patients with JIA-associated uveitis who experience loss of response to ADA.[107,127] GLM is FDA approved for use in pediatric patients with polyarticular JIA and PsA but not in uveitis.[86] In our practice, golimumab is not routinely used in the treatment of pediatric uveitis or JIA; however, the following is the regimen for this drug: 50 mg subcutaneously monthly if weight is superior to 40 kg.[108]

3.3.1.5. Etanercept. There is no evidence to support the efficacy of ETA in pediatric NIU. Although there is evidence to support its use in several rheumatological conditions,[119] ETA failed to control inflammation in 2 studies of JIA-uveitis (evidence level 2/3).[178,185] A questionnaire study to pediatric rheumatologists treating more than 300 JIA patients with ETA, concluded that patients with relapsing uveitis remain at high risk of developing uveitis flares despite ETA treatment.[178] There is no evidence to support the use of etanercept in pediatric uveitis. There is secondary evidence, not evaluated in our review, that infers etanercept may alter the rate of uveitis in children with JIA[62] and may, although this did not reach statistical significance, be associated with new onset-uveitis.[41]

3.4. Anti-TNF biosimilars

Biosimilars are biological medications with no clinically meaningful safety and efficacy differences from the originator drug with significant cost savings to widen access.[14,122] There is limited evidence supporting anti-TNF biosimilars in the pediatric population and even less in pediatric NIU.[122] Available evidence from real-world studies confirms the efficacy and safety of biosimilars in patients with JIA (evidence level 3). Obstacles to their use include patients' and families' anxieties regarding device type, color and consistency, safety, and efficacy.[167] In adults, a few studies support the efficacy and safety of ADA and IFX biosimilars in NIU. [43,58,105,188] In children, 1 study confirmed the efficacy and safety of IFX biosimilars in 26 children (44 eyes) with NIU with a median follow-up time of 14 months (evidence level 4).[51] A further study enrolling adults and children (6–17 years old) concluded that ADA biosimilar was effective and well-tolerated in Behçet uveitis (evidence level 4).[186] A recent real-life study compared originator ADA with biosimilar ADA in pediatric rheumatic diseases. It concluded about no significant difference between the biosimilar and the originator product in terms of efficacy and safety, being one of the analyzed outcomes the number of uveitic flares.[198] There are no studies about ADA biosimilars exclusively in pediatric NIU.

In the UK, biosimilar biologic drugs are now routinely used in several specialties, including in the management of NIU. A national policy recommended switching all patients from the originator drug to a biosimilar. Any switch from an effective agent to a biosimilar in children's uveitis must be managed with caution including adequate patient and family counseling and continuous treatment provision. Continuous pharmacovigilance programs to address biosimilar efficacy, safety, and acceptance among children and their families are necessary.[144,156,210]

3.5. Primary nonresponse/secondary loss of response to anti-TNF treatment and biological switching

A loss of or failure of response to a biologic agent can be immunogenic, pharmacokinetic, or pharmacodynamic. In active disease, serum drug trough levels and antidrug antibodies should be checked to determine the mechanism of failure.[132] Commercial assays are routinely available for ADA and IFX, including biosimilar drug testing.[74,109,171] Antidrug antibodies can reduce serum drug levels, via a neutralizing effect and/or increasing drug clearance.[66,203] Treatment emergent antidrug antibodies are associated with a lack of concurrent MTX treatment;[60] their presence is also associated with a lower likelihood of response to a biologic dose increase,[77] and switching to an alternative bDMARD if uveitis is active should be strongly considered. The significance of antidrug antibodies in patients in drug-induced disease remission is uncertain and treatment is usually continued with close supervision.[131,132] Therefore, routine screening for antidrug antibodies is not supported and testing is advised if treatment failure or reduced efficacy is observed. In patients with NIU refractory to standard dose bDMARD with low drug trough levels and negative antidrug antibodies (pharmacokinetic failure) dose escalation should be considered before switching agents (off-label).[37,169,190] In our practice, in children refractory to standard dosing, the IFX infusion interval is reduced, initially to 6–7 weekly and up to 4 weekly; ADA may be increased to weekly injections (off-label), with an assessment of response up to 3 months. Further large studies to evaluate the safety, efficacy, and patient/family acceptability of enhanced dosing biologic treatment algorithms are necessary. Detailed information about ADA and IFX trough levels, antidrug antibodies measurement and dose enhancement, may be found in supplemental file 1.

For treatment failure in JIA-U with first anti-TNF therapy (ADA) at standard dosing, the ACR/Arthritis Foundation conditionally recommends this algorithm:

1. Escalating the dose and/or shortening the dosing interval before switching to an alternative anti-TNF agent:[11] : There is emerging evidence supporting the efficacy and

safety of off-label weekly ADA in refractory NIU in adults and children (evidence level 2–3) alongside efficacy and safety evidence in JIA.[40,114] In 1 study, 63% of 19 patients achieved control with weekly dosing with no serious adverse effects.[169] A further study of weekly ADA in 69 children with JIA or NIU (n = 17) found an overall positive clinical response in 90% of patients.[37] Neither study reported any increased risk of serious infection.

2. In treatment failure with above-standard anti-TNF dosing, experts conditionally recommend switching to a second anti-TNF agent before switching to a different category biologic.[11] Infliximab is the usual second-line choice and if unsuccessful, alternative biologic therapies include tocilizumab, abatacept, golimumab, rituximab (no consensus reached by the Childhood Arthritis and Rheumatology Research Alliance [CARRA] panel). [10]
3. Alternative approaches, with limited evidence, include switching csDMARD treatment to a non-MTX option including MMF, AZA, leflunomide, or ciclosporin (however, no expert consensus was reached on the specific agent).[10]

The washout period (the time taken for serum levels of the biologic agent to reduce to a negligible amount) is usually taken to be roughly the sum of 5 terminal half-lives. Half-life information for each biologic agent is listed under individual monographs. As a general rule, at least 2 half-life of the previous biologic treatment should be omitted before commencing the next agent but available literature to support this is limited and may be conflicting.[156] For biologic agents where washout periods are prolonged, a clinical decision regarding the risk of disease progression or flare versus the risk of oversuppressing the immune system and leaving patients more vulnerable to infection must be made.

3.6. Deescalation of treatment with MTX and/or ADA

Solid evidence in the literature to indicate the optimal duration of treatment with ADA/MTX is lacking[39,45,90,110]; however, some expert opinions and published guidelines for JIA have suggested that reducing or suspending DMARD might be attempted if drug-induced disease remission is maintained for more than 24 months.[10,39,82,173] In our practice, remission is regarded as an inactive disease under systemic DMARD therapy, but with no systemic steroids (a low dose of topical steroids could be accepted in selected cases). There is very little literature guiding deescalation regime for MTX and/or anti-TNF therapy. Consequently, there is variation in practice in discontinuing treatment once remission has been achieved. This choice depends on systemic disease control (if present) and should always be a shared decision between the ophthalmologist, the pediatric rheumatologist, and the patient/family. In our practice, gradual dose reduction or increasing spacing between doses (e.g., increasing time between ADA administrations from 2–3 weeks or IFX from 6 to 8 weeks) is preferred over the abrupt withdrawal of treatment. There is currently no evidence as to the optimum period of disease remission prior to stopping treatment, nor whether to taper or stop treatment completely. The ADJUST (discontinuing ADA in patients with controlled JIA-U) study is the first randomized controlled trial to assess the efficacy of discontinuing ADA after demonstrating control of JIA-associated uveitis for at least 12 months, which will support decision making. This trial will also assess evidence of antidrug antibodies emergence while increasing interval of ADA administration, a topic that lacks robust evidence.[4] A small (N = 31), single-center, single-arm, unblinded interventional study showed an impressively low rate of JIA flares (12.9% within 2 years) with a very slow, stepwise taper of anti-TNF.[29] During dose deescalation, early detection of uveitis recurrence is crucial, and this is achieved with diligent ophthalmological follow-up.[1,111]

3.7. Other biologic agents

Overall, there is limited evidence, particularly controlled trial data, to support the use of nonanti-TNF bDMARDs in pediatric uveitis. Further high-quality studies to evaluate the efficacy and safety of rescue therapies for disease refractory to MTX and anti-TNF are necessary as a significant proportion of patients fail to respond or maintain sustained disease remission with these agents.[162]

3.7.1. Tocilizumab

Tocilizumab (TCZ) is a humanized recombinant anti-interleukin-6 (IL-6) receptor antibody. Increased IL-6 (a proinflammatory cytokine) levels have been found in serum,[35] aqueous,[54] and vitreous,[154] in patients with NIU. Tocilizumab is licensed for JIA (standard dose 8 mg/kg 4-weekly). Systemic administration proved to be promising in safety and efficacy in adult NIU, especially in the presence of macular edema.[112,134] Retrospective and limited prospective studies have shown some efficacy in uveitis. The use of intravenous TCZ in adults with NIU is supported by significantly improved visual, anatomic, and inflammatory outcomes (STOP TRIAL - evaluating the safety, tolerability, and efficacy of TCZ in patients with NIU).[208] A multicenter phase 2 trial (APTITUDE study) assessed the efficacy of TCZ in 21 children with JIA-U who were refractory to MTX and TNF inhibitors. Those weighing ≥30 kg were dosed with 162 mg of TCZ every 2 weeks while participants weighing <30 kg were dosed with 162 mg of TCZ every 3 weeks through a s/c injection. The study did not meet its primary endpoint (treatment response defined as a 2-step decrease, or decrease to 0, from baseline in the level of anterior chamber inflammation) as 7(33%) of 21 participants achieved treatment response at week 12. Thirteen (62%) of 21 patients were classified as nonresponders, 8 of whom reached 12 weeks of treatment. Of the 6 patients who continued treatment after 12 weeks, 4 (67%) were classed as treatment responders at 24 weeks. There was resolution of 3 out of the 4 macular edema cases. Adverse effects associated with administration of TCZ included injection site reactions (38%), ALT rises (14%) and blood triglyceride increases in 14%.[123,160,161] There is also some supporting low-grade evidence for moderate efficacy in JIA-U, intermediate and panuveitis from case reports/series and anti-IL-6 therapy (evidence level 4)[21,189,196] There is limited evidence (evidence level 3) to support the efficacy of Intravenous rather than s/c TCZ in NIU refractory to MTX/anti-TNF, with more favorable outcomes (67.5% responsiveness).[21,30,124,158,189,193,196,205] Maleki et al and Ramanan et al hypothesized that intraocular inflammation requires higher doses of TCZ via the intravenous route, than

joint inflammation, possibly because of the blood-aqueous and blood-retinal barriers. Further large studies to explore efficacy, safety, and optimal dose/route of administration are necessary.[20,124]

3.7.2. Abatacept

Abatacept (ABA) is a soluble fusion protein and prevents T-cell activation through interaction with CD80 and CD86 on antigen presenting cells.[78] There is inconclusive evidence to support the use of ABA in pediatric uveitis refractory to anti-TNF (evidence level 4).[55,100,121,129] Tappenier et al reported outcomes of ABA in 21 patients with severe JIA-U refractory to MTX and at least 1 biologic agent and 48% of patients failed treatment and sustained response to ABA was uncommon.[210] Birolo et al found no statistical difference in the efficacy of ABA used as first- or second-line biologic agent in JIA-U.[26] Zulian et al suggested sustained improvement in severe anti-TNF resistant JIA-U in 7 pediatric patients [211] and Marrani et al documented the ability of ABA to induce remission and spare systemic steroid therapy in 3 pediatric patients through a long follow-up period (minimum 18 months).[128]

3.7.3. Secukinumab

There is no evidence to support anti-IL17 therapy in pediatric uveitis. In adult NIU, s/c secukinumab failed to control and prevent recurrence and its use is not supported (evidence level 2).[45,46]

3.7.4. Rituximab

There is limited evidence to support the use of rituximab, a chimeric monoclonal antibody targeting CD20 antigen on B cells, in severe JIA-U refractory to at least 1 anti-TNF. Rituximab has demonstrated efficacy in achieving long-term control of NIU and reduction of systemic treatment burden, in 2 case series (evidence level 4),[84,138] with repeat infusions described to sustain control. In particular, efficacy has been described in aggressive and recalcitrant forms of pediatric NIU who have not responded to previous other bDMARD.[137–139] (evidence level 3 and 4)

3.7.5. Janus kinase (JAK) inhibitors

Binding of a number of cytokines and growth factors to their receptors results in phosphorylation and activation of receptor-associated Janus kinase (JAK), recruitment of transcription factors of the signal transducer and activator of transcription (STAT) family, their translocation to the nucleus and induction of transcription. Intracellular signal transduction involves combinations of four JAK isoforms (JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2).[148,149,192] JAK inhibitors are small molecules administered orally that act on JAK proteins, which belong to the tyrosine-kinase family and are signaling mediators that act downstream of pro-inflammatory cytokines involved in the pathological processes of many immune and inflammatory diseases.[67,97,120] There is no evidence in the literature to support the use of JAK inhibitors in children with NIU; however, an open-label, multicenter, ADA active-controlled phase 3 clinical trial (JUVEBRIGHT), evaluating the efficacy and safety of baricitinib for the treatment of JIA-U and chronic ANA-positive anterior uveitis without systemic features, despite prior treatment with topical corticosteroids and MTX or bDMARD, is ongoing. The primary endpoint is the proportion of patients with response at 24 weeks.[163]

4. Safe management of systemic therapies

4.1. General considerations

Optimal management of pediatric uveitis involves a multidisciplinary team, including specialist pediatric uveitis and rheumatology nurses, pediatric rheumatologists, psychological support, orthoptic and optometry support, and play specialists. All decisions on initiating and monitoring systemic treatment should be made in conjunction with the pediatric rheumatology department.

4.2. Corticosteroids

To ensure that corticosteroids are used safely, investigations prior to treatment and during treatment are essential.[117] These are shown in Table 1.

A patient who has used systemic corticosteroids at a supra-physiological dose for over 1 month is at risk of developing adrenal suppression.[44,172] In 1 study, 42% of children on corticosteroids for 6 months had deranged synacthen tests.[172] There is no evidence to support a particular strategy for managing children with uveitis at risk of adrenal suppression, and individual endocrinology advice should be sought for safe corticosteroid taper and withdrawal and management of adrenal insufficiency.

4.3. Monitoring regimes for MTX, ADA, and MMF

4.3.1. MTX baseline and monitoring

For all DMARDs, baseline information should be obtained before starting treatment. For MTX this is as follows: height, weight, and body surface area, full blood count (FBC) and differential white cell count, erythrocyte sedimentation rate (ESR), C reactive protein (CRP), transaminases, renal function tests with glomerular filtration rate, urinalysis, varicella zoster virus (VZV) serology, measles, mumps, and rubella (MMR) titers. If the child proves to be negative to VZV, vaccination should be offered prior to starting MTX, but careful consideration must be taken in regards of delaying treatment to introduce vaccination.[165] Non-UK guidelines also recommend hepatitis and tuberculin testing before starting therapy.[146]

After starting treatment, FBC and liver function monitoring is required every 2 weeks until a stable dose is achieved.[135,165] If this is stable after 1 month, then monthly check is needed for 3 months and afterwards every 3 months.[28] Guidelines derived from the ACR also recommend albumin monitoring every 4–8 week initially, and then every 12–16 weeks,[151] with monthly monitoring for the next 6 months. Once stable dose is achieved, creatinine clearance and urinalysis should be checked once every 6 months.[28]

In any of the following cases, it is recommended to reduce or withhold the dose and discuss with pediatric rheumatologist:[28,165]

- AST (aspartate aminotransferase) or ALT (alanine aminotransferase) >3 times above upper level of the normal, although some guidelines recommend withholding MTX when AST or ALT > 2 times above the upper level of normal. Elevated liver enzymes have been reported as 1 of the most common side effects of MTX treatment in children with JIA treated with MTX,[183] occurring in about half of patients on at least 1 occasion during this study. Concurrent AST and ALT abnormalities were observed 83% of the time[102,206] and this is often a dose-dependent phenomenon.[165,183] Current guidelines allow transaminases to be raised up to 2 or 3 times the upper limit of normal.[135,165] These have been reported to resolve on subsequent testing in 80% of children, generally within less than 4 weeks.[102,106,202] If transaminitis persists or increases further above 3 times of the upper limit, MTX is discontinued for 2 doses, or the dose is reduced, after which liver enzymes are rechecked. If levels have returned to normal, MTX can be recommenced at the previous dose; if further elevations occur, the MTX dose should then be reduced by 20%.[165] There is little evidence of significant long term toxicity or liver damage such as cirrhosis caused by MTX.[102,106,165]
- Full blood count. (Hematological abnormalities are rare in children taking s/c MTX)
  - Platelets <150 × 10^9/L
  - White cell count <3 × 10^9/L – neutrophils <1.5 × 10^9/L, lymphocytes less than 0.5 × 10^9/L (Intercurrent infections may cause transient dips in white cell count and/or neutrophils)
  - Hemoglobin less than 90 mg/dL (without another identifiable cause).
- Rash or severe oral ulcers, new or increasing dyspnea or cough as possibility of pulmonary toxicity.
- Stomatitis and diarrhea may be the first sign of gastrointestinal toxicity and withdrawal of treatment is recommended. Alopecia is seen in some patients, but hair grows back after stopping the medication.[59]

4.3.2. ADA baseline monitoring

Baseline information should be obtained before commencing treatment[5]:

- Infection screening for tuberculosis.
  - Interferon-gamma release assay investigation.
  - Chest X-ray (not more than 6 prior to ADA institution). Chest X-ray is not mandatory and its performance is dependent on local population risk and prevalence; however, if taken, a report stating no evidence of tuberculosis (TB) should be sought.
- Screening for hepatitis B and C and human immunodeficiency virus (HIV).
  - Most children do not need the testing, and different guidelines exist according to the population risk.
- Infection screening for VZV and MMR titers.

Patients on ADA should have 3-monthly FBC, ESR, CRP, blood urea nitrogen, electrolytes, AST, and ALT.

If any of the following are abnormal, the practitioner should consider withholding/reducing the dose:

- Neutrophils <1.0 × 10^9/L
- Platelets <150 × 10^9/L
- AST/ALT >3 times normal upper limit

4.3.3. MMF baseline and monitoring

Baseline bloods as for other DMARDs are required. FBC, creatinine / calculated GFR, ALT, AST, and albumin are required every 2 weeks until on stable dose for 6 weeks, then 3-monthly once stable. If WBC < 3.5 × 109/L, neutrophils < 2.0 × 109/L, platelets < 150 × 109/L, unexplained reduction in albumin <30 g/L, creatinine increase >30% over 12 months and/or calculated GFR <60 mL/min or > 2-fold rise in AST, ALT from upper limit of reference range, the dose should be adjusted or MMF stopped.[141]

5. Management of vaccination, risk of infection or demyelination, and psychological health

5.1. Demyelination

While the association between demyelination and ADA in adults is clear, it is rare in children, and only a few cases are described.[133,177] In a study including 268 patients on weekly ADA for JIA, there was an isolated case report of a single patient developing multiple sclerosis.[40] For safety, appropriate assessment and counseling is needed prior to starting treatment.[5] In our center, we perform clinical assessment and ask for a family history of demyelination. We do not advise offering indiscriminate pretreatment brain magnetic resonance imaging to all treatment candidates.

5.2. Vaccination issues

The presence of immunomodulatory drugs can interfere with the effectiveness and safety of vaccinations.[59] Safe and effective vaccination is crucial in pediatric patients with rheumatic diseases given the increased risks of infections.[87] According to the EULAR recommendation, when indicated according to national guidelines, nonlive vaccines can be administered to pediatric patients with rheumatic diseases using systemic corticosteroids, csDMARD and bDMARD, including anti-TNF therapy.[81] It is recommended to withhold live-attenuated vaccines in pediatric patients with rheumatic diseases on high-dose csDMARD, high-dose systemic corticosteroids or bDMARD therapy; however, vaccination can be considered in some cases, weighing the risk of infections versus the hypothetical risks of vaccination, and treatment should not be delayed if there is sight-threatening disease.[81]

In patients on both MTX or ADA, inactivated vaccines should be given according to the normal immunization schedule (including human papilloma virus [HPV]). Patients on csDMARDs and bDMARDs should not receive live vaccines. For patients on MTX and/or ADA, VZV vaccine and MMR vaccines, if needed, ideally should be given at least weeks before initiation of treatment. Patients should also receive annual influenza immunization. Pneumococcal vaccine booster should also be considered, depending on the age of the child and their routine vaccination status. Patients

without VZV immunity may need VZV vaccine and, in the event of VZV exposure in a patient with negative VZV IgG serology prophylactic antivirals can be considered and intravenous antiviral therapy if they develop a symptomatic infections.[81,87,135]

Because of the lack of safety data, BCG vaccination should not be administered to patients on csDMARDs (including MTX) or bDMARDs.[5,59]

There is scarce evidence about the safety and efficacy of COVID-19 vaccines in children and young people with rheumatic diseases, and there is no evidence regarding exclusively children on immunosuppressant treatment for NIU. Early literature on the subject suggests that patients (including adults) with rheumatic disease have fears of potential disease exacerbation and additional adverse events.[34] An observational cross sectional single center study with 228 children with rheumatic disease suggests no increased in the COVID-19 vaccination-related adverse effects.[16] A study assessing the humoral response and safety of vaccine in a cohort of approximately 40 patients with pediatric rheumatic diseases receiving immunosuppressant treatments showed that these patients are able to mount an effective humoral response after 2 dose regimens of BNT162b2 mRNA vaccine safely without interrupting their current treatments.[6] Specifically, in adolescents and young adults with rheumatic diseases, a study with 246 subjects indicated an acceptable safety profile of COVID-19 vaccines.[79] It has been acknowledged in the literature that further studies examining causes of concerns of parents and children with rheumatic diseases is crucial to ensure effective strategies of COVID-19 vaccination programs in these patients.[7] Currently, a primary vaccination schedule for people who are immunosuppressed at or around the time of their first or second dose of the COVID-19 vaccine is 3 doses rather than 2. Additionally, those aged 12 or over in this group who have completed their primary course (3 doses) of COVID-19 vaccine will be due for a booster (as a fourth dose) at least 3 months after administration of their third primary dose. Recommendation for children and adolescents in adherence to national guidelines for COVID vaccination for immunosuppressive should be followed.[75]

5.3. Risk of infection in patients on corticosteroids, conventional synthetic disease-modifying antirheumatic drugs and biological disease-modifying antirheumatic drugs

Pediatric patients with rheumatic diseases are at increased risk of infections, owing to the immunosuppressive effect of the disease or its treatment[48]; however, a myriad of conflicting results and variability in reported risk can be found in the literature. As an example, a systematic review of 38 studies, including 22 randomized controlled trials, in 2015 showed that, among children taking short-course oral corticosteroids, infection was the most serious adverse event, reported in 1%.[9] It has been shown that among children with JIA, the rate of infection was not increased with MTX or TNF inhibitor use, but was significantly increased with high-dose steroid use.[24] Among 3,467 treatment courses for patients with JIA in a German registry, the total rate of serious infections was low, with a total of 28 infections in 26 patients reported. Treatment with ADA increased the risk for serious infection slightly compared to MTX only, but risks on bDMARD monotherapy did not differ from that of combination therapy with MTX and ADA.[22] Lee and coworkers report a 2.7-fold increase in the risk of serious bacterial infection for new use of TNF inhibitor monotherapy (n = 482) compared with new use of csDMARD monotherapy (n = 2013) in children with JIA.[113] In the SYCAMORE trial, which assessed the efficacy and safety of ADA in children with active JIA-associated uveitis, 13% of children had mild infection or infestation, the most common being viral infection, followed by nasopharyngitis, tonsillitis, urinary tract, and respiratory tract infections.[162] Occasional reports of appendicitis and VZV infection in children with NIU treated with ADA exist in the literature.[142] In a study looking at patients using weekly ADA for various indications, 5% had an infection requiring hospitalization and 40% of patients had an infection requiring antimicrobial treatment.[40] Results of 7 global, randomized studies evaluating the safety of ADA in pediatric patients who participated in clinical trials (577 patients with JIA, psoriasis, and Crohn disease) showed that serious infections (4.0 events/100 patients) were the most frequent serious adverse events across indications. The most commonly reported was pneumonia (1% of patients). Patients who received concurrent systemic corticosteroids had a greater incidence and rate of infections and serious infections compared with patients who did not.[89]

The risk of contracting TB is increased in patients in endemic areas treated with immunosuppressive drugs, especially bDMARDs. The risk of reactivation of latent infection is recognized specifically with TNF inhibitors; TB often presents atypically, posing challenges to diagnosis.[70,81,99] Treatment of latent TB before starting biologic is key to ensuring safety and must be done under close supervision by the multidisciplinary team (according to local practices).[52,207]

Regarding coronavirus disease 2019 (COVID-19), there is no literature on the risk of immunosuppressant therapy in pediatric uveitis. Data from the COVID-19 global rheumatology alliance physician-reported registry suggest that corticosteroid exposure of $\geq$10 mg/day is associated with higher odds of hospitalization. In contrast, anti-TNF exposure is associated with decreased odds of hospitalization. The use of csDMARD was unassociated with increased odds of hospitalization; however, this study was not explicitly done in the pediatric population.[68] Specifically, in a study of more than 400 children with rheumatic diseases (JIA, among others), immunosuppressive treatment was not associated with the additional risk of severe COVID-19.[103] In general, the use of $\geq$10 mg/day of prednisolone is associated with an increased rate of infection in JIA patients,[115] and a study from the British Society for Pediatric and Adolescent Rheumatology showed an increased incidence of medically significant infections among patients treated with etanercept compared to MTX.[42] Early data on the risk of COVID-19 infection in children suggested the low frequency of severe disease complications in pediatric patients with rheumatic conditions.[195]

5.4. Psychological health and quality of life

Patient and family interviews alongside exploration of expert clinician experiences provide valuable understanding and description of the significant and often profound physical, social, and psychological challenges faced by patients and their

families. Children may experience disrupted schooling and academic progress, psychosocial and emotional stress, altered and strained relationships with parents and siblings, alongside altered growth, development and vision loss.[8,47,69,179]

Knight and coworkers found that children with rheumatological diseases have a higher rate of unmet mental health needs.[3] These include depression, anxiety, and other forms of mental health problem related to their quality of life.[140] It was concluded that treatment strategies for mental health in rheumatology patients are lacking and we need a better understanding of how to manage and support these children and their families.[170] It is recognized from expert opinion and patient/parent interviews, that children with uveitis face unique issues aside from vision loss and fear of blindness including the burden of chronic disease, treatment, and monitoring regimes, particularly regular blood tests and injections, and treatment toxicities. Physical, academic, interpersonal, and psychosocial challenges affect children and extend to their family members.[10,47] There is a lack of evidence on how best to address these issues in pediatric uveitis clinical services. The EYE-Q is a valuable tool to measure visual function and health-related quality of life in children with uveitis.[13,130]

5.5. *Multidisciplinary management of pediatric uveitis*

There is a paucity of high-grade evidence for the management of pediatric uveitis, particularly for non-JIA-U.[39,61,190] Management of uveitis in children is complicated by disease heterogeneity and underlying systemic conditions. Furthermore, systemic disease may not be apparent at the onset of uveitis. Referral to medical specialties is typically guided by the child's history, but there was no consensus amongst UK specialists on referring asymptomatic children to rheumatology.[187] (evidence level 4) When starting systemic immunosuppression, there is level 3 evidence and expert consensus[187] for referral to rheumatologist or clinical nurse specialist for initiation of csDMARD therapy and use of local general practitioner or pediatrician for monitoring if appropriate. Similarly, bDMARD is typically prescribed via pediatric rheumatology services.[39,190]

There is heterogeneity in pediatric uveitis services, with no clear guidance for organizing services and staff for the management of ocular inflammation, sequelae of uveitis, particularly cataract and glaucoma, and systemic conditions. For example, in the UK, children with uveitis may be cared for by a uveitis specialist managing children or by a pediatric ophthalmologist managing complex uveitis, but there is no mandatory referral pathway to specialist pediatric uveitis services and no major guidelines for the delivery of specialist multidisciplinary support services. Special considerations in managing children, including amblyopia, higher risk of uveitic glaucoma, drug dosing, pediatric specific drug risks, and treatment compliance, must be acknowledged and considered by services to protect patient and family well-being[12,69] (evidence level 4 expert/international workshop).

6. Conclusion

NIU in children and adolescents poses enormous hurdles to comprehensive care delivery in this vulnerable age group. Systemic treatment includes corticosteroid, non-corticosteroid nonbiologic therapies, and biologic therapies. Management of this chronic condition requires long-term therapy, frequent blood tests for toxicity monitoring, drug escalation, and withdrawal/alteration of therapies in cases of adverse events or nonefficacy. The risk and impact of vision loss, treatment complexities, and the burden of the disease for patients and their families, including their psychological health and quality of life, must be considered. All these complex issues should be ideally managed in a multidisciplinary setting.

7. Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Method of literature search

Literature searches were performed using PubMed. The last literature search was performed in June 2022. The following search terms were used, isolated and/or in combination: "pediatric uveitis," "children uveitis," "juvenile idiopathic arthritis uveitis," "biologics", "biological disease-modifying antirheumatic drugs", "adalimumab," "methotrexate," "mycophenolate mofetil," "anti-TNF biosimilars," "multidisciplinary," "multidisciplinary management". Combinations of these terms with appropriate Boolean operators were also used. The following filters were applied: clinical study; clinical trial; controlled clinical trial; multicenter study; observational study; randomized controlled trial; review; meta-analysis. The articles retrieved were reviewed for their title, abstract, and language (non-English articles were excluded). Significant nonpeer-reviewed publications, such as guidelines, were included. Additional publications were included from a search of studies cited within the publications identified in the initial literature search.

The great majority included studies in this review were performed in pediatric populations. However, due to lack of evidence of systemic therapy in pediatric uveitis, other studies were also considered.

The following cited studies were performed strictly in adults and information was extrapolated to write this review.

- Chung JH, Van Stavern GP, Frohman LP. Adalimumab-associated optic neuritis. J Neurol Sci 244:133–6.
- Deaner JD, Srivastava SK, Hajj-Ali RA, et al. Recurrence rates of inflammation after switching from the originator infliximab to biosimilar infliximab-abda for noninfectious uveitis. Am J Ophthalmol 2021;225:172–7.
- Dick AD, Tugal-Tutkun I, Foster S, et al. Secukinumab in the treatment of noninfectious uveitis: Results of 3 randomized, controlled clinical trials. Ophthalmology 2013;120:777–87. doi:10.1016/j.ophtha.2012.09.040.
- Fabiani C, Vitale A, Emmi G, et al. The role of biosimilars in uveitis: long-term real-world outcomes of the switch from original to biosimilar TNF-alpha inhibitors. Front Pharmacol 2019;10. doi:10.3389/FPHAR.2019.01468.

- Liberman P, Berkenstock MK, Burkholder BM, Chaon BC, Thorne JE. Escalation to weekly adalimumab for the treatment of ocular inflammation. Ocul Immunol Inflamm Published online 2020. doi:10.1080/09273948.2020.1749857.
- MR S. Mycophenolate mofetil therapy in the management of inflammatory bowel disease – a retrospective case series and review. J Crohn's Colitis 8:890–7.
- Tugal-Tutkun I, Mudun A, Urgancioglu M, et al. Efficacy of infliximab in the treatment of uveitis that is resistant to treatment with the combination of azathioprine, cyclosporine, and corticosteroids in Behçet's disease: an open-label trial. Arthritis Rheum 2005;52:2478–84. doi:10.1002/art.21231.
- Wang SL, Hauenstein S, Ohrmund L, et al. Monitoring of adalimumab and antibodies-to-adalimumab levels in patient serum by the homogeneous mobility shift assay. J Pharm Biomed Anal 79:39–44. doi:10.1016/j.jpba.2013.01.031.
- YJ Sepah, MA S, DS C, et al. Primary (month-6) outcomes of the STOP-uveitis study: evaluating the safety, tolerability, and efficacy of tocilizumab in patients with noninfectious uveitis. Am J Ophthalmol (v;183:71-80). doi:10.1016/j.ajo.2017.08.019.

The following cited studies included both adults and children and information were extrapolated to write this review.

- Gianfrancesco M, Hyrich KL, Al-Adely S, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 global rheumatology alliance physician-reported registry. Ann Rheum Dis 2020;79:859–66. doi:10.1136/ANNRHEUMDIS-2020-217871.
- Pilunni D, Santuccio C, Sottosanti L, Felicetti P, Navarra P. Relationship between injection site reactions and different adalimumab formulations. Analysis of the adverse events reported in Italy in the period 2016-2019. Eur Rev Med Pharmacol Sci 2021;25:3300–5. doi:10.26355/EURREV_202104_25468.

Soheilian M, Ebrahimiadib N, Hedayatfar A, Hosseini M, Zarei M, Anjidani N. Efficacy of biosimilar adalimumab in the treatment of Behçet's uveitis. Ocul Immunol Inflamm. Published online 2021. doi:10.1080/09273948.2021.1900276.

CRediT authorship contribution statement

Inês Leal: Conceptualization, Writing – original draft. **Laura R. Steeples:** Conceptualization, Validation, Writing – original draft, Writing – review & editing, Supervision. **Shiao Wei Wong:** Validation, Writing – original draft. **Chiara Giuffrè:** Validation, Writing – original draft. **Sasa Pockar:** Validation, Writing – original draft. **Vinod Sharma:** Validation, Writing – original draft. **Elspeth K.Y. Green:** Validation, Writing – original draft. **Janine Payne:** Writing – original draft, Validation. **Nicholas P. Jones:** Validation, Writing – review & editing, Supervision. **Alice Sieu Eng Chieng:** Validation, Writing – original draft, Writing – review & editing, Supervision. **Jane Ashworth:** Conceptualization, Validation, Writing – original draft, Writing – review & editing, Supervision.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.survophthal.2023.01.002.

REFERENCES

1. Heiligenhaus A, Minden K, Tappeiner C, et al. Update of the evidence-based, interdisciplinary guideline for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis. Semin Arthritis Rheum. 2019;49:43–55.
2. Upadhyay A, Mishra OP, Prasad R, Upadhyay SK, Schaefer F. Behavioural abnormalities in children with new-onset nephrotic syndrome receiving corticosteroid therapy: results of a prospective longitudinal study. Paediatr Nephrol. 2016;31:233–8. https://doi.org/10.1007/s00467-015-3216-1.
3. Knight A, Weiss P, Morales K, et al. Identifying differences in risk factors for depression and anxiety in pediatric chronic disease: a matched cross-sectional study of youth with lupus/mixed connective tissue disease and their peers with diabetes. J Pediatr. 2015;167:1397–1403.e1. https://doi.org/10.1016/j.jpeds.2015.07.048.
4. Acharya NR, Ebert CD, Kelly NK, et al. Discontinuing adalimumab in patients with controlled juvenile idiopathic arthritis-associated uveitis (ADJUST-adalimumab in juvenile idiopathic arthritis-associated uveitis stopping trial): study protocol for a randomised controlled trial. Trials. 2020;21:887https://doi.org/10.1186/S13063-020-04796-Z.
5. Adalimumab use in paediatric and adolescent rheumatology, Information for health proffesionals. *Br Soc Rheumatgol Paediatr Adolesc Guid* https://www.rheumatology.org.uk/Portals/0/Documents/Guidelines/PaediatricguidelinesAdalimumab_Paediatric_Rheumatology.pdf?ver=2020-03-19-150326-343.
6. Akgün Ö, Çakmak F, Guliyeva V, et al. Humoral response and safety of BNT162b2 mRNA vaccine in children with rheumatic diseases under immunomodulatory treatment: a preliminary study. Rheumatology (Oxford). 2022;61:4482–90. https://doi.org/10.1093/RHEUMATOLOGY/KEAC140.
7. Akgün Ö, Kayaalp GK, Demirkan FG, et al. Exploring the attitudes, concerns, and knowledge regarding COVID-19 vaccine by the parents of children with rheumatic disease: cross-sectional online survey. Vaccine. 2022;40:1829–36. https://doi.org/10.1016/J.VACCINE.2022.01.061.
8. Solebo AL, Rahi JS, Dick AD, et al. Areas of agreement in the management of childhood non-infectious chronic anterior uveitis in the UK. Br J Ophthalmol. 2020;104:11–6. https://doi.org/10.1136/bjophthalmol-2018-313789.
9. Aljebab F, Choonara I, Conroy S. Systematic review of the toxicity of short-course oral corticosteroids in children archives of disease in childhood. Archives of Disease in Childhood. 2016;101:337–65.
10. ST Angeles-Han, Lo MS, Henderson LA, et al. Childhood arthritis and rheumatology research alliance consensus treatment plans for juvenile idiopathic arthritis-associated and idiopathic chronic anterior uveitis. Arthritis Care Res. 2019;71:482–91.
11. ST Angeles-Han, Ringold S, Beukelman T, et al. American College of Rheumatology/Arthritis Foundation Guideline for the screening, monitoring, and treatment of juvenile

idiopathic arthritis-associated uveitis. Arthritis Rheumatol. 2019;71:864–77.
12. ST Angeles-Han, Ringold S, Beukelman T, et al. American College of Rheumatology/Arthritis Foundation Guideline for the screening, monitoring, and treatment of juvenile idiopathic arthritis–associated uveitis. Arthritis Care Res. 2019;71:703–16. https://doi.org/10.1002/acr.23871.
13. ST Angeles-Han, Yeh S, McCracken C, et al. Using the effects of youngsters' eyesight on quality of life questionnaire to measure visual outcomes in children with uveitis. Arthritis Care Res (Hoboken). 2015;67:1513–20. https://doi.org/10.1002/acr.22627.
14. Aragon Cuevas O, Hedrich CM. Biosimilars in pediatric rheumatology and their introduction into routine care. Clin Immunol. 2020:216. https://doi.org/10.1016/J.CLIM.2020.108447.
15. Ardoin SP, Kredich D, Rabinovich E, Schanberg LE, Jaffe GJ. Infliximab to treat chronic non-infectious uveitis in children: retrospective case series with long-term follow-up. Am J Ophthalmol. 2007;144. https://doi.org/10.1016/j.ajo.2007.08.018.
16. Arslanoglu Aydin E, Baglan E, Bagrul I, Tuncez S, Ozdel S, Bulbul M. Safety of COVID-19 vaccines and disease flares after vaccines in children with rheumatic disease. Postgrad Med. 2022:1–6. Published online Published online. https://doi.org/10.1080/00325481.2022.2074700.
17. Ashkenazy N, Saboo US, Abraham A, Ronconi C, Cao JH. Successful treatment with infliximab after adalimumab failure in pediatric non-infectious uveitis. *J AAPOS.* 2019;151(e1-151.e5). doi:10.1016/j.jaapos.2019.02.006.
18. Ramanan AV, Dick AD, Jones AP, et al. Adalimumab in combination with methotrexate for refractory uveitis associated with juvenile idiopathic arthritis: a RCT. Health Technol Assess. 2019;23:1–140. https://doi.org/10.3310/hta23150.
19. Ramanan AV, Dick AD, Jones AP, et al. Adalimumab plus methotrexate for uveitis in juvenile idiopathic arthritis. N Engl J Med. 2017;376:1637–46. https://doi.org/10.1056/NEJMoa1614160.
20. Ramanan AV, Dick AD, Guly C, et al. Tocilizumab in patients with anti-TNF refractory juvenile idiopathic arthritis-associated uveitis (APTITUDE): a multicentre, single-arm, phase 2 trial, *Lancet Rheumatol*. 2. 2020:e135–41. https://doi.org/10.1016/S2665-9913(20)30008-4.
21. Babu K, Sudheer B, Rao AP Intravenous tocilizumab in idiopathic pediatric uveitis with refractory cystoid macular edema - a case report. *Indian J Ophthalmol* 2019;67:975-977.
22. Becker I, Horneff G. Risk of serious infection in juvenile idiopathic arthritis patients associated with tumor necrosis factor inhibitors and disease activity in the German biologics in Pediatric Rheumatology Registry.2017
23. Beukelman T, Ringold S, Davis TE, et al. CARRA Registry investigators. Disease-modifying antirheumatic drug use in the treatment of juvenile idiopathic arthritis: a cross-sectional analysis of the CARRA Registry. J Rheumatol. 2012;39.
24. Beukelman T, Xie F, Chen L, et al. Rates of hospitalized bacterial infection associated with juvenile idiopathic arthritis and its treatment. Arthritis Rheum. 2012;64.
25. Biester S, Deuter C, Michels H. Adalimumab in the therapy of uveitis in childhood. Br J Ophthalmol. 2007;91:319–24.
26. Birolo C, Zannin ME, Arsenyeva S, et al. Comparable efficacy of abatacept used as first-line or second-line biological agent for severe juvenile idiopathic arthritis-related uveitis. J Rheumatol. 2016;43:2068–73. https://doi.org/10.3899/JRHEUM.151389.
27. Bou R, Adán A, Borrás F, et al. Clinical management algorithm of uveitis associated with juvenile idiopathic arthritis: interdisciplinary panel consensus. Rheumatol Int. 2015;35:777–85.
28. British Society for rheumatology paediatric and adolescent guidance notes, 2022, Br Soc Rheumatgoloy, https://www.rheumatology.org.uk/practice-quality/guidelines/paediatric-adolescent-guidance Published online.
29. Cai Y, Liu X, Zhang W, Xu J, Cao L. Clinical trial of etanercept tapering in juvenile idiopathic arthritis during remission. Rheumatol Int. 2013;33:2277–82. https://doi.org/10.1007/S00296-012-2642-7.
30. Calvo-Río V. Anti–interleukin-6 receptor tocilizumab for severe juvenile idiopathic arthritis–associated uveitis refractory to anti–tumor necrosis factor therapy: a multicenter study of twenty-five patients. Arthritis Rheumatol. 2017;69:668–75.
31. Cann M, Ramanan AV, Crawford A, et al. Outcomes of non-infectious paediatric uveitis in the era of biologic therapy. Pediatr Rheumatol. 2018;16:1–9. https://doi.org/10.1186/s12969-018-0266-5.
32. Cantarini L, Simonini G, Frediani B, Pagnini I, Galeazzi M, Cimaz R. Treatment strategies for childhood noninfectious chronic uveitis: an update. Expert Opin Investig Drugs. 2012;21:1–6. https://doi.org/10.1517/13543784.2012.636350.
33. Chang PY, Giuliari GP, Shaikh M, Thakuria P, Makhoul D, Foster CS. Mycophenolate mofetil monotherapy in the management of paediatric uveitis. Eye. 2011;25.
34. Chen J, Cai W, Liu T, et al. The COVID-19 vaccine: attitudes and vaccination in patients with autoimmune inflammatory rheumatic diseases. Rheumatol Autoimmun. 2022;15. https://doi.org/10.1002/RAI2.12028 Published online.
35. Chen W, Zhao B, Jiang R, et al. Cytokine expression profile in aqueous humor and sera of patients with acute anterior uveitis. Curr Mol Med. 2015;15:543–9.
36. Chung JH, Van Stavern GP, Frohman LP. Adalimumab-associated optic neuritis. J Neurol Sci. 2006;244:133–6.
37. Correll CK, Bullock DR, Cafferty RM, Vehe RK. Safety of weekly adalimumab in the treatment of juvenile idiopathic arthritis and pediatric chronic uveitis. Clin Rheumatol. 2018;37:549–53. https://doi.org/10.1007/s10067-017-3890-4.
38. In: Clinical Commissioning Policy Statement: Biologic Therapies for the treatment of Juvenile Idiopathic Arthritis (JIA). Reference: NHS England E03X04. author: Specialised Commissioning Team, NHS England. 2015 2015.
39. Constantin T, Foeldvari I, Anton J, et al. Consensus-based recommendations for the management of uveitis associated with juvenile idiopathic arthritis: the SHARE initiative. Ann Rheum Dis. 2018;77:1107–17.
40. Correll CK, Bullock DR, Cafferty RM, Vehe RK. Safety of weekly adalimumab in the treatment of juvenile idiopathic arthritis and pediatric chronic uveitis. Clin Rheumatol. 2018:37.
41. Davies R, D DC, Kearsley-Fleet L, et al. The risk of uveitis in patients with JIA receiving etanercept: the challenges of analysing real-world data. *Rheumatol* 59(PG-1391-1397):1391-1397. doi:10.1093/rheumatology/kez449.
42. Davies R, Southwood TR, Kearsley-Fleet L, Lunt M, Hyrich KL. Medically significant infections are increased in patients with juvenile idiopathic arthritis treated with etanercept: results from the british society for paediatric and adolescent rheumatology etanercept Cohort Study. Arthritis Rheumatol (Hoboken, NJ). 2015;67:2487–94. https://doi.org/10.1002/ART.39197.
43. Deaner JD, Srivastava SK, Hajj-Ali RA, et al. Recurrence rates of inflammation after switching from the originator infliximab to biosimilar infliximab-abda for noninfectious uveitis. Am J Ophthalmol. 2021;225:172–7. https://doi.org/10.1016/J.AJO.2020.08.005.

44. Ovchinsky A, Schulman S, Rosenfeld RM. Adenotonsillectomy as a treatment option for poststreptococcal uveitis. Laryngoscope. 112. 2002 2002. p. 658–60. https://doi.org/10.1097/00005537-200204000-00012.
45. Dick AD, Rosenbaum JT, HA Al-Dhibi, et al. Guidance on noncorticosteroid systemic immunomodulatory therapy in noninfectious uveitis: fundamentals of care for uveitis (FOCUS) initiative. Ophthalmology. 2018;125:757–73. https://doi.org/10.1016/j.ophtha.2017.11.017.
46. Dick AD, Tugal-Tutkun I, Foster S, et al. Secukinumab in the treatment of noninfectious uveitis: results of three randomized, controlled clinical trials. Ophthalmology. 2013;120:777–87. https://doi.org/10.1016/j.ophtha.2012.09.040.
47. Parker DM, Angeles-Han ST, Stanton AL, Holland GN. Chronic anterior uveitis in children: psychosocial challenges for patients and their families. Am J Ophthalmol. 2018;191:xvi–xxiv. https://doi.org/10.1016/j.ajo.2018.03.028.
48. Doran MF, Crowson CS, Pond GR. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. *Arthritis Rheum* 46:2287–93.
49. Doycheva D, Deuter C, Stuebiger N, Biester S, Zierhut M. Mycophenolate mofetil in the treatment of uveitis in children. *Br J Ophthalmol* 91:180–184.
50. Doycheva D, Zierhut M, Blumenstock G, et al. Mycophenolate sodium for the treatment of chronic non-infectious uveitis of childhood. Br J Ophthalmol. 2016;100:1071–5. https://doi.org/10.1136/bjophthalmol-2015-306701.
51. Sözeri B, Kardeş E, Salı E, Çakır D, Demir F. Drug survival of the infliximab biosimilar (CT-P13) in paediatric patients with non-infectious uveitis. Clin Exp Rheumatol. 2021;39:907–12. https://doi.org/10.55563/clinexprheumatol/r4gnxm.
52. Duarte R, Campainha S, Cotter J, et al. Position paper on tuberculosis screening in patients with immune mediated inflammatory diseases candidates for biological therapy. Acta Reumatol Port. 2012;37:253–9.
53. Echchilali K, Kenza K, Leila L, et al. Budd-Chiari syndrome revealing a very vascular juvenile Behcet's disease. Clin Exp Rheumatol. 2018;36:S164.
54. El-Asrar AM, Struyf S, Kangave D, et al. Cytokine profiles in aqueous humor of patients with different clinical entities of endogenous uveitis. Clin Immunol. 2011;139:177–84.
55. Elhai M, Deslandre CJ, Kahan A. Abatacept for refractory juvenile idiopathic arthritis-associated uveitis: two new cases. Comment on the article by Zulian et al. Arthritis Care Res. 2011:63.
56. Engelhard SB, Bajwa A, Reddy AK. Causes of uveitis in children without juvenile idiopathic arthritis. Clin Ophthalmol. 2015;9:1121–8. https://doi.org/10.2147/OPTH.S83950.
57. ES S, AD D, AV R. Uveitis associated with juvenile idiopathic arthritis. *Nat Rev Rheumatol.* 2015; 11(PG-338-48):338-348. doi:10.1038/nrrheum.2015.20.
58. Fabiani C, Vitale A, Emmi G, et al. The role of biosimilars in uveitis: long-term real-world outcomes of the switch from original to biosimilar TNF-alpha inhibitors. Front Pharmacol. 2019;10:1468https://doi.org/10.3389/FPHAR.2019.01468.
59. Ferrara G, Mastrangelo G, Barone P, et al. Methotrexate in juvenile idiopathic arthritis: advice and recommendations from the MARAJIA expert consensus meeting. Pediatr Rheumatol Online J. 2018;16:46.
60. Foeldvari I, Klotsche J, Simonini G, et al. Proposal for a definition for response to treatment, inactive disease and damage for JIA associated uveitis based on the validation of a uveitis related JIA outcome measures from the Multinational Interdisciplinary Working Group for uveitis in childhood. Pediatr Rheumatol Online J. 2019;17:66.
61. Foeldvari I, Maccora I, Petrushkin H, et al. New and updated recommendations for the treatment of juvenile idiopathic arthritis associated uveitis and idiopathic chronic anterior uveitis. Arthritis Care Res (Hoboken). 2022. https://doi.org/10.1002/ACR.24963 Published online.
62. Foeldvari I, Nielsen S, Kümmerle-Deschner J, et al. Tumor necrosis factor-α blocker in treatment of juvenile idiopathic arthritis-associated uveitis refractory to second-line agents: results of a multinational survey. J Rheumatol. 2007;34:1146–50.
63. Foeldvari I, Wierk A. Methotrexate is an effective treatment for chronic uveitis associated with juvenile idiopathic arthritis. J Rheumatol. 2005;32:362–5.
64. Friling R, Kramer M, Snir M, Axer-Siegel R, Weinberger D, Mukamel M. Clinical course and outcome of uveitis in children. J AAPOS. 2005;9:3. https://doi.org/10.1016/j.jaapos.2005.04.005.
65. Hodgins GE, Saltz SB, Gibbs EP, Gonzalez R, Regan J, Nemeroff C. Steroid-induced psychosis in the pediatric population: a new case and review of the literature. J Child Adolesc Psychopharmacol. 2018;28:354–9. https://doi.org/10.1089/cap.2018.0017.
66. Garcês S, Demengeot J, Benito-Garcia E. The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: a systematic review of the literature with a meta-analysis. Ann Rheum Dis. 2013;72. https://doi.org/10.1136/annrheumdis-2012-202220.
67. GhoreschI K. Modulation of innate and adaptive immune responses by tofacitinib (CP-690,550. J Immunol. 2011;186:4234–43.
68. Gianfrancesco M, Hyrich KL, Al-Adely S, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis. 2020;79:859–66. https://doi.org/10.1136/ANNRHEUMDIS-2020-217871.
69. Holland GN, Stiehm ER. Special considerations in the evaluation and management of uveitis in children. *Am J Ophthalmol.* 2003; 135(PG-867-78): 867-878. doi:10.1016/s0002-9394(03)00314-3.
70. Godfrey MS, Friedman LN. Tuberculosis and biologic therapies: anti-tumor necrosis factor-α and beyond. Clin Chest Med. 2019;40:721–39. https://doi.org/10.1016/J.CCM.2019.07.003.
71. Goebel JC, Roesel M, Heinz C, Michels H, Ganser G, Heiligenhaus A. Azathioprine as a treatment option for uveitis in patients with juvenile idiopathic arthritis. Br J Ophthalmol. 2011;95.
72. Goodman SM, Menon I, Christos PJ, Smethurst R, Bykerk VP. Management of perioperative tumour necrosis factor α inhibitors in rheumatoid arthritis patients undergoing arthroplasty: a systematic review and meta-analysis. Rheumatology (Oxford). 2016;55:573–82. https://doi.org/10.1093/RHEUMATOLOGY/KEV364.
73. Gordon DM, McLean JM. Effects of pituitary adrenocorticotrophic hormone (ACTH) therapy in ophthalmologic conditions. *JAMA* 142:1271–1276.
74. Gorovits B, Baltrukonis DJ, Bhattacharya I, et al. Immunoassay methods used in clinical studies for the detection of anti-drug antibodies to adalimumab and infliximab. Clin Exp Immunol. 2018;192:348–65. https://doi.org/10.1111/CEI.13112.
75. GOV.UK. COVID-19: guidance for people whose immune system means they are at higher risk. GOV.UK; 2022 Published https://www.gov.uk/government/publications/covid-19-guidance-for-people-whose-immune-system-means-they-are-at-higher-risk/covid-19-guidance-for-people-whose-immune-system-means-they-are-at-higher-risk.
76. Gunduz GU, Yalcinbayir O, Cekic S, Yildiz M, Kilic SS. Anti-tumor necrosis factor treatment in the management of

pediatric noninfectious uveitis: infliximab versus adalimumab. J Ocul Pharmacol Ther. 2021;37:236–40. https://doi.org/10.1089/JOP.2020.0081.
77. Gunzinger J, Moore P, Athimalaipet R, Dick A. Adalimumab in the treatment of pediatric patients with chronic noninfectious anterior uveitis. Expert Rev Ophthalmol. 2021;16:231–41. https://doi.org/10.1080/17469899.2021.1935240.
78. H. R, Stadecker MJ. Costimulatory B7 molecules in the pathogenesis of infectious and autoimmune diseases. *N Engl J Med* 335:1369–1377.
79. Haslak F, Gunalp A, Cebi MN, et al. Early experience of COVID-19 vaccine-related adverse events among adolescents and young adults with rheumatic diseases: a single-center study. Int J Rheum Dis. 2022;25:353–63. https://doi.org/10.1111/1756-185X.14279.
80. Hawkins MJ, Dick AD, Lee RJ, et al. Managing juvenile idiopathic arthritis-associated uveitis. Surv Ophthalmol. 2016;61:197–210.
81. Heijstek MW, Bruin LM, Bijl M, et al. EULAR recommendations for vaccination in paediatric patients with rheumatic diseases. *Ann Rheum Dis*;70.
82. Heiligenhaus A, Minden K, Tappeiner C, et al. Update of the evidence based, interdisciplinary guideline for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis. Semin Arthritis Rheum. 2019;49:43–55. https://doi.org/10.1016/j.semarthrit.2018.11.004.
83. Heiligenhaus A, Mingels A, Heinz C, Ganser G. Methotrexate for uveitis associated with juvenile idiopathic arthritis: value and requirement for additional anti-inflammatory medication. *Eur J Ophthalmol* 17:743–8.
84. Heiligenhaus A, Miserocchi E, Heinz C, Gerloni V, Kotaniemi K. Treatment of severe uveitis associated with juvenile idiopathic arthritis with anti-CD20 monoclonal antibody (rituximab. *Rheumatol (Oxford).* 2011;50: doi:10.1093/rheumatology/ker107.
85. Hemady RK, Baer JC, Foster CS. Immunosuppressive drugs in the management of progressive, corticosteroid-resistant uveitis associated with juvenile rheumatoid arthritis. Int Ophthalmol Clin. Winter. 1992:32.
86. Highlights of prescribing information SIMPONI. Accessed 2022, https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/SIMPONI-pi.pdf.
87. Holroyd CR, Seth R, Bukhari M, et al. The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis-Executive summary. *Rheumatol (Oxford)* 1;58:22.
88. Hornbeak DM, Thorne JE. Immunosuppressive therapy for eye diseases: effectiveness, safety, side effects and their prevention. Taiwan J Ophthalmol. 2015;5(4):156–63. https://doi.org/10.1016/J.TJO.2015.03.004.
89. Horneff G, Seyger MMB, Arikan D, et al. Safety of adalimumab in pediatric patients with polyarticular juvenile idiopathic arthritis, enthesitis-related arthritis, psoriasis, and Crohn's disease. J Pediatr. 2018;201:166–75.
90. Horton S, Jones AP, Guly CM, et al. Adalimumab in juvenile idiopathic arthritis-associated uveitis: 5-year follow-up of the Bristol participants of the SYCAMORE trial. Am J Ophthalmol. 2019;207:170–4.
91. Humphreys JH, Warner A, Costello R, Lunt M, Verstappen SMM, Dixon WG. Quantifying the hepatotoxic risk of alcohol consumption in patients with rheumatoid arthritis taking methotrexate. Ann Rheum Dis. 2017;76:1509–14. https://doi.org/10.1136/ANNRHEUMDIS-2016-210629.
92. Ilowite NT, Sandborg CI, Feldman BM, et al. Algorithm development for corticosteroid management in systemic juvenile idiopathic arthritis trial using consensus methodology. Pediatr Rheumatol Online J. 2012;10:31https://doi.org/10.1186/1546-0096-10-31.
93. Imagawa T, Takei S, Umebayashi H, et al. Efficacy, pharmacokinetics, and safety of adalimumab in pediatric patients with juvenile idiopathic arthritis in Japan. Clin Rheumatol. 2012;31:1713–21. https://doi.org/10.1007/S10067-012-2082-5.
94. Jabs DA. Immunosuppression for the uveitides. Ophthalmology. 2018;125:193. https://doi.org/10.1016/J.OPHTHA.2017.08.007.
95. Jain R, Ferrante P, Reddy GT, Lightman S. Clinical features and visual outcome of intermediate uveitis in children. Clin Exp Ophthalmol. 2005;33. https://doi.org/10.1111/j.1442-9071.2005.00938.x.
96. Jani M, Barton A, Warren RB, Griffiths CEM, Chinoy H. The role of DMARDs in reducing the immunogenicity of TNF inhibitors in chronic inflammatory diseases. Rheumatology (Oxford). 2014;53:213. https://doi.org/10.1093/RHEUMATOLOGY/KET260.
97. Johnston JA. Phosphorylation and activation of the Jak-3 Janus kinase in response to interleukin-2. Nature. 1994;370:151–3.
98. Kahn P, Weiss M, Imundo LF, Levy DM. Favorable response to high-dose infliximab for refractory childhood uveitis. *Ophthalmology.* 2006; 4(e2). doi:10.1016/j.ophtha.2006.01.005.
99. Kamal KM, Madhavan SS, Hornsby JAA. Use of tumor necrosis factor inhibitors in rheumatoid arthritis: a national survey of practicing United States rheumatologists. Jt Bone Spine. 2006;73.
100. Kenawy N, Cleary G, Mewar D, Beare N, Chandna A, Pearce I. Abatacept: a potential therapy in refractory cases of juvenile idiopathic arthritis-associated uveitis. Graefes Arch Clin Exp Ophthalmol. 2011;249:297–300. https://doi.org/10.1007/S00417-010-1523-6.
101. Khalifa YM, Acharya NR, Bailony MR. Treatment of pediatric Vogt-Koyanagi-Harada syndrome with infliximab. Ocul Immunol Inflamm. 2010;18:218–22. PG-218-222 PG-218-222. https://doi.org/10.3109/09273941003739910.
102. Kocharla L, Taylor J, Weiler T, Ting T V, Luggen M, Brunner HI. Monitoring methotrexate toxicity in juvenile idiopathic arthritis. J Rheumatol. 2009;36. https://doi.org/10.3899/jrheum.090482.
103. Koker O, Demirkan FG, Kayaalp G, et al. Does immunosuppressive treatment entail an additional risk for children with rheumatic diseases? A survey-based study in the era of COVID-19. Rheumatol Int. 2020;40:1613–23. https://doi.org/10.1007/S00296-020-04663-9.
104. Kruh JN, Yang P, Suelves AM, Foster CS. Infliximab for the treatment of refractory noninfectious uveitis: a study of 88 patients with long-term follow-up. Ophthalmology. 2014;121:358–64. https://doi.org/10.1016/j.ophtha.2013.07.019.
105. Kumar N, Follestad T, Sen HN, Austeng D. A Systematic switch from originator infliximab to biosimilar infliximab in patients with non-infectious uveitis. Am J Ophthalmol. 2021;225:178–84. https://doi.org/10.1016/J.AJO.2020.10.013.
106. Lahdenne P, Rapola J. Ykujiki HJm Haapasaari J. Hepatotoxicity and patient with juvenile idiopathic arthritis receiving longterm methotrexate therapy. J Rheumatol. 2002;29:2442–5.
107. Lanz S, Seidel G, Skrabl-Baumgartner A. Golimumab in juvenile idiopathic arthritis-associated uveitis unresponsive to adalimumab. Pediatr Rheumatol. 2021;19. https://doi.org/10.1186/s12969-021-00630-1.
108. Lanz S, Skrabl-Baumgartner A, Andrea S. ORCID: http://orcid.org/0000-0001-7797-3124 GAOSB. Golimumab in juvenile idiopathic arthritis-associated uveitis unresponsive to

adalimumab. Pediatr Rheumatol. 2021;19:132. doi:10.1186/s12969-021-00630-1 .
109. Laserna-Mendieta EJ, Salvador-Martín S, Marín-Jiménez I, et al. Comparison of a new rapid method for determination of serum anti-adalimumab and anti-infliximab antibodies with two established ELISA kits. J Pharm Biomed Anal. 2021;198:114003https://doi.org/10.1016/J.JPBA.2021.114003.
110. Leal I, Miranda V, Fonseca C, et al. The 2021 Portuguese Society of Ophthalmology joint guidelines with paediatric rheumatology on the screening, monitoring and medical treatment of juvenile idiopathic arthritis-associated uveitis. Acta Reum Port. 2022;1:49–62.
111. Leal I, Miranda V, Fonseca C, et al. The 2021 Portuguese Society of Ophthalmology joint guidelines with paediatric rheumatology on the screening, monitoring and medical treatment of juvenile idiopathic arthritis-associated uveitis. ARP Rheumatol. 2022;1:49–62. Accessed May 30.
112. Leclercq M, Desbois AC, Domont F, et al. Biotherapies in Uveitis. J Clin Med. 2020;9:3599. https://doi.org/10.3390/jcm9113599.
113. Lee WJ, Lee TA. Risk of serious bacterial infection associated with tumour necrosis factor-alpha inhibitors in children with juvenile idiopathic arthritis. Rheumatology. 2018;57:273–82.
114. Liberman P, Berkenstock MK, Burkholder BM, Chaon BC, Thorne JE. Escalation to weekly adalimumab for the treatment of ocular inflammation. Ocul Immunol Inflamm. 2020;29(7–8):1564–8. https://doi.org/10.1080/09273948.2020.1749857.
115. Licciardi F, Giani T, Baldini L, Favalli EG, Caporali R, Cimaz R. COVID-19 and what pediatric rheumatologists should know: a review from a highly affected country. Pediatr Rheumatol Online J. 2020;18:35https://doi.org/10.1186/S12969-020-00422-Z.
116. Little JA, Sen ES, Strike H, et al. The safety and efficacy of noncorticosteroid triple immunosuppressive therapy in treating refractory chronic non-infectious uveitis in childhood. J Rheumatol. 2014;41. https://doi.org/10.3899/jrheum.130594.
117. Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy Asthma Clin Immunol. 2013;9:30https://doi.org/10.1186/1710-1492-9-30.
118. Lopez-Gonzalez R, Loza E, Jover JA, et al. Treatment of refractory posterior uveitis with infliximab: a 7-year follow-up study. 2009;38:58-62. doi:10.1080/03009740802366076.
119. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ. Etanercept in children with polyarticular juvenile rheumatoid arthritis. *New Engl J Med* 342:763–9.
120. Macchi P. Mutations of Jak-3 gene in patients with autosomal severe combined immune deficiency (SCID. Nature. 1995;377:65–8.
121. Maccora I, Fusco E, Marrani E, Ramanan A V, Simonini G. Changing evidence over time: updated meta-analysis regarding anti-TNF efficacy in childhood chronic uveitis. Rheumatol (Oxford). 2021. https://doi.org/10.1093/rheumatology/keaa595.
122. Maccora I, Lombardi N, Crescioli G, et al. OBSIDIAn - real world evidence of originator to BioSImilar drug switch in juvenile idiopathic arthritis. Rheumatology (Oxford). 2021;61:1518–28. https://doi.org/10.1093/RHEUMATOLOGY/KEAB572.
123. Maccora I, Sen ES, Ramanan AV. Update on noninfectious uveitis in children and its treatment. Curr Opin Rheumatol. 2020;32:395–402. https://doi.org/10.1097/BOR.0000000000000723.
124. Maleki A. Tocilizumab employment in the treatment of resistant juvenile idiopathic arthritis associated uveitis. Ocul Immunol Inflamm. 2021;29:14–20.
125. Maleki A, Anesi SD, Look-Why S, Manhapra A, Foster CS. Pediatric uveitis: A comprehensive review. Surv Ophthalmol. 2022;67(2):510–29. https://doi.org/10.1016/j.survophthal.2021.06.006.
126. Malik AR, Pavesio C. The use of low dose methotrexate in children with chronic anterior and intermediate uveitis. Br J Ophthalmol. 2005;89:806–8. PG-806-808 PG-806-808. https://doi.org/10.1136/bjo.2004.054239.
127. Marelli L, Romano M, Pontikaki I, et al. Long term experience in patients with JIA-associated uveitis in a large referral center. Front Pediatr. 2021;9:682327https://doi.org/10.3389/FPED.2021.682327.
128. Marrani E, Paganelli V, Cimaz R, Simonini G, de Libero C. Long-term efficacy of abatacept in pediatric patients with idiopathic uveitis: a case series. Graefe's Arch Clin Exp Ophthalmol. 2015;253:1813–6. PG-1813-1816 PG-1813-1816. https://doi.org/10.1007/s00417-015-3140-x.
129. Marrani E, Paganelli V, de Libero C, Cimaz R, Simonini G. Long-term efficacy of abatacept in pediatric patients with idiopathic uveitis: a case series. Graefes Arch Clin Exp Ophthalmol. 2015;253:1813–6. https://doi.org/10.1007/S00417-015-3140-X.
130. Mastrangelo G, Foeldvari I, Anton J, Simonini G. Defining outcome measures in juvenile idiopathic arthritis associated uveitis by a systematic review analysis: do we need a consensus? Pediatr Rheumatol Online J. 2019;17:40.
131. McHarg M, Bellur S, Kongwattananon W, Vitale S, Sen HN, Kodati S. Anti-drug antibodies to monoclonal TNF inhibitors in non-infectious uveitis. Invest Ophthalmol Vis Sci. 2022;63:3194.
132. McKay KM, Apostolopoulos N, Chou B, Leveque TK, Van Gelder RN. Anti-adalimumab antibodies in patients with non-infectious ocular inflammatory disease: a case series. Ocul Immunol Inflamm. 2021;30:1721–5. Published online Published online. https://doi.org/10.1080/09273948.2021.1936565.
133. McLean LP, Cross RK. Adverse events in IBD: to stop or continue immune suppressant and biologic treatment. *Expert Rev Gastroenterol Hepatol*
134. Mesquida M, Leszczynska A, Llorenç V, Adán A. Interleukin-6 blockade in ocular inflammatory diseases. Clin Exp Immunol. 2014;176(3):301–9. https://doi.org/10.1111/cei.12295.
135. Methotrexate use in paediatric and adolescent rheumatology, Information for health proffesionals. *Br Soc Rheumatgoloy Paediatr Adolesc Guid. British Society for Rheumatology* https://www.rheumatology.org.uk/practice-quality/guidelines/paediatric-adolescent-guidance.
136. Methrotrexate guidelines for the use in children, NICE guidelines. https://bnfc.nice.org.uk/drug/methotrexate.html
137. Miserocchi E, Modorati G. Rituximab for noninfectious uveitis. Dev Ophthalmol. 2012;51:98–109. https://doi.org/10.1159/000336188.
138. Miserocchi E, Modorati G, Berchicci L, Pontikaki I, Meroni P, Gerloni V. Long-term treatment with rituximab in severe juvenile idiopathic arthritis-associated uveitis. Br J Ophthalmol. 2016;100:782 LP - 786. https://doi.org/10.1136/bjophthalmol-2015-306790.
139. Miserocchi E, Pontikaki I, Modorati G, Gattinara M, PL M, Gerloni V. Anti-CD 20 monoclonal antibody (rituximab) treatment for inflammatory ocular diseases. *Autoimmun Rev* 11(PG-35-9):35-39. doi:10.1016/j.autrev.2011.07.001.
140. ML K. Population-based study of outcomes of patients with juvenile idiopathic arthritis (JIA) compared to non-JIA

subjects. Semin arthritis Rheum. 2017;46. https://doi.org/10.1016/j.semarthrit.2016.07.003.
141. Mycophenolate mofetil therapy in the management of inflammatory bowel disease – a retrospective case series and review. J Crohn's Colitis, 8, 2014, 890–897.
142. Muñoz-Gallego A, Barral E, Enríquez E, Tejada P, Barceló A, J de I. Adalimumab for the treatment of refractory noninfectious paediatric uveitis. *Int Ophthalmol.* 2017; 37(PG-719-725):719-725. doi:10.1007/s10792-016-0293-5.
143. Murdaca G, Spanò F, Contatore M, et al. Immunogenicity of infliximab and adalimumab: what is its role in hypersensitivity and modulation of therapeutic efficacy and safety? Expert Opin Drug Saf. 2016;15:43–52. https://doi.org/10.1517/14740338.2016.1112375.
144. Mysler E, Azevedo VF, Danese S, et al. Biosimilar-to-biosimilar switching: what is the rationale and current experience? Drugs. 2021;81:1859–79. https://doi.org/10.1007/S40265-021-01610-1/FIGURES/10.
145. NICE 2017. Adalimumab and dexamethasone for treating non-infectious uveitis, National Institute for Health and Care Excellence. 2021 2021 Published 2017. Accessed February 5 https://www.nice.org.uk/guidance/ta460/chapter/1-Recommendations.
146. Niehues T, Lankisch P. Recommendations for the use of methotrexate in juvenile idiopathic arthritis. Paediatr Drugs. 2003;8:347–56. https://doi.org/10.2165/00148581-200608060-00003.
147. Paediatric Formulary Committee. BNF for Children (online) London: BMJ Group, Pharmaceutical Press, and RCPCH Publications. Accessed 5, June 2022. http://www.medicinescomplete.com.
148. O'Shea JJ. JAKs and STATs in immunity, immunodeficiency, and cancer. N Engl J Med. 2013;368:161–70.
149. O'Shea JJ, Kontzias A, Yamaoka K, Tanaka Y, Laurence A. Janus kinase inhibitors in autoimmune diseases. *Ann Rheum Dis* 72:111-115.
150. Onel KB, Horton DB, Lovell DJ, et al. American College of Rheumatology guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for oligoarthritis, temporomandibular joint arthritis, and systemic juvenile idiopathic arthritis. Arthritis Rheumatol. 2022;74:553–69. https://doi.org/10.1002/art.42037.
151. Ortiz-Alvarez O, Morishita K, Avery G, Green J, Petty RE, Tucker LB. Guidelines for blood test monitoring of methotrexate toxicity in juvenile idiopathic arthritis. J Rheumatol. 2004;31:2501–6.
152. Oxford Centre for Evidence-Based Medicine: Levels of evidence (March 2009) — centre for evidence-based medicine (CEBM) U of O, Https://www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009. No Title.
153. Pasadhika S, Kempen JH, Newcomb CW, et al. Azathioprine for ocular inflammatory diseases. Am J Ophthalmol. 2009. https://doi.org/10.1016/j.ajo.2009.05.008 Published online.
154. Perez VL, Papaliodis GN, Chu D, Anzaar F, Christen W, Foster CS. Elevated levels of interleukin 6 in the vitreous fluid of patients with pars planitis and posterior uveitis: the Massachusetts eye & ear experience and review of previous studies. Ocul Immunol Inflamm. 2004;12:193–201.
155. Pilunni D, Santuccio C, Sottosanti L, Felicetti P, Navarra P. Relationship between injection site reactions and different adalimumab formulations. Analysis of the adverse events reported in Italy in the period 2016-2019. Eur Rev Med Pharmacol Sci. 2021;25:3300–5. https://doi.org/10.26355/EURREV_202104_25468.
156. Positioning statements on physician-led switching for biosimilar medicines. https://www.medicinesforeurope.com/docs/M-Biosimilars-Overview-of-positions-on-physician-led-switching.pdf%0D.
157. Quartier P, Baptiste A, Despert V, et al. ADJUVITE: A double-blind, randomised, placebo-controlled trial of adalimumab in early onset, chronic, juvenile idiopathic arthritis-associated anterior uveitis. Ann Rheum Dis. 2018;77:1003–11. https://doi.org/10.1136/annrheumdis-2017-212089.
158. Quesada-Masachs E, Caballero CM. Subcutaneous tocilizumab may be less effective than intravenous tocilizumab in the treatment of juvenile idiopathic arthritis–associated uveitis. *J Rheumatol* 44:260-261. doi:10.3899/jrheum.160908.
159. Rajaraman RT, Kimura Y, Li S, Haines K, Chu DS. Retrospective case review of pediatric patients with uveitis treated with infliximab. *Ophthalmology*;113. doi:10.1016/j.ophtha.2005.09.037.
160. Ramanan AV, Dick AD, Guly C, et al. Tocilizumab in patients with anti-TNF refractory juvenile idiopathic arthritis-associated uveitis (APTITUDE): a multicentre, single-arm, phase 2 trial. Lancet Rheumatol. 2020;2:e135–41. https://doi.org/10.1016/S2665-9913(20)30008-4.
161. Ramanan AV, Dick AD, Jones AP, et al. A phase II trial protocol of Tocilizumab in anti-TNF refractory patients with JIA-associated uveitis (the APTITUDE trial). BMC Rheumatol. 2018;2:4https://doi.org/10.1186/S41927-018-0010-2.
162. Ramanan AV, Dick AD, Jones AP, et al. Adalimumab plus methotrexate for uveitis in juvenile idiopathic arthritis. N Engl J Med. 2017;376:1637–46. https://doi.org/10.1056/nejmoa1614160.
163. Ramanan AV, Guly CM, Keller SY, et al. Clinical effectiveness and safety of baricitinib for the treatment of juvenile idiopathic arthritis-associated uveitis or chronic anterior antinuclear antibody-positive uveitis: study protocol for an open-label, adalimumab active-controlled phase 3 clinical trial (JUVE-BRIGHT). Trials. 2021;22. https://doi.org/10.1186/S13063-021-05651-5.
164. Ramanan AV, Dick AD, Benton D, et al. A randomised controlled trial of the clinical effectiveness, safety and cost-effectiveness of adalimumab in combination with methotrexate for the treatment of juvenile idiopathic arthritis associated uveitis (SYCAMORE Trial). Trials. 2014;15:14. https://doi.org/10.1186/1745-6215-15-14.
165. Ramanan AV, Whitworth P, Baildam EM. Use of methotrexate in juvenile idiopathic arthritis. Arch Dis Child. 2003:12598376. https://doi.org/10.1136/adc.88.3.197.
166. Reimold AM. New indications for treatment of chronic inflammation by TNF-alpha blockade. *Am J Med.* 2003; *Sci* 325:75–92.
167. Renton WD, Leveret H, Guly C, Smee H, Leveret J, Ramanan AV. Same but different? A thematic analysis on adalimumab biosimilar switching among patients with juvenile idiopathic arthritis. Pediatr Rheumatol Online J. 2019;17:67https://doi.org/10.1186/S12969-019-0366-X.
168. Richards JC, Tay-Kearney ML, Murray K, Manners P. Infliximab for juvenile idiopathic arthritis-associated uveitis. Clin Exp Ophthalmol. 2005. https://doi.org/10.1111/j.1442-9071.2005.01062.x.
169. Roberts JE, Nigrovic PA, Lo MS, Chang MH. Weekly adalimumab, an effective alternative for refractory uveitis in children. J Clin Rheumatol. 2022. https://doi.org/10.1097/RHU.0000000000001707.
170. Rubinstein TB, Davis AM, Rodriguez M, et al. Addressing Mental Health in Pediatric Rheumatology. Curr Treat Options in Rheum. 2018;4:55–72. https://doi.org/10.1007/s40674-018-0092-4.
171. Rusche H, Marrani E, Real-Fernandez F, et al. A peptide-based anti-Adalimumab antibody assay to monitor immune response to biologics treatment in juvenile idiopathic

arthritis and childhood chronic non-infectious uveitis. Sci Reports. 2021;11:1–13. https://doi.org/10.1038/s41598-021-95920-9.
172. S. WR, J. D, C. B, C.L. D, G. VV, N. A. A search for variables predicting cortisol response to low-dose corticotropin stimulation following supraphysiological doses of glucocorticoids. *J Pediatr*. 2013; 163:484–488 1. doi:10.1016/j.jpeds.2013.01.011.
173. Santos MJ, Conde M, Mourão AF, et al. 2016 update of the Portuguese recommendations for the use of biological therapies in children and adolescents with Juvenile Idiopathic Arthritis. Acta Reumatol Por. 2018;2018:72–90.
174. Sardar E, Dusser P, Rousseau A, Bodaghi B, Labetoulle M, Koné-Paut I Retrospective study evaluating treatment decisions and outcomes of childhood uveitis not associated with juvenile idiopathic arthritis. *J Pediatr* 186:131–137. doi:10.1016/j.jpeds.2017.03.052.
175. Saurenmann RK, Levin A V, Rose JB, et al. Tumour necrosis factor alpha inhibitors in the treatment of childhood uveitis. Rheumatol (Oxford. 2006;45. https://doi.org/10.1093/rheumatology/kel030.
176. Schatz CS, Uzel JL, Leininger L, Danner S, Terzic J, Fischbach M. Immunosuppressants used in a steroid-sparing strategy for childhood uveitis. *J Pediatr Ophthalmol Strabismus* 44:28–34.
177. Schiff MH, Burmester GR, Kent JD. Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. *Ann Rheum Dis* 65:889–894.
178. Schmeling H, Horneff G. Etanercept and uveitis in patients with juvenile idiopathic arthritis. Rheumatology. 2005;44:1008–11. https://doi.org/10.1093/rheumatology/keh658.
179. Sen ES, Morgan MJ, MacLeod R, et al. Cross sectional, qualitative thematic analysis of patient perspectives of disease impact in juvenile idiopathic arthritis-associated uveitis. Pediatr Rheumatol. 2017;15:1–8. https://doi.org/10.1186/S12969-017-0189-6/TABLES/3.
180. Sen ES, Ramanan AV. Juvenile idiopathic arthritis-associated uveitis. Best Pract Res Clin Rheumatol. 2017;31:517–34. https://doi.org/10.1016/j.berh.2018.01.002.
181. Simonini G, Cantarini L. Current therapeutic approaches to autoimmune chronic uveitis in children. Autoimmun Rev. 2010:9.
182. Simonini G, Druce K, Cimaz R, Macfarlane GJ, Jones GT. Current evidence of anti-tumor necrosis factor ?? treatment efficacy in childhood chronic uveitis: a systematic review and meta-analysis approach of individual drugs. Arthritis Care Res. 2014;66:1073–84. https://doi.org/10.1002/acr.22214.
183. Simonini G, Paudyal P, Jones GT, Cimaz R, Macfarlane GJ. Current evidence of methotrexate efficacy in childhood chronic uveitis: a systematic review and meta-analysis approach. Rheumatol. 2013;52:825–31. https://doi.org/10.1093/rheumatology/kes186.
184. Simonini G, Zannin ME, Caputo R, et al. Loss of efficacy during long-term infliximab therapy for sight-threatening childhood uveitis. Rheumatol (Oxford). 2008:47. https://doi.org/10.1093/rheumatology/ken298.
185. Smith J a., Thompson DJS, Whitcup SM, et al. A randomized, placebo-controlled, double-masked clinical trial of etanercept for the treatment of uveitis associated with juvenile idiopathic arthritis. *Arthritis Care Res* 2005;53:18-23. doi:10.1002/art.20904.
186. Soheilian M, Ebrahimiadib N, Hedayatfar A, Hosseini M, Zarei M, Anjidani N. Efficacy of biosimilar adalimumab in the treatment of Behçet's uveitis. Ocul Immunol Inflamm. 2021;30:1495–500. https://doi.org/10.1080/09273948.2021.1900276.
187. Solebo AL, Rahi JS, Dick AD, et al. Areas of agreement in the management of childhood non-infectious chronic anterior uveitis in the UK. Br J Ophthalmol. 2020;104:11–6.
188. Sota J, Gentileschi S, Vitale A, et al. Effectiveness of SB5, an adalimumab biosimilar, in patients with noninfectious uveitis: a real-life monocentric experience. Asia-Pacific J Ophthalmol. 2021;10:360–5. https://doi.org/10.1097/APO.0000000000000380.
189. Sousa-Neves F, Braga J, Teixeira S, et al. Tocilizumab in refractory juvenile idiopathic arthritis with associated uveitis: a case report. Acta Reumatol Port. 2019;44:151–4. PG-151-154.
190. ST AH, MS L, LA H, et al. Childhood arthritis and rheumatology research alliance consensus treatment plans for juvenile idiopathic arthritis-associated and idiopathic chronic anterior uveitis. *Arthritis Care Res* 71(PG-482-491):482-491. doi:10.1002/acr.23610.
191. Stanbury RM, Graham EM. Systemic corticosteroid therapy: side effects and their management. Br J Ophthalmol. 1998;82:704–8. https://doi.org/10.1136/bjo.82.6.704.
192. Tanaka Y. The JAK inhibitors: do they bring a paradigm shift for the management of rheumatic diseases? Rheumatology. 2019;58:1–3.
193. Tappeiner C, Mesquida M, Adán A. evidence for tocilizumab as a treatment option in refractory uveitis associated with juvenile idiopathic arthritis. J Rheumatol. 2016;43:2183–8.
194. Tappeiner C, Roesel M, Heinz C, Michels H, Ganser G, Heiligenhaus A. Limited value of cyclosporine A for the treatment of patients with uveitis associated with juvenile idiopathic arthritis. Eye (Lond). 2009;23(5):1192–8. https://doi.org/10.1038/eye.2008.174.
195. Yildiz M, Haslak F, Adrovic A, Sahin S, Barut K, Kasapcopur O. The frequency and clinical course of COVID-19 infection in children with juvenile idiopathic arthritis. Clin Exp Rheumatol. 2020;38:1271–2.
196. Tsang AC, Roth J, Gottlieb C. Tocilizumab for severe chronic anterior uveitis associated with juvenile idiopathic arthritis in a pediatric patient. Ocul Immunol Inflamm. 2014;22:155–7. PG-155-157 PG-155-157. https://doi.org/10.3109/09273948.2013.866254.
197. Tugal-Tutkun I, Mudun A, Urgancioglu M, et al. Efficacy of infliximab in the treatment of uveitis that is resistant to treatment with the combination of azathioprine, cyclosporine, and corticosteroids in Behçet's disease: an open-label trial. Arthritis Rheum. 2005;52:2478–84. https://doi.org/10.1002/art.21231.
198. Ulu K, Çakan M, Çağlayan Ş, et al. Real-life data on efficacy and safety of original adalimumab and biosimilar adalimumab (ABP 501) in pediatric rheumatic diseases. Expert Opin Biol Ther. 2022:1–7. https://doi.org/10.1080/14712598.2022.2123703.
199. Utz VM, Bulas S, Lopper S, et al. Effectiveness of long-term infliximab use and impact of treatment adherence on disease control in refractory, non-infectious pediatric uveitis. Pediatr Rheumatol Online J. 2019;17:79https://doi.org/10.1186/S12969-019-0383-9.
200. V MU, S B, S L, et al. Effectiveness of long-term infliximab use and impact of treatment adherence on disease control in refractory, non-infectious pediatric uveitis. *Pediatr Rheumatol Online J.* 2019; 29;17:7 doi:10.1186/s12969-019-0383-9.
201. Viswanathan V, KJ M. Management of children with juvenile idiopathic arthritis. *Indian J Pediatr.* 2016; 83(PG-63-70):63-70. doi:10.1007/s12098-015-1966-1.
202. Wallace CA, Bleyer WA, Sherry DD, Salmonson KL, Wedgewood RJ. Toxicirty and serum levels of methotrexate in children with juvenile rheumatoid arthritis. Arthritis Rheum. 1989;32:677–81.

203. Wang SL, Hauenstein S, Ohrmund L, et al. Monitoring of adalimumab and antibodies-to-adalimumab levels in patient serum by the homogeneous mobility shift assay. *J Pharm Biomed Anal* 79:39–44. doi:10.1016/j.jpba.2013.01.031.
204. Warren RB, Weatherhead SC, Smith CH, et al. British Association of Dermatologists' guidelines for the safe and effective prescribing of methotrexate for skin disease 2016. Br J Dermatol. 2021:175. https://doi.org/10.1111/bjd.14816.
205. Wennink RAW, Ayuso VK, Vries LA, Vastert SJ, Boer JH. Tocilizumab as an effective treatment option in children with refractory intermediate and panuveitis. *Ocul Immunol Inflamm.* 2021; 2;29:21. doi:10.1080/09273948.2020.1712431.
206. Wieringa WG, Armbrust W, Legger GE, Los LI. Efficacy of high-dose methotrexate in pediatric non-infectious uveitis. Ocul Immunol Inflamm. 2019;27:1305–13. https://doi.org/10.1080/09273948.2018.1529800.
207. Xie X, Li F, Chen JW, Wang J. Risk of tuberculosis infection in anti-TNF-α biological therapy: from bench to bedside. J Microbiol Immunol Infect. 2014;47:268–74. https://doi.org/10.1016/J.JMII.2013.03.005.
208. YJ STOPUS, et al. Primary (month-6) outcomes of the STOP-uveitis study: evaluating the safety, tolerability, and efficacy of tocilizumab in patients with noninfectious uveitis. Am J Ophthalmol. 2017;(v;183::71–80. https://doi.org/10.1016/j.ajo.2017.08.019.
209. Zannin ME, Birolo C, Gerloni VM, et al. Safety and efficacy of infliximab and adalimumab for refractory uveitis in juvenile idiopathic arthritis: 1-year follow-up data from the Italian Registry. J Rheumatol. 2013;40:23118110. https://doi.org/10.3899/jrheum.120583.
210. Zhou X, Chen Z, Bi X. An Update review of biosimilars of adalimumab in psoriasis - bioequivalence and interchangeability. Drug Des Devel Ther. 2021;15:2987–98. https://doi.org/10.2147/DDDT.S317382.
211. Zulian F, Balzarin M, Falcini F, et al. Abatacept for severe anti–tumor necrosis factor α refractory juvenile idiopathic arthritis–related uveitis. Arthritis Care Res (Hoboken). 2010;62:821–5. https://doi.org/10.1002/acr.20115.

Curr Treat Options in Rheum (2017) 3:1–16
DOI 10.1007/s40674-017-0057-z

Pediatric Rheumatology (M Becker and J Harris, Section Editors)

An Update on Treatment of Pediatric Chronic Non-infectious Uveitis

Arjun B. Sood, MD[1]
Sheila T. Angeles-Han, MD, MSc[2,*]

Address
[1]Department of Ophthalmology, Emory University School of Medicine, Atlanta, GA, US
[*,2]Department of Pediatrics, University of Cincinnati, Division of Rheumatology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, MLC 4010, Cincinnati, OH, 45229, USA
Email: Sheila.Angeles-Han@cchmc.org

Published online: 26 January 2017
* Springer International Publishing AG 2017

This article is part of the Topical Collection on *Pediatric RheumatoLogy*

Keywords Uveitis] Pediatric uveitis] Methotrexate] Juvenile idiopathic arthritis] Infliximab] Adalimumab

Opinion statement

There are no standardized treatment protocols for pediatric non-infectious uveitis. Topical corticosteroids are the typical first-line agent, although systemic corticosteroids are used in intermediate, posterior, and panuveitic uveitis. Corticosteroids are not considered to be long-term therapy due to potential ocular and systemic side effects. In children with severe and/or refractory uveitis, timely management with higher dose disease-modifying anti-rheumatic drugs (DMARDs) and biologic agents is important. Increased doses earlier in the disease course may lead to improved disease control and better visual outcomes. In general, methotrexate is the usual first-line steroid-sparing agent and given as a subcutaneous weekly injection at 90.5 mg/kg/dose or 10–15 mg/m^2 due to better bioavailability. Other DMARDs, for instance mycophenolate, azathioprine, and cyclosporine, are less common treatments for pediatric uveitis. Anti-tumor necrosis factor-alpha agents, primarily infliximab and adalimumab, are used as second-line agents in children refractory to methotrexate or as first-line treatment in those with severe complicated disease at presentation. Infliximab may be given at a minimum of 7.5 mg/kg/dose every 4 weeks after loading doses, and up to 20 mg/kg/dose. Adalimumab may be given up to 20 or 40 mg weekly. In children who fail anti-tumor necrosis factor-alpha agents, develop anti-tumor necrosis factor-alpha antibodies, experience adverse effects, or have difficulty with tolerance, there is less data available regarding subsequent treatment. Promising results have been noted with tocilizumab infusions every 2–4 weeks, abatacept monthly infusions, and rituximab.

Introduction

Uveitis is a broad term for inflammation involving the eye. It is classified according to the location of the inflammatory process, either anterior, intermediate, posterior, or panuveitis [1, 2]. Uveitis can be secondary to an infectious etiology, such as tuberculosis, *Toxocara canis*, toxoplasmosis, herpes virus, lyme, and syphilis [3]. Ocular inflammation can also be associated with an underlying systemic condition, including juvenile idiopathic arthritis (JIA), sarcoidosis, tubulointerstitial nephritis and uveitis (TINU), inflammatory bowel disease, Vogt-Koyanagi-Harada (VKH), and Behcet's disease [4]. Frequently, however, uveitis is not associated with an underlying condition and is termed Bidiopathic^ [4].

In pediatric rheumatology, JIA is the most commonly associated disease, and uveitis is typically anterior and bilateral. Pediatric uveitis accounts for 5–10% of patients with uveitis [5]. Thorne et al. reported a prevalence of pediatric uveitis of 31 per 100,000 patients. Of 291 pediatric cases in this study, nearly 95% were non-infectious uveitis, and JIA was associated with 26.2% of these cases [6•].

Prolonged intraocular inflammation can lead to significant visual impairment and blindness. Uveitis is estimated to cause 30,000 new cases of legal blindness each year [6•]. The problem is compounded in pediatric patients where there is often a delay in presentation and diagnosis. Furthermore, children commonly experience a chronic course with frequent remission and relapse that can lead to significant ocular morbidity [7]. Ocular complications such as cataract, glaucoma, posterior synechiae, and band keratopathy occur in up to 50% of children, vision loss (visual acuity 20/50 or worse) occurs in up to 50% of children, and legal blindness (visual acuity 20/200 or worse) occurs in up to 25% [8–11]. Early diagnosis and treatment can mitigate these complications and potentially reduce the burden of visual impairment and blindness.

Evidence suggests an environmental trigger in a genetically susceptible individual leads to a release of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-alpha) and interleukins (IL) [12–15]. With this understanding, an immunomodulatory therapy approach is a useful strategy for the management of non-infectious uveitis. However, there is a lack of randomized controlled studies in the treatment of pediatric uveitis. Most evidence is based on expert opinion or clinical experience and management remains non-standardized [16••]. As a result, multi-disciplinary panels have proposed treatment algorithms in an effort to standardize care [17–19]. Despite the lack of level one and two evidence, immunomodulatory therapy remains the most effective approach to control ocular inflammation, reduce exposure to systemic corticosteroids, and decrease the incidence of vision loss and blindness.

The focus of this review is to report the current treatment options for pediatric non-infectious uveitis. We will focus on medications described in pediatric uveitis patients enrolled in the Childhood Arthritis and Rheumatology Research Alliance (CARRAnet) Registry, a large registry of North American pediatric rheumatology patients to examine practice patterns of pediatric rheumatologists [16••]. Furthermore, we suggest a stepwise approach to the use of immunomodulatory therapy, in particular JIA, which is the most common rheumatologic condition in childhood (Fig. 1).

Treatment

Pharmacologic treatment

The goal for treatment of pediatric non-infectious uveitis is threefold: (1) resolve intraocular inflammation, (2) achieve remission and prevent recurrences, and (3) preserve vision and prevent ocular complications [8]. Corticosteroids (CS) are the first-line treatment for non-infectious uveitis and are effective for acute inflammation [2]. The mechanism of action involves modulating gene expression of pro-inflammatory cytokines. CS can achieve this effect either through local or systemic administration and the mode of administration typically depends on location of uveitis [15]. Local treatments include topical drops or periocular and intraocular injections or implants.

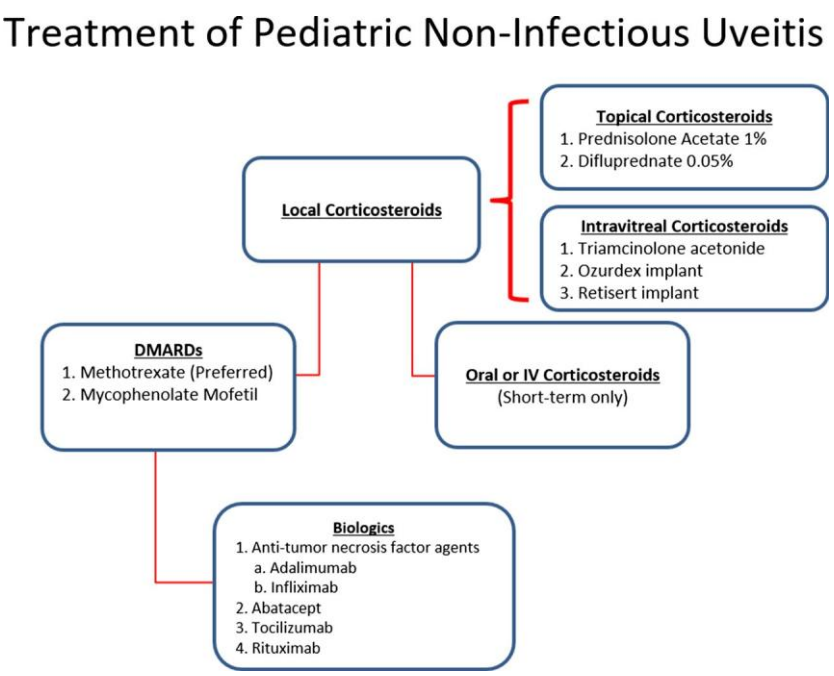


Fig. 1. Stepwise approach to the treatment of pediatric non-infectious uveitis. Topical corticosteroids are the typical first-line agent in anterior uveitis. Systemic corticosteroids may be used for rapid control of inflammation in intermediate, posterior, or panuveitic uveitis. In children with severe and/or refractory uveitis, DMARDs are the next step in management with methotrexate being the preferred agent. Anti-TNF agents are used as second-line agents in children refractory to methotrexate or as a first-line treatment in children with severe and complicated disease at presentation. In patients who fail anti-TNF agents, there is no agreement on subsequent therapy. Alternative biologics include abatacept, tocilizumab, and rituximab. Many patients require a combination of medications or require short-term systemic corticosteroids for intermittent flares.

Local corticosteroids

Topical corticosteroids are first-line treatment in anterior segment inflammation and were used in 90% of patients with idiopathic uveitis enrolled in the CARRAnet Registry [16••]. The most commonly used topical CS is prednisolone acetate 1%, which is administered at a frequency corresponding to the severity of inflammation. Topical difluprednate 0.05% (Durezol) is a more potent medication with superior intraocular penetration and requires less frequent dosing [20]. However, long-term use of topical CS, in particular Durezol, is associated with corticosteroid-induced ocular hypertension and cataracts [21, 22]. Evidence has shown that the need for 92 drops a day leads to increased ocular complications.

Periocular or intraocular injections of triamcinolone acetonide (TA) have been effective at treating intermediate, posterior, and panuveitis by providing a high concentration of drug at the site of inflammation [20]. While systemic side effects are minimized, local TA injections in the pediatric population often require general anesthesia, which poses its own risk to the patient. Moreover, the relatively short duration of action necessitates frequent repeat injections [23]. Longer duration intraocular therapy includes Dexamethasone implant (Ozurdex) and 0.59-mg Fluocinolone acetonide implant (Retisert) [23–28]. Ozurdex implantation lasts 6 months whereas Retisert implantation lasts for

nearly 3 years, which reduces the overall risk associated with anesthesia compared to repeat TA injections [24, 26]. An emerging option is a 0.19-mg Fluocinolone acetonide injectable (Illuvien) that was FDA approved for the management of diabetic retinopathy. Reddy et al. reported good outcomes on the off-label use of Illuvien in the management of uveitis and macular edema [29]. While more studies are needed, especially in the pediatric population, the Illuvien implant is a promising medication that lasts for nearly 3 years and is significantly less expensive than Retisert. Suprachoroidal TA administration is a novel route that is currently under investigation as another local treatment option for non-infectious uveitis [30]. As with all forms of local therapy, in particular periocular and intraocular CS, there is a high risk for cataract formation, elevated intraocular pressure, and worsening of pre-existing glaucoma [30–33].

Systemic corticosteroids

Systemic steroids are excellent for acute control of inflammation that is refractory to local therapy, especially in children with intermediate, posterior, or panuveitis. Approximately 94% of children with idiopathic uveitis in the CARRA registry were treated with systemic steroids during the disease course [16••]. Oral prednisone can be prescribed at a starting dose of 1–2 mg/kg body weight and tapered according to the inflammatory response. Intravenous (IV) corticosteroids are occasionally used in cases of severe ocular inflammation, including Behcet's disease, serpiginous choroiditis, or uveitis with optic nerve involvement [2]. However, long-term use of systemic steroids has potential adverse effects in the pediatric patient that include growth retardation, hyperglycemia, weight gain, hypertension, osteoporosis, peptic ulcers, cataracts, and glaucoma [23, 24].

Topical and systemic corticosteroids are not considered long-term treatment of chronic uveitis and there should not be a delay in initiating DMARDs or biologics.

Immunosuppressive therapy

Due to steroid toxicity, it is prudent to initiate steroid-sparing disease-modifying anti-rheumatic drugs (DMARDs) and biologics early in the disease course to control ocular inflammation and prevent complications and vision loss [15]. Options for long-term immunosuppression include first-line conventional immunotherapy with methotrexate (MTX), and less commonly, mycophenolate mofetil (MMF), and cyclosporine A (CsA).

Methotrexate

Methotrexate was used to treat 76% of patients with idiopathic juvenile uveitis enrolled in the CARRA Registry making it the most frequently used steroid-sparing agent [16••]. There are several reports of its use in pediatric patients with uveitis [34–38]. MTX is a folic acid analog that inhibits DNA replication and RNA transcription in B and T lymphocytes [2]. The recommended starting dose is 10–15 mg/m^2 once a week orally or subcutaneously. Dosing can be increased to 30 mg/m^2 if administered by the subcutaneous route. There is a

lack of evidence for preferred administration route. However, parenteral administration achieved higher efficacy and bioavailability in adult patients with rheumatoid arthritis and pediatric patients with JIA [39–43]. Foeldvari et al. reported good outcomes in JIA-associated uveitis (JIA-U) wherein 84% (21/25) of patients achieved remission after a mean treatment dose of 15.6 mg/m^2 (range 10–25 mg/m^2) for an average of 4.25 months (range 1–12) [37]. A recent meta-analysis suggests MTX is effective in controlling inflammation in pediatric non-infectious uveitis wherein the proportion of responding subjects in nine eligible studies was 0.73 (95% confidence interval 0.66–0.1) [44•]. Common side effects associated with MTX in children include gastrointestinal (GI) toxicity (oral ulcers, nausea, vomiting) and hepatorenal toxicity. Patients must have routine lab work to evaluate blood count and liver function (AST/ALT). In addition, folic acid should be supplemented on a daily basis to prevent GI-related toxicity.

Methotrexate is considered first-line therapy in most patients with chronic non-infectious uveitis and can be an effective treatment for ocular inflammation.

Mycophenolate mofetil

MMF inhibits inosine monophosphate dehydrogenase, which is an enzyme critical to the de novo pathway of purine synthesis [45]. Unlike other cell types, lymphocytes lack alternative pathways for purine synthesis and are therefore selectively suppressed by MMF [2]. The optimal dose for uveitis is unknown, but most pediatric rheumatologists initiate therapy at dosages used in pediatric renal transplant recipients—600 mg/m^2 twice daily or 2–3 g/day in divided doses. To date, there are only two reports of MMF therapy in pediatric uveitis [46, 47]. Chang et al. reported on 52 children with autoimmune uveitis treated with MMF monotherapy wherein 73% achieved uveitis control after 2 months. Approximately 60% (16/25) of patients with JIA-U achieved quiescence for at least 2 years of therapy. Furthermore, visual acuity was stable or improved in 94% [47]. MMF may be useful in the management of pediatric non-infectious uveitis, although less in JIA-U since it may not be as effective for arthritis compared to other agents. Side effects include hair loss, fatigue, gastrointestinal discomfort, and leukopenia [2, 15].

Cyclosporine A

CsA belongs to the class of calcineurin inhibitors (CNIs) whose mechanism is to block the activity of calcineurin, an enzyme that facilitates gene expression of IL-2 and other cytokines [48]. Down-regulation of these molecules impairs T cell proliferation resulting in immunosuppression. There are only a few studies reporting outcomes with CsA in pediatric non-infectious uveitis [49–52]. Tappeiner et al. reported on 82 patients with JIA-U, the largest retrospective series to date. CsA monotherapy had minimal efficacy in this study, with only 6/25 (24%) achieving inactivity. Efficacy increased to 48.6% (35/72) when combined with other immunosuppressive medications, suggesting the optimal role for CsA in treating pediatric non-infectious uveitis is as adjunct therapy [52]. Pediatric dosing of CsA is recommended between 2.5 and 5 mg/kg/day in divided doses to avoid systemic side effects [53]. Nephrotoxicity, hypertension, hepatotoxicity, anemia, nausea, vomiting, hirsutism, and hypercholesterolemia

are potential side effects [15]. Routine testing should include renal and liver function and blood pressure monitoring [2].

CsA is infrequently used to treat pediatric non-infectious uveitis, and other agents are preferred.

Biologics

Biologics represent a newer class of medications used to treat ocular inflammation. These agents target molecules in the immune system that play a key role in the ocular inflammatory process [54]. For example, TNF-alpha, interleukins (IL), and interferons are pro-inflammatory cytokines produced by immune cells and are consistently elevated in serum and aqueous fluid of patients with uveitis [55, 56]. Experimental autoimmune uveitis studies in animals also confirm the role of TNF-alpha in mediating intraocular inflammation [57–59]. Therefore, targeting these molecules with biologic therapy appears to be an attractive approach for long-term control of uveitis refractory to corticosteroids or conventional immunotherapy. Therapeutic options within the class of biologics include anti-TNF-alpha agents, anti-IL agents, and anti-B and T lymphocyte agents [19]. Screening for hepatitis and tuberculosis before initiation is important. Anti-TNF-alpha agents, specifically infliximab (IFX) and adalimumab (ADA), have been most commonly used with excellent success [60].

Anti-tumor necrosis factor agents

Infliximab

Infliximab is a chimeric (75% humanized, 25% mouse) monoclonal antibody that binds to and inhibits circulating and membrane bound TNF-alpha [61]. It is FDA approved for several autoimmune conditions, including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and inflammatory bowel disease [54]. Numerous prospective and retrospective studies support IFX's use for non-infectious uveitis, but dosage and interval vary [62, 63, 64•, 65–67]. Kahn et al. reported on 17 patients with refractory uveitis (10 JIA-U, 2 VKH, 2 sarcoidosis, 3 idiopathic) treated with 10–20 mg/kg of IFX every 4–8 weeks [64•]. Intraocular inflammation was undetectable after the first or second infusion in 76% (13/17). High-dose IFX was effective and well tolerated in all patients in this series. Ardoin et al. reported on a cohort of 16 children with uveitis (5 JIA-U, 11 idiopathic) treated with 8.2 mg/kg median dose (range 2.0 to 12.9) of IFX at median frequency of 5.6 weeks (range 4 to 10). At 1 year, 64% had no active inflammation and increased to 79% if criteria were modified to include zero inflammation or a 2-step decrease in AC inflammation. Furthermore, all patients were on topical CS at baseline, whereas by 12 months, approximately 69% (11/16) of patients discontinued use [67]. Sukumaran et al. compared varied doses of IFX: low dose (G10 mg/kg), moderate dose (≥10–15 mg/kg), and high dose (≥15–20 mg/kg) every 4 weeks in 34 children with refractory non-infectious uveitis [68]. After 1 year, there was significant improvement in anterior chamber cells, flare, and VA in all groups. However, escalated doses may be necessary to achieve disease control since 935%

required an increase in dose to ≥10 mg/kg, and 94% were on high dose at end of study.

IFX is administered intravenously with a loading dose of 3–5 mg/kg at weeks 0, 2, and 6 followed by maintenance dosing at 5 –10 mg/kg every 4–8 weeks. Additionally, methotrexate is recommended as an adjunct to prevent the formation of anti-TNF antibodies. In refractory uveitis, an increased dose of 20 mg/kg has been used successfully [64•, 68, 69]. Potential side effects include increased susceptibility to infections, reactivation of tuberculosis or histoplasmosis, malignancy, and development of lupus-like syndrome [2, 54]. Mild and moderate infusion reactions occurred in 17% of patients in one study [70].

IFX can be an effective treatment for uveitis but is often needed at high doses. There has been variability in the dosing and interval of IFX administration which may have led to the differences in patient outcomes.

Adalimumab

Adalimumab (ADA) is a fully humanized monoclonal antibody that also binds to and inhibits TNF-alpha and is the only US Food and Drug Administration (FDA)-approved non-corticosteroid medication for the treatment of non-infectious uveitis [71]. Jaffe et al. recently published results from a multinational phase 3 randomized controlled trial assessing the efficacy and safety of ADA for adults with non-infectious intermediate, posterior, or panuveitic uveitis [72••]. All 217 patients had active, vision threatening, non-infectious uveitis and were randomly assigned to ADA 80-mg dose at baseline followed by 40-mg doses every 2 weeks (110 patients) or placebo (107 patients). They described a significantly lower risk of treatment failure compared to placebo wherein treatment failure occurred at 24 weeks in the ADA group and 13 weeks in the placebo group (HR, 0.50; 99% confidence interval, 0.36 to 0.70; P G 0.001).

Nguyen et al. reported on 229 patients with inactive uveitis on 10–35 mg/day of oral prednisone to maintain uveitis inactivity [73••]. They were randomly assigned to ADA (115 patients) or placebo (114 patients). Prednisone was tapered to 0 mg by week 19. Treatment failure was increased in the placebo group (61 (55%)) compared to the ADA group (45 (39%)), and there was significant improvement in time to treatment failure in patients receiving ADA.

Several prospective and retrospective studies support ADA treatment for pediatric uveitis [74–79, 80•, 81–84]. Diaz-Llopis et al. reported a prospective multi-center study of 131 patients (39 with JIA-U) treated with ADA for 6 months [75]. Children received 40 mg of ADA subcutaneously (SC) every other week (children between ages 4 and 12 received 24 mg/m^2 body surface area up to maximum dose of 40 mg SC every other week). There was a statistically significant decrease in anterior chamber and vitreous inflammation and overall gain in visual acuity [75].

There are reports on the development of antibodies against ADA (AAA) in other diseases, leading to decreased drug efficacy and adverse effects. Recently, Cordero-Coma described 25 patients (2 JIA-U) with active refractory uveitis who were followed prospectively for 6 months [85]. At least three trough serum ADA and AAA were measured prior to ADA administration. Only 11 (44%) had a complete clinical response, seven (28%) had a partial response, and seven (25%) no response. There were increased ADA levels in responders and an association between worse uveitis outcome in patients with permanent AAA (4

(14%)). Development of AAA was not associated with use of other immunosuppressive agents which is interesting since methotrexate is often used in conjunction with IFX for JIA. The relevance of measurement of ADA trough levels and AAA remains unclear.

ADA is administered subcutaneously at a dose of 10 - 40 mg every 2 weeks. In children with severe uveitis, dose and interval of administration can be increased to 40 mg weekly to increase efficacy. Side effects are similar to IFX, including increased susceptibility to infections and reactivation of TB or histoplasmosis [2].

Reports on the successful use of ADA in pediatric uveitis and ease of administration at home versus infusions make it an excellent option for many families.

Golimumab

There have been limited reports on Golimumab, a fully humanized anti-TNF monoclonal antibody that is administered subcutaneously every 4 weeks. Miserocchi et al. examined 13 patients with JIA-U and 4 with HLA-B27 spondyloarthropathy who had an inadequate response to other TNF-alpha blockers or other biologics such as rituximab and abatacept [86]. Patients received golimumab 50 mg every 4 weeks as subcutaneous injections. They were all ≥18 years of age and had anterior uveitis or panuveitis. Response was evident in 14 patients, wherein two of the non-responders had JIA-U. At the last visit, 12 of 17 had inactive disease. This is a promising anti-TNF therapy for uveitis patients.

Emerging therapies

Abatacept

Abatacept (ABA) is a soluble fusion protein composed of human cytotoxic T lymphocyte antigen 4 (CTLA-4) and modified FC domain of human IgG. It binds to CD80/CD86 on antigen-presenting cells and prevents activation of T cells [87]. Abatacept is FDA approved for JIA and RA, but off-label use in pediatric and adult uveitis has been reported [87–89, 90•, 91]. In 2008, we first reported on a 16-year-old female with psoriatic arthritis with long-standing uveitis that was refractory to conventional IMT and biologics, including trials of rituximab, IFX, etanercept, and daclizumab. Abatacept infusions were started at 10 mg/kg. Ocular inflammation rapidly improved and remained well controlled 18 months after initiation of therapy [87]. A recent case series described three children with idiopathic uveitis that was successfully controlled with Abatacept [89]. However, Tappeiner et al. reported on the visual outcomes in 21 patients with JIA-U [90•]. All patients had severe and chronic uveitis with mean duration of 7.5 years and were treated with 10 mg/kg, max 750 mg every 4 weeks. Patients had previously failed tCS, systemic CS, methotrexate, and several biologics (IFX, etanercept, ritixuimab, golimumab). Uveitis inactivity was achieved in 11 patients after starting ABA (median time of 6 months) but recurred in eight of these patients. Abatacept failed to suppress inflammation in 10/21 (48%) of patients. In addition, new onset complications occurred in

three, and best corrected visual acuity (BCVA) did not significantly improve. Hence, ABA did not appear to be effective in this cohort compared to earlier studies. Birolo et al. compared ABA as a first-line or second-line biologic agent in 31 patients with severe JIA-U after 12 months of follow-up [92•]. Fourteen received ABA as first-line biologic therapy (at least 6 months of MTX) and 17 as a second-line biologic agent. Clinical remission was achieved in 54.8% of the total patients (17/31), but there was no significant difference in improvement in those who received ABA as first line (57%) versus second line (52.9) [92•]. Dosing is 10 mg/kg at 0 and 15 days followed by monthly administration [2]. Side effects include infections, gastrointestinal disorders, and low risk for malignancy [2, 20].

There are reports on the use of Abatacept in children with uveitis, but attainment of remission varied.

Tocilizumab

Interleukin-6 (IL-6) is a cytokine produced by T cells, B cells, and monocytes. Signaling through IL-6 appears to play a critical role in the immune system, including T cell activation, immunoglobulin secretion, and angiogenesis [93, 94]. The importance of IL-6 in mediating ocular inflammation has also been demonstrated in animal models of experimental uveitis that show that treatment with anti-IL6 receptor antibody reduces uveitic inflammation [95]. Furthermore, elevated IL-6 concentrations were noted in vitreous fluid of patients with VKH, Behcet's, sarcoidosis, and idiopathic uveitis compared to controlled non-uveitic patients [95]. Therefore, targeting IL-6 appears to be an attractive approach.

Tocilizumab (TCZ) is an IL-6 receptor antibody approved for RA and JIA and is an emerging treatment for uveitis and cystoid macular edema [93, 94, 96••, 97, 98, 99••]. It is a humanized recombinant antibody that binds the IL-6 receptor, leading to inhibition of the downstream signaling of IL-6 and pro-inflammatory effects. Tappeiner et al. reported on 17 patients treated with TCZ for chronic refractory JIA-U, including systemic corticosteroids, DMARDs, and 1 TNF-alpha inhibitor [97]. Patients were treated with intravenous TCZ 8 mg/kg body weight at 4 week intervals and were followed for a mean of 8.5 months. Inactive uveitis was observed in 10/17 patients after at least one follow-up, but there was a recurrence in three. In seven patients who did not respond to TCZ, four had improved ocular activity, two had no change, and one worsened. Additionally, four patients experienced new ocular complications during treatment, and there was no significant change in BCVA at the end of follow-up. There were no adverse events requiring discontinuation of TCZ in this study. In 2016, Silpa-archa et al. reported their experience with Tocilizumab in 17 patients with recalcitrant ocular inflammatory disease (10 uveitis, 6 scleritis, 1 orbital pseudotumor) [94]. In the uveitis cohort, five patients (age range 14–50 years) had inflammation associated with JIA. After 9 months of treatment, 71% of uveitis and 50% of scleritis patients achieved the primary outcome: absence of inflammation and achievement of steroid sparing. However, serious side effects requiring cessation of therapy were reported in 24% of patients, including neutropenia, severe angioedema, dizziness, and abdominal pain. Recently, Calvo-Rio et al. reported on the use of TCZ in 25 patients with JIA-U refractory to conventional IMT and at least one biologic agent including anti-

TNF-alpha drugs, abatacept, rituximab, and anakinra [99••]. Dosing was 8 mg/kg IV every 2, 4, or 8 weeks or 2.9 mg/kg/subcutaneously every week. At 6 months of follow-up in 23 patients, BCVA improved and anterior chamber cells decreased in 79%. This was consistent at 1 year in 15/17 patients (88%). Clinical trials evaluating the efficacy of TCZ in non-infectious intermediate, posterior, or panuveitis (STOP-Uveitis) and JIA-U are on-going (www.clinicaltrials.gov) [93].

TCZ is a promising treatment for pediatric uveitis, but additional studies are needed to determine optimal dosing and intervals.

Rituximab

Rituximab is a chimeric antibody directed against the B cell marker CD20 thereby inducing B cell apoptosis [100••]. Rituximab initially gained FDA approval in 1997 for the treatment of lymphoma and leukemia [101]. Since then, the medication has been approved for RA, microscopic polyangiitis, and granulomatosis with polyangiitis [54]. Rituximab's use in ocular conditions has been limited, but several reports have shown efficacy for the management of scleritis, peripheral ulcerative keratitis, VKH, and more recently, in JIA-U [102–105]. Miserocchi et al. reported on a cohort of eight patients (15 eyes) with severe JIA-U treated with rituximab who were previously resistant to IMT and TNF-alpha inhibitors [106]. The mean follow-up time on rituximab was 44.75 months with a mean number of 8.75 infusions. Uveitis was inactive in all patients at last follow-up, and improvement was noted 4 months after the first infusion. Mean systemic CS dose before initiating rituximab was 18 mg/day and decreased to 1.8 mg/day at final follow-up, with discontinuation in six patients. Similarly, conventional IMT was discontinued in 5/8 patients and reduced from MTX + CSA to only MTX in one patient. The two remaining patients continued with baseline MTX throughout rituximab treatment. These are promising results for refractory uveitis associated with JIA, but further prospective trials need to be conducted to assess the efficacy of rituximab in pediatric uveitis.

Rituximab is given intravenously and dosed at 1000 mg on days 1 and 14 and repeated after 6 months if needed. Effect on B cells lasts 6 to 9 months making this an attractive biologic compared to anti-TNF-alpha agents that require more frequent dosing [107]. Side effects include infusion reactions, which can be mitigated with corticosteroids, as well as neutropenia, heart failure, and rarely progressive multifocal leukoencephalopathy.

Future directions

Several challenges exist in the timely and optimal treatment of children with uveitis. There is a lack of randomized controlled trials, and adalimumab is the only FDA-approved drug for non-infectious intermediate, posterior, and panuveitic uveitis in adults. Thus, treatment is usually guided by collective expertise, case reports/case series, retrospective studies, and panel guidelines [17–19].

Advances have emerged in the study of biomarkers for early detection of disease, indicators of active disease, and targeted therapy. Potential biomarkers associated with pediatric chronic anterior uveitis and JIA-associated uveitis were detected in the iris, serum, and aqueous humor, but most studies have been

conducted in adults with varied involvement and associated diseases. Alterations in the inflammatory cells, autoantibodies, cytokines, chemokines, and soluble adhesion molecules have been reported, most recently erythrocyte sedimentation rate (ESR), plasma cells, interleukin-29/interferon-λ1, S100A8/A9, and S100A12 [108–118]. The analysis of tear fluid for biomarkers in chronic anterior non-infectious uveitis is a potential non-invasive collection method [119–121]. With further developments in research and science, the potential exists to utilize markers to inform clinicians of optimal therapy choice as we gain more insight into promising drug targets.

Conclusions

Chronic pediatric non-infectious uveitis can lead to severe ocular complications and permanent vision loss. Timely and optimal management improves visual outcomes. There are no standardized treatments and few randomized controlled trials for pediatric uveitis. We report on conventional DMARDs and anti-tumor necrosis factor agents but also discuss newer biologics for children with refractory uveitis. Additional studies are needed to determine optimal treatment and dose in this population.

Compliance with Ethical Standards

Conflict of Interest

Arjun B. Sood, MD, and Sheila T. Angeles-Han, MD, MSc, declare that they have no conflict of interest.

Dr. Angeles-Han was supported by Award Number K23EY021760 from the National Eye Institute and also by a grant from the American College of Rheumatology Research and Education Foundation Career Development Bridge Funding Award. However, these did not support this study.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005;140(3):509–16.
2. Simonini G, Cantarini L, Bresci C, Lorusso M, Galeazzi M, Cimaz R. Current therapeutic approaches to autoimmune chronic uveitis in children. Autoimmun Rev. 2010;9(10):674–83.
3. Dhoot DS, Martin DF, Srivastava SK. Pediatric infectious posterior uveitis. Int Ophthalmol Clin. 2011;51(1):113–28.
4. Kim SJ. Diagnosis and management of noninfectious pediatric uveitis. Int Ophthalmol Clin. 2011;51(1):129–45.
5. Levy-Clarke GA, Nussenblatt RB, Smith JA. Management of chronic pediatric uveitis. Curr Opin Ophthalmol. 2005;16(5):281–8.

6. • Thorne JE, Suhler E, Skup M, Tari S, Macaulay D, Chao J, et al. Prevalence of noninfectious uveitis in the United States: a claims-based analysis. JAMA ophthalmology. 2016.

Provide?s information of the epidemiology of uveitis in the United States.

7. Holland GN, Denove CS, Yu F. Chronic anterior uveitis in children: clinical characteristics and complications. Am J Ophthalmol. 2009;147(4):667–78.e5.
8. Gregory 2nd AC, Kempen JH, Daniel E, Kacmaz RO, Foster CS, Jabs DA, et al. Risk factors for loss of visual acuity among patients with uveitis associated with juvenile idiopathic arthritis: the Systemic Immunosuppressive Therapy for Eye Diseases Study. Ophthalmology. 2013;120(1):186–92.
9. Angeles-Han ST, Rabinovich CE. Uveitis in children. Curr Opin Rheumatol. 2016;28(5):544–9.
10. Vitale AT, Graham E, de Boer JH. Juvenile idiopathic arthritis-associated uveitis: clinical features and complications, risk factors for severe course, and visual outcome. Ocul Immunol Inflamm. 2013;21(6):478–85.
11. Edelsten C, Lee V, Bentley CR, Kanski JJ, Graham EM. An evaluation of baseline risk factors predicting severity in juvenile idiopathic arthritis associated uveitis and other chronic anterior uveitis in early childhood. Br J Ophthalmol. 2002;86(1):51–6.
12. Hersh AO, Prahalad S. Immunogenetics of juvenile idiopathic arthritis: a comprehensive review. J Autoimmun. 2015;64:113–24.
13. Angeles-Han S, Prahalad S. The genetics of juvenile idiopathic arthritis: what is new in 2010? Curr Rheumatol Rep. 2010;12(2):87–93.
14. Glass DN, Giannini EH. Juvenile rheumatoid arthritis as a complex genetic trait. Arthritis Rheum. 1999;42(11):2261–8.
15. Cantarini L, Simonini G, Frediani B, Pagnini I, Galeazzi M, Cimaz R. Treatment strategies for childhood non-infectious chronic uveitis: an update. Expert Opin Investig Drugs. 2012;21(1):1–6.
16. •• Henderson LA, Zurakowski D, Angeles-Han ST, Lasky A, Rabinovich CE, Lo MS. Medication use in juvenile uveitis patients enrolled in the Childhood Arthritis and Rheumatology Research Alliance Registry. Pediatr Rheumatol Online J. 2016;14(1):9.

Provid?es information on the practice patterns of the majority of pediatric rheumatologists in North America for pediatric non-infectious uveitis.

17. Heiligenhaus A, Michels H, Schumacher C, Kopp I, Neudorf U, Niehues T, et al. Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis. Rheumatol Int. 2012;32(5):1121–33.
18. Bou R, Adan A, Borras F, Bravo B, Calvo I, De Inocencio J, et al. Clinical management algorithm of uveitis associated with juvenile idiopathic arthritis: interdisciplinary panel consensus. Rheumatol Int. 2015;35(5):777–85.
19. Levy-Clarke G, Jabs DA, Read RW, Rosenbaum JT, Vitale A, Van Gelder RN. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. Ophthalmology. 2014;121(3):785–96.e3.
20. Mehta PJ, Alexander JL, Sen HN. Pediatric uveitis: new and future treatments. Curr Opin Ophthalmol. 2013;24(5):453–62.
21. Thorne JE, Woreta FA, Dunn JP, Jabs DA. Risk of cataract development among children with juvenile idiopathic arthritis-related uveitis treated with topical corticosteroids. Ophthalmology. 2010;117(7):1436–41.
22. Slabaugh MA, Herlihy E, Ongchin S, van Gelder RN. Efficacy and potential complications of difluprednate use for pediatric uveitis. Am J Ophthalmol. 2012;153(5):932–8.
23. Tomkins-Netzer O, Talat L, Seguin-Greenstein S, Bar A, Lightman S. Outcome of treating pediatric uveitis with dexamethasone implants. Am J Ophthalmol. 2016;161:110–5.e1-2.
24. Bratton ML, He YG, Weakley DR. Dexamethasone intravitreal implant (Ozurdex) for the treatment of pediatric uveitis. J AAPOS: Off Publ Am Assoc Pediatr Ophthalmol Strabismus/Am Assoc Pediatr Ophthalmol Strabismus. 2014;18(2):110–3.
25. Patel CC, Mandava N, Oliver SC, Braverman R, Quiroz-Mercado H, Olson JL. Treatment of intractable posterior uveitis in pediatric patients with the fluocinolone acetonide intravitreal implant (Retisert). Retina (Philadelphia, Pa). 2012;32(3):537–42.
26. Kempen JH, Altaweel MM, Holbrook JT, Jabs DA, Louis TA, Sugar EA, et al. Randomized comparison of systemic anti-inflammatory therapy versus fluocinolone acetonide implant for intermediate, posterior, and panuveitis: the multicenter uveitis steroid treatment trial. Ophthalmology. 2011;118(10):1916–26.
27. Sella R, Oray M, Friling R, Umar L, Tugal-Tutkun I, Kramer M. Dexamethasone intravitreal implant (Ozurdex(R)) for pediatric uveitis. Graefe's Arch Clin Exp Ophthalmol = Albrecht Von Graefes Arch Klin Exp Ophthalmol. 2015;253(10):1777–82.
28. Taylor SR, Tomkins-Netzer O, Joshi L, Morarji J, McLoone E, Lightman S. Dexamethasone implant in pediatric uveitis. Ophthalmology. 2012;119(11):2412–e2.
29. Reddy AK, Burkholder BM, Khan IR, Thorne JE. Iluvien implantation for uveitis and uveitic macular edema. Ocular immunology and inflammation. 2016:1–2.
30. Goldstein DA, Do D, Noronha G, Kissner JM, Srivastava SK, Nguyen QD. Suprachoroidal corticosteroid administration: a novel route for local treatment of noninfectious uveitis. Translat Vis Sci Technol. 2016;5(6):14.
31. Bollinger KE, Smith SD. Prevalence and management of elevated intraocular pressure after placement of an intravitreal sustained-release steroid implant. Curr Opin Ophthalmol. 2009;20(2):99–103.
32. Rhee DJ, Peck RE, Belmont J, Martidis A, Liu M, Chang J, et al. Intraocular pressure alterations following

intravitreal triamcinolone acetonide. Br J Ophthalmol. 2006;90(8):999–1003.
33. Kersey JP, Broadway DC. Corticosteroid-induced glaucoma: a review of the literature. Eye (London, England). 2006;20(4):407–16.
34. Chan AY, Liu DT. Methotrexate and chronic uveitis associated with juvenile idiopathic arthritis. The Journal of rheumatology. 2006;33(1):198; author reply
35. Weiss AH, Wallace CA, Sherry DD. Methotrexate for resistant chronic uveitis in children with juvenile rheumatoid arthritis. J Pediatr. 1998;133(2):266–8.
36. Heiligenhaus A, Mingels A, Heinz C, Ganser G. Methotrexate for uveitis associated with juvenile idiopathic arthritis: value and requirement for additional anti-inflammatory medication. Eur J Ophthalmol. 2007;17(5):743–8.
37. Foeldvari I, Wierk A. Methotrexate is an effective treatment for chronic uveitis associated with juvenile idiopathic arthritis. J Rheumatol. 2005;32(2):362–5.
38. Malik AR, Pavesio C. The use of low dose methotrexate in children with chronic anterior and intermediate uveitis. Br J Ophthalmol. 2005;89(7):806–8.
39. Braun J, Kastner P, Flaxenberg P, Wahrisch J, Hanke P, Demary W, et al. Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. Arthritis Rheum. 2008;58(1):73–81.
40. Hoekstra M, Haagsma C, Neef C, Proost J, Knuif A, van de Laar M. Bioavailability of higher dose methotrexate comparing oral and subcutaneous administration in patients with rheumatoid arthritis. J Rheumatol. 2004;31(4):645–8.
41. Herman RA, Veng-Pedersen P, Hoffman J, Koehnke R, Furst DE. Pharmacokinetics of low-dose methotrexate in rheumatoid arthritis patients. J Pharm Sci. 1989;78(2):165–71.
42. Zuber Z, Turowska-Heydel D, Sobczyk M, Banach-Gornicka M, Rusnak K, Piszczek A, et al. Methotrexate efficacy and tolerability after switching from oral to subcutaneous route of administration in juvenile idiopathic arthritis. Reumatol. 2016;54(1):19–23.
43. Franova J, Fingerhutova S, Kobrova K, Srp R, Nemcova D, Hoza J, et al. Methotrexate efficacy, but not its intolerance, is associated with the dose and route of administration. Pediatr Rheumatol Online J. 2016;14(1):36.
44. • Simonini G, Paudyal P, Jones GT, Cimaz R, Macfarlane GJ. Current evidence of methotrexate efficacy in childhood chronic uveitis: a systematic review and meta-analysis approach. Rheumatol (Oxford, England). 2013;52(5):825–31.
Review?s the literature and provides information on the use of methotrexate.
45. Budde K, Glander P, Bauer S, Braun K, Waiser J, Fritsche L, et al. Pharmacodynamic monitoring of mycophenolate mofetil. Clin Chem Lab Med. 2000;38(11):1213–6.
46. Doycheva D, Deuter C, Stuebiger N, Biester S, Zierhut M. Mycophenolate mofetil in the treatment of uveitis in children. Br J Ophthalmol. 2007;91(2):180–4.
47. Chang PY, Giuliari GP, Shaikh M, Thakuria P, Makhoul D, Foster CS. Mycophenolate mofetil monotherapy in the management of paediatric uveitis. Eye (London, England). 2011;25(4):427–35.
48. Anglade E, Yatscoff R, Foster R, Grau U. Next-generation calcineurin inhibitors for ophthalmic indications. Expert Opin Investig Drugs. 2007;16(10):1525–40.
49. Walton RC, Nussenblatt RB, Whitcup SM. Cyclosporine therapy for severe sight-threatening uveitis in children and adolescents. Ophthalmology. 1998;105(11):2028–34.
50. Kilmartin DJ, Forrester JV, Dick AD. Cyclosporin A therapy in refractory non-infectious childhood uveitis. Br J Ophthalmol. 1998;82(7):737–42.
51. Kotaniemi K. Late onset uveitis in juvenile-type chronic polyarthritis controlled with prednisolone, cyclosporin A and methotrexate. Clin Exp Rheumatol. 1998;16(4):469–71.
52. Tappeiner C, Roesel M, Heinz C, Michels H, Ganser G, Heiligenhaus A. Limited value of cyclosporine A for the treatment of patients with uveitis associated with juvenile idiopathic arthritis. Eye (London, England). 2009;23(5):1192–8.
53. Feutren G, Mihatsch MJ. Risk factors for cyclosporine-induced nephropathy in patients with autoimmune diseases. International Kidney Biopsy Registry of Cyclosporine in Autoimmune Diseases. N Engl J Med. 1992;326(25):1654–60.
54. Pasadhika S, Rosenbaum JT. Update on the use of systemic biologic agents in the treatment of noninfectious uveitis. Biologics: Targets Ther. 2014;8:67–81.
55. Santos Lacomba M, Marcos Martin C, Gallardo Galera JM, Gomez Vidal MA, Collantes Estevez E, Ramirez Chamond R, et al. Aqueous humor and serum tumor necrosis factor-alpha in clinical uveitis. Ophthalmic Res. 2001;33(5):251–5.
56. Perez-Guijo V, Santos-Lacomba M, Sanchez-Hernandez M, Castro-Villegas Mdel C, Gallardo-Galera JM, Collantes-Estevez E. Tumour necrosis factor-alpha levels in aqueous humour and serum from patients with uveitis: the involvement of HLA-B27. Curr Med Res Opin. 2004;20(2):155–7.
57. Dick AD, Forrester JV, Liversidge J, Cope AP. The role of tumour necrosis factor (TNF-alpha) in experimental autoimmune uveoretinitis (EAU). Prog Retin Eye Res. 2004;23(6):617–37.
58. Nakamura S, Yamakawa T, Sugita M, Kijima M, Ishioka M, Tanaka S, et al. The role of tumor necrosis factor-alpha in the induction of experimental autoimmune uveoretinitis in mice. Invest Ophthalmol Vis Sci. 1994;35(11):3884–9.
59. Sartani G, Silver PB, Rizzo LV, Chan CC, Wiggert B, Mastorakos G, et al. Anti-tumor necrosis factor alpha

therapy suppresses the induction of experimental autoimmune uveoretinitis in mice by inhibiting antigen priming. Invest Ophthalmol Vis Sci. 1996;37(11):2211–8.

60. Lerman MA, Burnham JM, Chang PY, Daniel E, Foster CS, Hennessy S, et al. Response of pediatric uveitis to tumor necrosis factor-alpha inhibitors. J Rheumatol. 2013;40(8):1394–403.
61. Cordero-Coma M, Sobrin L. Anti-tumor necrosis factor-alpha therapy in uveitis. Surv Ophthalmol. 2015;60(6):575–89.
62. Richards JC, Tay-Kearney ML, Murray K, Manners P. Infliximab for juvenile idiopathic arthritis-associated uveitis. Clin Exp Ophthalmol. 2005;33(5):461–8.
63. Rajaraman RT, Kimura Y, Li S, Haines K, Chu DS. Retrospective case review of pediatric patients with uveitis treated with infliximab. Ophthalmology. 2006;113(2):308–14.
64. • Kahn P, Weiss M, Imundo LF, Levy DM. Favorable response to high-dose infliximab for refractory childhood uveitis. Ophthalmology. 2006;113(5):860–4.e2.
This stu?dy describes the successful use of increased doses of inflixmab in pediatric uveitis.
65. Sobrin L, Kim EC, Christen W, Papadaki T, Letko E, Foster CS. Infliximab therapy for the treatment of refractory ocular inflammatory disease. Arch Ophthalmol (Chicago, Ill : 1960). 2007;125(7):895–900.
66. Tugal-Tutkun I, Ayranci O, Kasapcopur O, Kir N. Retrospective analysis of children with uveitis treated with infliximab. J AAPOS: Off Publ Am Assoc Pediatr Ophthalmol Strabismus/Am Assoc Pediatr Ophthalmol Strabismus. 2008;12(6):611–3.
67. Ardoin SP, Kredich D, Rabinovich E, Schanberg LE, Jaffe GJ. Infliximab to treat chronic noninfectious uveitis in children: retrospective case series with long-term follow-up. Am J Ophthalmol. 2007;144(6):844–9.
68. Sukumaran S, Marzan K, Shaham B, Reiff A. High dose infliximab in the treatment of refractory uveitis: does dose matter? ISRN Rheumatol. 2012;2012:765380.
69. Tambralli A, Beukelman T, Weiser P, Atkinson TP, Cron RQ, Stoll ML. High doses of infliximab in the management of juvenile idiopathic arthritis. J Rheumatol. 2013;40(10):1749–55.
70. Aeschlimann FA, Hofer KD, Cannizzaro Schneider E, Schroeder S, Lauener R, Saurenmann RK. Infliximab in pediatric rheumatology patients: a retrospective analysis of infusion reactions and severe adverse events during 2246 infusions over 12 years. J Rheumatol. 2014;41(7):1409–15.
71. Balevic SJ, Rabinovich CE. Profile of adalimumab and its potential in the treatment of uveitis. Drug Design, Dev Ther. 2016;10:2997–3003.
72. •• Jaffe GJ, Dick AD, Brezin AP, Nguyen QD, Thorne JE, Kestelyn P, et al. Adalimumab in patients with active noninfectious uveitis. N Engl J Med. 2016;375(10):932–43.
Import?ant study that describes the efficacy of adalimumab in adult uveitis patients.
73. •• Nguyen QD, Merrill PT, Jaffe GJ, Dick AD, Kurup SK, Sheppard J, et al. Adalimumab for prevention of uveitic flare in patients with inactive non-infectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial. Lancet (London, England). 2016;388(10050):1183–92.
Anothe?r important study that describves the efficacy of adalimumab in adult uveitis using RCT.
74. Castiblanco C, Meese H, Foster CS. Treatment of pediatric uveitis with adalimumab: the MERSI experience. J AAPOS: Off Publ Am Assoc Pediatr Ophthalmol Strabismus/Am Assoc Pediatr Ophthalmol Strabismus. 2016;20(2):145–7.
75. Diaz-Llopis M, Salom D, Garcia-de-Vicuna C, Cordero-Coma M, Ortega G, Ortego N, et al. Treatment of refractory uveitis with adalimumab: a prospective multicenter study of 131 patients. Ophthalmology. 2012;119(8):1575–81.
76. Vazquez-Cobian LB, Flynn T, Lehman TJ. Adalimumab therapy for childhood uveitis. J Pediatr. 2006;149(4):572–5.
77. Bravo-Ljubetic L, Peralta-Calvo J, Noval S, Pastora-Salvador N, Abelairas-Gomez J, Merino R. Adalimumab therapy for refractory childhood uveitis. J AAPOS: Off Publ Am Assoc Pediatr Ophthalmol Strabismus/Am Assoc Pediatr Ophthalmol Strabismus. 2013;17(5):456–9.
78. Garcia-De-Vicuna C, Diaz-Llopis M, Salom D, Bou R, Diaz-Cascajosa J, Cordero-Coma M, et al. Usefulness of adalimumab in the treatment of refractory uveitis associated with juvenile idiopathic arthritis. Mediat Inflamm. 2013;2013:560632.
79. Magli A, Forte R, Navarro P, Russo G, Orlando F, Latanza L, et al. Adalimumab for juvenile idiopathic arthritis-associated uveitis. Graefe's Arch Clin Exp Ophthalmol = Albrecht Von Graefes Arch Klin Exp Ophthalmol. 2013;251(6):1601–6.
80. • Simonini G, Taddio A, Cattalini M, Caputo R, de Libero C, Parentin F, et al. Superior efficacy of Adalimumab in treating childhood refractory chronic uveitis when used as first biologic modifier drug: Adalimumab as starting anti-TNF-alpha therapy in childhood chronic uveitis. Pediatr Rheumatol Online J. 2013;11:16.
The au?thors provide a review of adalimumab for pediatric uveitis.
81. Jeroudi A, Angeles-Han ST, Yeh S. Efficacy of adalimumab for pediatric Vogt-Koyanagi-Harada syndrome. Ophthalmic Surg, Lasers Imaging Retina. 2014;45(4):332–4.
82. Kim JB, Jeroudi A, Angeles-Han ST, Grossniklaus HE, Yeh S. Adalimumab for pediatric sympathetic ophthalmia. JAMA Ophthalmol. 2014;132(8):1022–4.
83. Zannin ME, Birolo C, Gerloni VM, Miserocchi E, Pontikaki I, Paroli MP, et al. Safety and efficacy of infliximab and adalimumab for refractory uveitis in juvenile idiopathic arthritis: 1-year followup data from the Italian Registry. J Rheumatol. 2013;40(1):74–9.

84. Tynjala P, Kotaniemi K, Lindahl P, Latva K, Aalto K, Honkanen V, et al. Adalimumab in juvenile idiopathic arthritis-associated chronic anterior uveitis. Rheumatol (Oxford, England). 2008;47(3):339–44.
85. Cordero-Coma M, Calleja-Antolin S, Garzo-Garcia I, Nunez-Garnes AM, Alvarez-Castro C, Franco-Benito M, et al. Adalimumab for treatment of noninfectious uveitis: immunogenicity and clinical relevance of measuring serum drug levels and antidrug antibodies. Ophthalmology. 2016;123(12):2618–25.
86. Miserocchi E, Modorati G, Pontikaki I, Meroni PL, Gerloni V. Long-term treatment with golimumab for severe uveitis. Ocul Immunol Inflamm. 2014;22(2):90–5.
87. Angeles-Han S, Flynn T, Lehman T. Abatacept for refractory juvenile idiopathic arthritis-associated uveitis—a case report. J Rheumatol. 2008;35(9):1897–8.
88. Kenawy N, Cleary G, Mewar D, Beare N, Chandna A, Pearce I. Abatacept: a potential therapy in refractory cases of juvenile idiopathic arthritis-associated uveitis. Graefe's Arch Clin Exp Ophthalmol = Albrecht Von Graefes Arch Klin Exp Ophthalmol. 2011;249(2):297–300.
89. Marrani E, Paganelli V, de Libero C, Cimaz R, Simonini G. Long-term efficacy of abatacept in pediatric patients with idiopathic uveitis: a case series. Graefe's Arch Clin Exp Ophthalmol = Albrecht Von Graefes Arch Klin Exp Ophthalmol. 2015;253(10):1813–6.
90. • Tappeiner C, Miserocchi E, Bodaghi B, Kotaniemi K, Mackensen F, Gerloni V, et al. Abatacept in the treatment of severe, longstanding, and refractory uveitis associated with juvenile idiopathic arthritis. J Rheumatol. 2015;42(4):706–11.
The au?thors provide data on the unsuccessful use of abatacept in a pediatric uveitis population.
91. Zulian F, Balzarin M, Falcini F, Martini G, Alessio M, Cimaz R, et al. Abatacept for severe anti-tumor necrosis factor alpha refractory juvenile idiopathic arthritis-related uveitis. Arthritis Care Res. 2010;62(6):821–5.
92. • Birolo C, Zannin ME, Arsenyeva S, Cimaz R, Miserocchi E, Dubko M, et al. Comparable efficacy of abatacept used as first-line or second-line biological agent for severe juvenile idiopathic arthritis-related uveitis. The Journal of rheumatology. 2016.
Interest?ing study that compares the use of abatacept as first line therapy vs. second-line therapy.
93. Lin P. Targeting interleukin-6 for noninfectious uveitis. Clin Ophthalmol (Auckland, NZ). 2015;9:1697–702.
94. Silpa-Archa S, Oray M, Preble JM, Foster CS. Outcome of tocilizumab treatment in refractory ocular inflammatory diseases. Acta Ophthalmol. 2016;94(6):e400–6.
95. Yoshimura T, Sonoda KH, Ohguro N, Ohsugi Y, Ishibashi T, Cua DJ, et al. Involvement of Th17 cells and the effect of anti-IL-6 therapy in autoimmune uveitis. Rheumatol (Oxford, England). 2009;48(4):347–54.
96. •• Tappeiner C, Heinz C, Ganser G, Heiligenhaus A. Is tocilizumab an effective option for treatment of refractory uveitis associated with juvenile idiopathic arthritis? J Rheumatol. 2012;39(6):1294–5.
This is?an important study that reports on tocilizumab as treatment for refractory uveitis.
97. Tappeiner C, Mesquida M, Adan A, Anton J, Ramanan AV, Carreno E, et al. Evidence for tocilizumab as a treatment option in refractory uveitis associated with juvenile idiopathic arthritis. The Journal of rheumatology. 2016.
98. Tsang AC, Roth J, Gottlieb C. Tocilizumab for severe chronic anterior uveitis associated with juvenile idiopathic arthritis in a pediatric patient. Ocul Immunol Inflamm. 2014;22(2):155–7.
99. •• Calvo-Rio V, Santos-Gomez M, Calvo I, Gonzalez-Fernandez MI, Lopez Montesinos B, Mesquida M, et al. Anti-IL6-R Tocilizumab for severe juvenile idiopathic arthritis-associated uveitis refractory to anti-TNF therapy. A multicenter study of 25 patients. Arthritis & rheumatology (Hoboken, NJ). 2016.
This is?another study that reports on tocilizumb as an emerging therapy for refractory pediatric uveitis.
100. •• Miserocchi E, Pontikaki I, Modorati G, Gattinara M, Meroni PL, Gerloni V. Anti-CD 20 monoclonal antibody (rituximab) treatment for inflammatory ocular diseases. Autoimmun Rev. 2011;11(1):35–9.
This is an? important article that describes the use of rituximab for pediatric uveitis.
101. Lerman MA, Rabinovich CE. The future is now: biologics for non-infectious pediatric anterior uveitis. Paediatr Drugs. 2015;17(4):283–301.
102. Freidlin J, Wong IG, Acharya N. Rituximab treatment for peripheral ulcerative keratitis associated with Wegener's granulomatosis. Br J Ophthalmol. 2007;91(10):1414.
103. Cheung CM, Murray PI, Savage CO. Successful treatment of Wegener's granulomatosis associated scleritis with rituximab. Br J Ophthalmol. 2005;89(11):1542.
104. Umran RM, Shukur ZY. Rituximab for sight-threatening refractory pediatric Vogt-Koyanagi-Harada disease. Modern rheumatology. 2015:1–3.
105. Caso F, Rigante D, Vitale A, Costa L, Bascherini V, Latronico E, et al. Long-lasting uveitis remission and hearing loss recovery after rituximab in Vogt-Koyanagi-Harada disease. Clin Rheumatol. 2015;34(10):1817–20.
106. Miserocchi E, Modorati G, Berchicci L, Pontikaki I, Meroni P, Gerloni V. Long-term treatment with rituximab in severe juvenile idiopathic arthritis-associated uveitis. Br J Ophthalmol. 2016;100(6):782–6.
107. Heiligenhaus A, Miserocchi E, Heinz C, Gerloni V, Kotaniemi K. Treatment of severe uveitis associated with juvenile idiopathic arthritis with anti-CD20 monoclonal antibody (rituximab). Rheumatol (Oxford, England). 2011;50(8):1390–4.
108. Kalinina Ayuso V, de Boer JH, Byers HL, Coulton GR, Dekkers J, de Visser L, et al. Intraocular biomarker

identification in uveitis associated with juvenile idiopathic arthritis. Invest Ophthalmol Vis Sci. 2013;54(5):3709–20.
109. Haasnoot AJ, van Tent-Hoeve M, Wulffraat NM, Schalij-Delfos NE, Los LI, Armbrust W, et al. Erythrocyte sedimentation rate as baseline predictor for the development of uveitis in children with juvenile idiopathic arthritis. Am J Ophthalmol. 2015;159(2):372–7.e1.
110. Kalinina Ayuso V, van Dijk MR, de Boer JH. Infiltration of plasma cells in the iris of children with ANA-positive anterior uveitis. Invest Ophthalmol Vis Sci. 2015;56(11):6770–8.
111. Godfrey WA, Lindsley CB, Cuppage FE. Localization of IgM in plasma cells in the iris of a patient with iridocyclitis and juvenile rheumatoid arthritis. Arthritis Rheum. 1981;24(9):1195–8.
112. Parikh JG, Tawansy KA, Rao NA. Immunohistochemical study of chronic nongranulomatous anterior uveitis in juvenile idiopathic arthritis. Ophthalmology. 2008;115(10):1833–6.
113. Sabates R, Smith T, Apple D. Ocular histopathology in juvenile rheumatoid arthritis. Ann Ophthalmol. 1979;11(5):733–7.
114. Walscheid K, Heiligenhaus A, Holzinger D, Roth J, Heinz C, Tappeiner C, et al. Elevated S100A8/A9 and S100A12 serum levels reflect intraocular inflammation in juvenile idiopathic arthritis-associated uveitis: results from a pilot study. Invest Ophthalmol Vis Sci. 2015;56(13):7653–60.
115. Haasnoot AM, Kuiper JJ, Hiddingh S, Schellekens PA, de Jager W, Imhof SM, et al. Ocular fluid analysis in children reveals interleukin-29/interferon-lambda1 as a biomarker for juvenile idiopathic arthritis-associated uveitis. Arthritis Rheumatol (Hoboken, NJ). 2016;68(7):1769–79.
116. Schmeling H, Mahler M, Levy DM, Moore K, Stevens AM, Wick J, et al. Autoantibodies to dense fine speckles in pediatric diseases and controls. J Rheumatol. 2015;42(12):2419–26.
117. Nordal EB, Songstad NT, Berntson L, Moen T, Straume B, Rygg M. Biomarkers of chronic uveitis in juvenile idiopathic arthritis: predictive value of antihistone antibodies and antinuclear antibodies. J Rheumatol. 2009;36(8):1737–43.
118. Sijssens KM, Rijkers GT, Rothova A, Stilma JS, de Boer JH. Distinct cytokine patterns in the aqueous humor of children, adolescents and adults with uveitis. Ocul Immunol Inflamm. 2008;16(5):211–6.
119. Velez G, Roybal CN, Colgan D, Tsang SH, Bassuk AG, Mahajan VB. Precision medicine: personalized proteomics for the diagnosis and treatment of idiopathic inflammatory disease. JAMA Ophthalmol. 2016;134(4):444–8.
120. Nekhai, S, Hynes, A, Ammosova, T, Obukhov, Y, Gaidar, E, Kononov, A, et.al. Hierarchical clustering methodology for exploration of proteomic profile in tears: seeking for markers of uveitis associated with juvenile idiopathic arthritis [abstract]. Arthritis & Rheumatol, 2014; 66: S168.
121. Angeles-Han S, Duong D, Yeh S, Patel P, Jenkins K, Prahalad S, Holland G. Identification of biomarkers using tear proteomics in children with chronic anterior uveitis [abstract]. Arthritis Rheumatol. 2016; 68 (suppl 10)

Graefe's Archive for Clinical and Experimental Ophthalmology (2024) 262:2601–2615
https://doi.org/10.1007/s00417-024-06422-z

INFLAMMATORY DISORDERS

Epidemiology, clinical features, and classification of 3,404 patients with uveitis: Colombian Uveitis Multicenter Study (COL-UVEA)

Alejandra de-la-Torre[1] · Germán Mejía-Salgado[1] · Carlos Cifuentes-González[1] · William Rojas-Carabali[1] · Miguel Cuevas[2] · Sandra García[3] · Carlos M. Rangel[4] · Claudia Durán[5] · Diana Isabel Pachón-Suárez[1] · Andrés Bustamante-Arias[6]

Received: 28 November 2023 / Revised: 9 February 2024 / Accepted: 17 February 2024 / Published online: 6 March 2024
© The Author(s) 2024

Abstract

Purpose To describe the epidemiology, clinical features, and classification of uveitis in a large cohort of Colombian patients.

Methods Data were collected from seven ophthalmological referral centers in the four main cities in Colombia. The study included patients with a confirmed diagnosis of uveitis from January 2010 to December 2022. Information on demographics, ophthalmic examination findings, uveitis classification, and etiology was recorded.

Results The study reviewed 3,404 clinical records of patients with uveitis. The mean age at diagnosis was 41.1 (SD 19.0) years, and 54.2% of the patients were female. Overall, 1,341(39.4%) were infectious, 626 (18.4%) non-infectious, and four masquerade syndromes (0.1%). The most common types of uveitis were unilateral (66.7%), acute (48.3%), and non-granulomatous (83%). Anterior uveitis was the most common anatomical localization (49.5%), followed by posterior uveitis (22.9%), panuveitis (22.3%), and intermediate uveitis (5.2%). A diagnosis was established in 3,252 (95.5%) cases; idiopathic was the most common cause (27.7%), followed by toxoplasmosis (25.3%) and virus-associated uveitis (6.4%). The age group between 30 and 50 exhibited the highest frequency of uveitis.

Conclusion This multicenter study comprehensively describes uveitis characteristics in Colombian patients, providing valuable insights into its demographic and clinical features. The study findings emphasize the need to continue updating the changing patterns of uveitis to improve diagnosis and treatment strategies for diseases associated with intraocular inflammation.

Keywords Uveitis · Classification · Epidemiology · Colombia · Toxoplasmosis

Key messages

What is known:

- Uveitis exhibits specific clinical and demographic characteristics concerning geographic location, ethnicity, age group, and sex.
- Epidemiological data in South America is scarce.

What is new?

- This is the first multicenter study conducted in South America, providing a detailed and representative analysis of this population's uveitis distribution and clinical features.
- Infectious uveitis is the most common etiology in Colombia, a South American country, with ocular toxoplasmosis as the most frequent cause. However, compared to previous studies, an increase in noninfectious conditions was observed.

✉ Alejandra de-la-Torre
alejadelatorre@yahoo.com

Extended author information available on the last page of the article

Introduction

The term "uveitis" encompasses several diseases characterized by intraocular inflammation. It can be infectious or noninfectious, including autoimmune, autoinflammatory, traumatic, post-surgical, drug-induced, and idiopathic. Each type of uveitis has particular demographic and clinical characteristics, but in general, they predominantly affect people of working age, generating a significant economic burden [1–3].

Uveitis prevalence oscillates from 36.2 to 730 per 100,000 inhabitants, and its incidence ranges from 17 to 52.4 per 100,000 inhabitants [4]. These values vary according to the region and the study design that informs them. Similarly, global epidemiological patterns vary due to the influence of several factors, such as environmental, socioeconomic, and epigenetic elements, contributing to different etiologies' prevalence in each region [5–8].

In Colombia, Polania et al. presented the demographic and clinical characteristics of 489 uveitis patients, indicating a notable transition from infectious to immune-mediated etiologies in the last few years as the leading cause of uveitis in the country's capital city [9]. However, data was collected from a single center and may only partially represent the broader reality. Therefore, this multicenter study aims to describe the epidemiology, clinical features, and classification of uveitis in a large cohort of Colombian patients from diverse cities nationwide.

Methods

Study design Multicenter cross-sectional study. It adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Ethics consideration The Ethics Committee of Universidad del Rosario approved this study. In addition, this study follows the ethical principles for human research established by the Helsinki Declaration, the Belmont Report, and Colombian Resolution 008430 of 1993.

Data source and study population We collected data from seven ophthalmological referral centers across four major cities (Bogotá, Cali, Medellín, and Bucaramanga) and spanning approximately 20 departments within Colombia. The data collection period was extended from January 2010 to December 2022. To ensure the privacy and confidentiality of the patients, all clinical information was procured using a unique identification code, thereby maintaining anonymity. Collected data include demographic details, medical history, specific etiological diagnosis (non-infectious, infectious, undetermined, and idiopathic), visual acuity, uveitis localization, onset, duration, clinical course, and ocular complications (cataract, uveitic glaucoma, macular edema, epiretinal membrane, vitreous hemorrhage, and retinal detachment, among others). Demographic data were primarily acquired during the initial patient visit by administering a questionnaire about uveitis risk factors and systemic symptoms supplemented with a comprehensive physical examination. Ocular findings were collected at the first consultation.

Co-investigators trained in data entry and management were responsible for filling the database to ensure consistency and reliability. Furthermore, two investigators independently verified the accuracy and completeness of the data. Uveitis patients with incomplete or inconsistent data or who were exclusively diagnosed with conditions such as keratitis, optic neuritis, and scleritis were excluded from the dataset ($n=92$).

Ophthalmological assessment Best-corrected visual acuity (BCVA) was measured with Snellen charts, and the values were converted to logarithms of minimal angle of resolution equivalent units (logMAR) for statistical calculations. All patients underwent a comprehensive evaluation by a uveitis specialist, including slit lamp biomicroscopy, intraocular pressure, and dilated fundus examination. Furthermore, clinical data, such as the time of initial uveitis diagnosis, the frequency of uveitis episodes, and laterality, were documented.

Uveitis definition Uveitis and anterior chamber grading classification were determined using the Standardization of Uveitis Nomenclature (SUN) criteria [10]. Vitreous haze was graded according to the National Eye Institute system with binocular indirect ophthalmoscopy [11].

Diagnosing systemic disease associated with uveitis was established in a multidisciplinary approach with other medical specialists, including internal medicine, rheumatologists, infectious diseases specialists, and pediatricians. The condition that was the most prominent or more likely related to uveitis was regarded as the primary diagnosis whenever two or more systemic diseases occurred concurrently with uveitis. The diagnosis of *ocular sarcoidosis* was made according to the SUN 2021 revised criteria [12] and the International Workshop on Ocular Sarcoidosis [13]. A chest X-ray was used as the screening tool for chest imaging; computed tomography scanning was used in cases of equivocal chest radiographs or cases with high suspicion of other grounds. Additionally, in instances where sarcoidosis was highly suspected, yet imaging results were inconclusive, it was ruled out using serological tests like Angiotensin-Converting Enzyme levels [14, 15].

Diagnosis of *Blau syndrome* was confirmed by NOD2 mutation [16]. The criteria for a diagnosis of *presumed ocular tuberculosis* included the identification of a tuberculous etiology by Quantiferon Gold TB positivity or Mantoux tuberculin skin test, having or not having abnormalities on chest X-ray, exclusion of other possible causes of uveitis and response to anti-tuberculosis treatment [17]. The diagnosis of the other systemic diseases was determined using the internationally standardized criteria for each disease.

Traumatic iritis was defined as inflammatory cells or flare in the anterior chamber in a patient with recent trauma and in whom infectious and non-infectious uveitis was ruled out. Lens-induced uveitis was defined as an immune reaction to lens material. Moreover, Idiopathic Persistent Iritis after cataract surgery (IPICS) was defined as a transient, non-infectious inflammatory response in the eye that occurs after surgical procedures [18].

Regarding viral uveitis, an initial panel of serology tests was conducted, which included screening for antibodies against Herpes simplex, Herpes zoster, and Cytomegalovirus. When available, patients with atypical presentations underwent aqueous-vitreous humor sampling and a Polymerase Chain Reaction (PCR) [19, 20]. A diagnosis of confirmed virus-associated uveitis was established if a positive result was obtained in PCR. In contrast, in cases where the diagnosis relied only on clinical features and response to antiviral therapy, it was categorized as suspected viral virus-associated uveitis. Furthermore, the diagnosis of ocular toxoplasmosis was made based on clinical criteria, which included positive anti-Toxoplasma IgG and/or IgM test results with an active creamy-white focal retinal lesion with/without hyperpigmented retinochoroidal scars [21].

In cases where an etiology could not be discovered due to a lack of follow-up of the patients, without having ruled out all possible diagnoses, it was considered undetermined. Idiopathic etiology was reserved for cases where the diagnosis could not be determined after ruling out infectious and noninfectious causes of uveitis. It is important to note that while 'Pars planitis' falls under the umbrella of idiopathic conditions, this term was exclusively applied to cases characterized by non-infectious intermediate uveitis accompanied with vitritis and either inferior vitreous inflammatory condensates (“snowballs”) or pars plana “snowbanks”, unassociated with a systemic disease [22].

Uveitis diagnoses were categorized into five groups for analytical clarity and precision. These groups include infectious, non-infectious (encompassing autoimmune, autoinflammatory, and mixed etiologies as delineated by McGonagle and McDermott) [23], masquerade syndromes, idiopathic, and undetermined. Additionally, the category labeled 'others' includes specific etiologies such as traumatic iritis, IPICS, lens-induced uveitis, and drug-induced uveitis.

Statistical analysis

For the univariate analysis, the continuous variables were reported as mean and standard deviation (SD) or median and interquartile range (IQR) (25th–75th percentile) depending on its distribution, for categorical variables as relative and absolute frequencies and percentages. All the analyses were done using Jamovi (Version 2.3).

Results

From 3,496 clinical records, we included 3,404 patients diagnosed with uveitis, of which 54.2% (n = 1,847) were female. The mean age at onset was 35.7 years, ranging from 1 to 96 years. Overall, 1,341(39.4%) were infectious, 626 (18.4%) non-infectious, and four masquerade syndromes (0.1%). Bilateral involvement was observed in 33% of cases (n = 1,124), while 66.7% (n = 2,270) presented with unilateral compromise. Table 1, Figs. 1 and 2 show a summary of the demographic information of the included patients.

In general, anterior uveitis was the most common localization (n = 1,687, 49.5%), followed by posterior uveitis (n = 780, 22.9%), panuveitis (n = 759, 22.3%), and intermediate uveitis (n = 178, 5.2%), as evidenced in Table 2. Both anterior and posterior uveitis more frequently presented with an acute course (50.9% and 57.9%, respectively), while intermediate uveitis and panuveitis showed a chronic course in most cases. Of all the anatomical localizations, panuveitis exhibited the highest incidence of complications, including cataracts (n = 256, 33.7%), retinal detachment (n = 138, 18.2%), and macular edema (n = 125, 16.5%). For a more comprehensive overview, please refer to Table 2.

A specific diagnosis was achieved in 3,252 (95.5%) cases. In 152 (4.5%) of the patients, the cause could not be determined (undetermined uveitis). Overall, idiopathic was the most common cause with 944 patients (27.7%), followed by toxoplasmosis with 858 cases (25.3%) and virus-associated anterior uveitis with 217 cases (6.4%). Regarding gender distribution, females were more commonly affected by idiopathic uveitis than men (60.6% vs 39.4%). On the contrary, men showed a higher prevalence of HLA-B27-associated acute anterior uveitis, accounting for 55.8% compared to 44.2% in women. There was a nearly equal distribution between the sexes for toxoplasmosis, with 433 cases (50.5%) in women and 425 cases (49.5%) in men. (Table 3).

In patients diagnosed with anterior uveitis, idiopathic was the most prevalent cause (n = 684, 40.8%), followed by virus-associated anterior uveitis (11.9%) (Table 4). On the other hand, in patients with intermediate uveitis, pars planitis remained the leading etiology (n = 130, 73%). In posterior uveitis and panuveitis cases, toxoplasmosis was

Table 1 Demographic characteristics of patients with uveitis in Colombia

Demographics	Anterior	Intermediate	Posterior	Panuveitis	Total
Age (years) mean ± SD					
At consultation	50.2 ± 17.8	33.5 ± 20.1	38.1 ± 19.5	42.7 ± 18.7	41.1 ± 19.0
At onset	46.2 ± 18.6	29.9 ± 20.8	29.4 ± 20.4	37.4 ± 18.7	35.7 ± 19.6
Gender *n* (%)					
Female	935 (50.6)	98 (5.4)	404 (21.9)	410 (22.2)	1,847 (54.2)
Male	752 (48.6)	78 (5.0)	373 (24.1)	345 (22.3)	1,548 (45.5)
Missing data	0	2 (22.2)	3 (33.3)	4 (44.4)	9 (0.2)
City of Origin *n* (%)					
Bogotá	578 (38.0)	69 (4.5)	452 (29.7)	422 (27.7)	1,521 (44.7)
Bucaramanga	106 (66.7)	0 (0.0)	23 (14.5)	30 (18.9)	159 (4.7)
Cali	697 (58.8)	58 (4.9)	201 (16.9)	230 (19.4)	1,186 (34.8)
Medellín	306 (56.9)	51 (9.5)	104 (19.3)	77 (14.3)	538 (15.8)
Etiology					
Infectious	339 (25.3)	19 (1.4)	634 (47.3)	349 (26.0)	1,341 (39.4)
Non-infectious	411 (65.7)	23 (3.7)	30 (4.8)	162 (25.8)	626 (18.4)
Masquerade	0 (0)	0 (0)	1 (25.0)	3 (75.0)	4 (0.11)
Idiopathic	684 (63.7)	123 (11.5)	77 (7.2)	190 (1.8)	1,074 (31.6)
Undetermined	89 (58.6)	8 (5.3)	18 (11.8)	37 (24.3)	152 (4.5)
Others	152 (80.4)	3 (1.6)	18 (9.5)	16 (8.5)	189 (5.6)
Missing data	12 (66.6)	2 (11.1)	2 (11.1)	2 (11.1)	18 (0.5)
Total *n* (%)	1,687 (49.6)	178 (5.2)	780 (22.9)	759 (22.3)	3,404 (100.0)

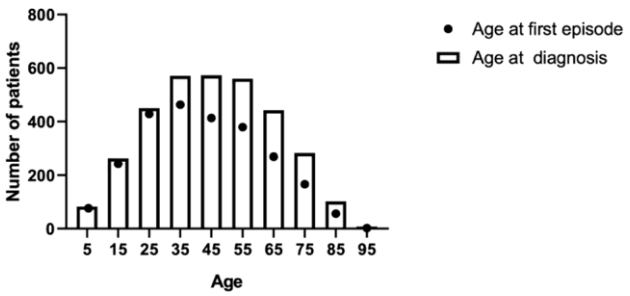


Fig. 1 Age distribution of the patients with uveitis in Colombia

the most prevalent cause (*n* = 548, 70.3%, and *n* = 266, 35%, respectively) (Table 4).

The age group between 30 and 50 years exhibited the highest prevalence of uveitis, regardless of uveitis localization. In the younger population (< 20 years), posterior uveitis was the most common localization, ranging from 35.5% to 44.6%. Conversely, among individuals over 60 years, anterior uveitis emerged as the most prevalent anatomical localization, ranging from 60.7% to 68.8%. Regarding specific diagnoses, toxoplasmosis was the most frequent in individuals under 40 (26.5% to 44%), while idiopathic cases were more common in those over 40 (29.1% to 49.1%). For detailed data, please refer to Tables 5, 6.

Discussion

In Colombia, two prior studies have focused on the epidemiology of uveitis. The first was conducted in 2009, encompassing 693 patients from two centers in Bogotá [24]. The second was conducted in 2023 by Polania et al., evaluating 489 patients from a single private center in Bogotá [9]. In the current study, patients from the Polania et al. study were incorporated and combined with six other referral centers from various Colombian cities.

In accordance with prior literature, the demographic group most significantly affected is working-age individuals [25, 26]. The mean age at uveitis diagnosis in our study population was 41.1 years, closely mirroring the findings of a previous single-center report [9]. However, a notable divergence exists in the mean duration between symptom onset and diagnosis, with the current study reporting 5.4 years compared to the previous report's 3.7 years. This discrepancy is concerning, given the substantial burden that delayed treatment initiation can impose in cases of uveitis.

The significant delay between the onset of uveitis symptoms and its diagnosis in Colombia may be attributed to the scarcity of uveitis specialists in the country. This leads to initial referrals of uveitis patients to general ophthalmologists or retina specialists, ultimately resulting in delayed diagnosis

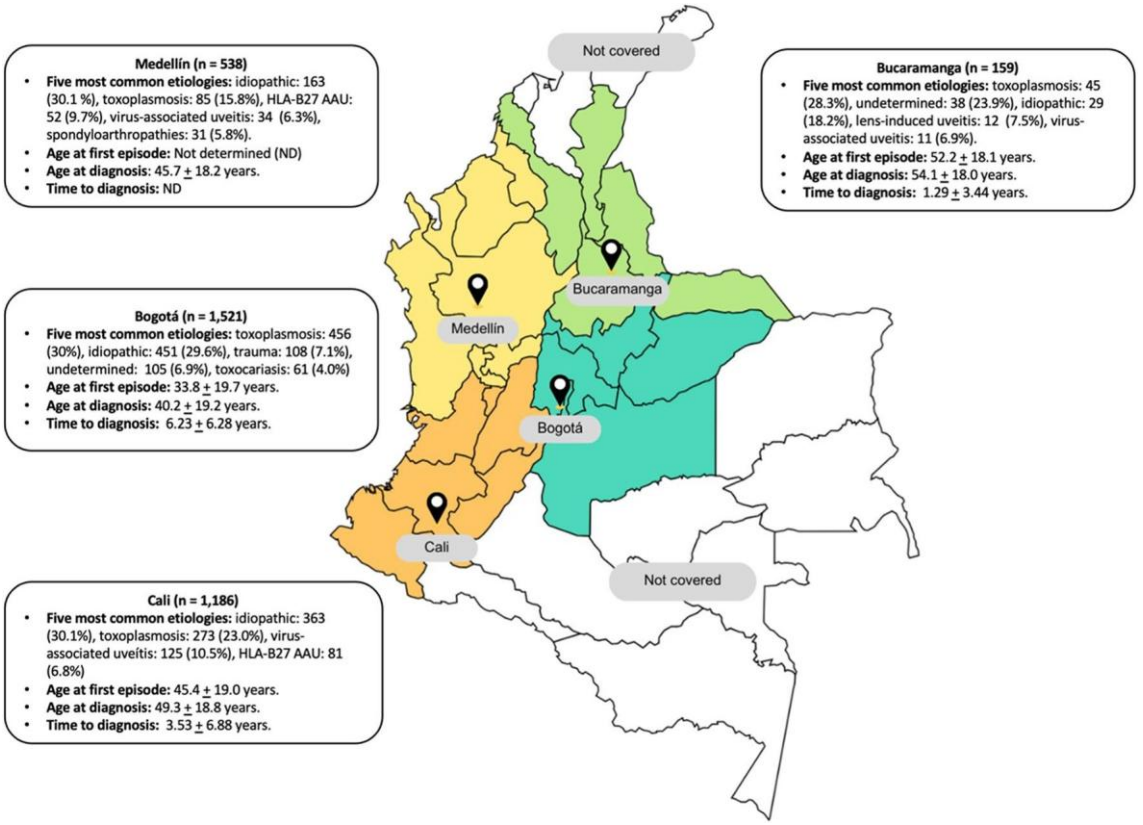


Fig. 2 Most common etiologies and ages of onset and diagnosis among the geographical areas covered. Colombian geographical map is divided by departments; yellow represents the areas covered by Medellín centers, orange areas covered by Cali's centers, green areas covered by Bucaramanga's centers, and aquamarine areas covered by Bogotá centers. Departments in white are areas where these centers usually do not have coverage. Distribution of main etiologies of uveitis across the different regions

and treatment. The frequency of complications related to anatomical localization of uveitis is presented in Table 2.

Regional differences were observed in the time from the initial uveitis presentation to diagnosis. Cali reported an average diagnosis time of 3.53 ± 6.88 years, while Bucaramanga had a lower average of 1.29 ± 3.44 years. Conversely, Bogotá exhibited a considerably a higher diagnosis time of 6.23 ± 6.28 years. This divergence can be attributed to the fact that Bogotá is the most populated city, where the waiting time to be attended could be longer due to high demand and low number of specialists [27].

Although Polania et al. found a higher incidence of uveitis among females [9], the present study shows similar proportions between males and females, similar to what other studies have reported [28]. Including more centers in this study contributes to the heightened representability of uveitis characteristics, which could account for the observed sex differences [29, 30]. Specifically, our study found a higher occurrence of idiopathic uveitis in females (60%). This observation suggests a potential link to the hypothesis that idiopathic uveitis may be influenced by underlying non-infectious conditions and the role of female hormones in stimulating autoimmune responses where inflammation plays a vital role [31]. However, further comprehensive research is essential to fully understand and substantiate these associations.

In the 2009 study, the prevailing characteristics of uveitis included a predominance of unilateral cases (73.4%), an acute clinical course (68.3%), and a non-granulomatous nature (90.6%) [24]. In contrast, Polania et al. in 2023 reported a shift with a higher prevalence of bilateral involvement (52.8%), recurrent presentations (47.6%), and a persistent non-granulomatous pattern (90.8%) [9]. In the current study, the most frequently encountered type of uveitis remains unilateral (66.7%), presenting acutely (48.3%) and maintaining a non-granulomatous nature (83.0%). These consistent features are typically associated with idiopathic uveitis, which emerged as the most prevalent etiology in our study.

Regarding the specific diagnoses, idiopathic uveitis emerged as the most prevalent cause, with toxoplasmosis occupying the second position and virus-associated uveitis

Table 2 Characteristics of uveitis in the Colombian population divided by anatomical site of inflammation

Characteristics	Anterior $N=1,687$	Intermediate $N=178$	Posterior $N=780$	Panuveitis $N=759$	Total $N=3,404$
Ocular involvement (%)					
Unilateral	1,184 (70.2)	68 (38.2)	569 (72.9)	449 (59.2)	2,270 (66.7)
Bilateral	502 (29.8)	108 (60.7)	208 (26.7)	306 (40.3)	1,124 (33.0)
Missing data	1 (0.1)	2 (1.1)	3 (0.4)	4 (0.5)	10 (0.2)
Course					
Acute	859 (50.9)	55 (30.9)	452 (57.9)	275 (36.2)	1,641 (48.3)
Chronic	421 (25.0)	83 (46.6)	192 (24.6)	329 (43.3)	1,025 (30.1)
Recurrent	400 (23.7)	35 (19.7)	124 (15.9)	146 (19.2)	705 (20.7)
Missing data	7 (0.4)	5 (2.8)	12 (1.5)	9 (1.2)	33 (0.9)
Type of Inflammation					
Non-granulomatous	1,485 (88.0)	150 (84.3)	638 (81.8)	546 (71.9)	2,819 (83.0)
Granulomatous	186 (11.0)	25 (14.0)	130 (16.7)	201 (26.5)	542 (15.9)
Missing data	16 (0.9)	3 (1.7)	12 (1.5)	12 (1.5)	43 (1.2)
Complications at consultation					
Cataract	293 (17.3)	41 (23.0)	77 (9.9)	256 (33.7)	667 (19.7)
Glaucoma	165 (9.8)	14 (7.9)	24 (3.1)	101 (13.3)	304 (9.0)
Macular edema	75 (4.4)	28 (15.7)	35 (4.5)	125 (16.5)	263 (7.8)
Epiretinal membrane	38 (2.3)	17 (9.6)	43 (5.5)	72 (9.5)	170 (5.0)
Vitreous hemorrhage	13 (0.8)	6 (3.4)	21 (2.7)	40 (5.3)	80 (2.4)
Retinal detachment	18 (1.1)	15 (8.4)	64 (8.2)	138 (18.2)	235 (6.9)
Band keratopathy	23 (1.4)	11 (6.2)	4 (0.5)	37 (4.9)	75 (2.2)
Bullous keratopathy	16 (0.9)	3 (1.7)	1 (0.1)	18 (2.4)	38 (1.1)
BCVA (LogMAR)	0.67 ± 0.75	0.76 ± 0.81	1.09 ± 0.93	1.35 ± 1.04	0.96 ± 0.88

BCVA Best corrected visual acuity

ranking third. This pattern of idiopathic uveitis as the predominant etiology is consistent with findings from studies conducted in developed and developing countries [32–38]. This study reinforces the transition in the predominant causes of uveitis in Colombia from infectious to immune-mediated etiologies [9].

Ocular toxoplasmosis remains one of the major causes of uveitis in South America. This is expected due to the higher seroprevalence of *Toxoplasma gondii* in South American countries (45.2%) compared to other regions like Europe (30%) or Western Pacific (11.2%) [39]. Also, clinical presentation tends to be more severe than in other regions [40, 41]. In Colombia, 47.1% of the population have positive IgG titers against *Toxoplasma gondii* and 10.5% of the population have reticochoroidal scars [42]. A nationwide population-based study, found an increasing trend in toxoplasmosis incidence between 2015 and 2019 [43]. This highlights the importance of ongoing patient education about *Toxoplasma gondii* infection. In this context, adhering to practical clinical guidelines is crucial [44].

For anterior uveitis, idiopathic etiology remained the primary cause, followed by virus-related etiologies such as Herpes simplex or zoster and HLA-B27-associated uveitis. Other studies in Colombia similarly report idiopathic uveitis as the leading cause [9]. The higher prevalence of virus-related uveitis in the present study compared to the study conducted by Polania et al. in 2023 could be attributed to the multicenter nature of the current study. This study included several geographic regions, each with differing prevalence of viral diseases, potentially influencing the observed increase [45].

For posterior uveitis and panuveitis, toxoplasmosis remained the primary cause; numerous factors contribute to this, including the Colombian geographical localization in a tropical area with high rainfall (pluviosity) [46] and the presence of certain strains with virulence factors like rhoptry virulent-alleles of proteins (ROP) 16 and ROP 18 [40, 41].

Intermediate uveitis was the least common localization of uveitis, accounting for only 5.2% of the cases, and it was most frequently associated with an idiopathic etiology (pars planitis); this aligns with the typical pattern observed in intermediate uveitis epidemiological data [32, 33, 35–38, 47]. Some studies report diseases like sarcoidosis, multiple sclerosis, and intraocular lymphoma as possible causes of intermediate uveitis [25, 48]. Although these diseases were present in our cohort, they did not represent a significant number of intermediate uveitis [4]. Etiological diagnosis of intermediate uveitis varies between age groups. In children,

171

Table 3 Laterality and gender distribution of uveitis etiologies in Colombia

Diagnosis	*N* 3404	%	Affected eye		Gender distribution	
			Bilateral *n* (%)	Unilateral *n* (%)	Female *n* (%)	Male *n* (%)
Idiopathic	944	27.73	336 (35.5)	607 (64.3)	572 (60.6)	372 (39.4)
Toxoplasmosis	858	25.34	179 (20.9)	679 (79.1)	433 (50.5)	425 (49.5)
Virus-associated uveitis (confirmed)	217	6.41	18 (8.3)	199 (91.7)	111 (51.2)	106 (48.8)
HLA-B27 Associated Acute Anterior Uveitis	165	4.87	67 (40.6)	98 (59.4)	73 (44.2)	92 (55.8)
Undetermined	152	4.5	48 (31.6)	11 (73.0)	87 (57.2)	72 (47.4)
Pars planitis	130	3.82	80 (61.5)	50 (38.4)	74 (56.9)	56 (43.1)
Traumatic iritis	114	3.37	1 (0.9)	113 (99.1)	21 (18.4)	93 (81.6)
Spondyloarthropathies	83	2.42	39 (47.0)	44 (53.0)	39 (47.0)	44 (53.0)
VKH	73	2.16	0	73 (100.0)	60 (82.2)	13 (17.8)
Toxocariasis	72	2.13	6 (8.3)	66 (91.7)	39 (54.2)	33 (45.8)
Undifferentiated autoinflammatory disease	67	1.98	42 (62.7)	25 (37.3)	42 (62.7)	25 (37.3)
Fuchs uveitis syndrome	52	1.54	14 (26.9)	38 (73.1)	31 (59.6)	21 (40.4)
Rheumatoid arthritis	44	1.30	24 (54.5)	20 (45.5)	37 (84.1)	7 (15.9)
Lens induced uveitis	39	1.15	6 (15.4)	33 (84.6)	19 (48.7)	20 (51.3)
Juvenile Idiopathic Arthritis	37	1.09	29 (78.4)	8 (21.6)	26 (70.3)	11 (29.7)
Syphilis	28	0.83	9 (32.1)	19 (67.9)	15 (53.6)	13 (46.4)
Cytomegalovirus – posterior segment infection	21	0.6	9 (42.9)	12 (57.1)	3 (14.3)	18 (85.7)
Presumed Ocular Tuberculosis	21	0.62	16 (76.2)	5 (23.8)	10 (47.6)	11 (52.4)
Granulomatous polyangiitis	19	0.56	5 (26.3)	14 (73.7)	11 (57.9)	8 (41.0)
SLE	15	0.44	8 (53.3)	7 (46.7)	14 (93.3)	1 (7.7)
Retinitis pigmentosa	15	0.44	13 (86.7)	2 (13.3)	6 (40.0)	9 (60.0)
Sarcoidosis (presumed)	15	0.44	13 (86.7)	2 (13.3)	12 (80.0)	3 (20.0)
Sarcoidosis (definite)	13	0.38	11 (84.6)	2 (15.4)	11 (84.6)	2 (15.4)
Drug-induced uveitis	13	0.38	4 (30.8)	9 (69.2)	13 (100.0)	0
HIV associated	13	0.38	7 (53.8)	6 (46.2)	2 (15.4)	11 (84.6)
Sjögren syndrome	13	0.38	5 (38.5)	8 (61.5)	11 (84.6)	2 (15.4)
Posner-Schlossman Syndrome	12	0.35	3 (25.0)	9 (75.0)	5 (41.7)	7 (58.3)
Behçet's disease	9	0.27	6 (66.7)	3 (33.3)	4 (44.4)	5 (55.6)
Endophthalmitis (acute)	9	0.27	1 (11.1)	8 (88.9)	4 (44.4)	5 (55.6)
Serpiginous Choroidopathy	9	0.24	7 (77.8)	2 (22.2)	4 (44.4)	5 (55.6)
Sympathetic ophthalmia	9	0.27	0	9 (100.0)	5 (55.6)	4 (44.4)
Ulcerative colitis	9	0.27	5 (55.6)	4 (44.4)	6 (66.7)	3 (33.3)
Multiple sclerosis	8	0.24	5 (62.5)	3 (37.5)	6 (75.0)	2 (25.0)
Virus-associated uveitis (suspected)	7	0.21	1 (14.3)	6 (85.7)	3 (42.9)	4 (57.1)
IPICS	6	0.17	1 (16.6%)	5 (83.3)	2 (33.3)	4 (66.6)
Immune recovery uveitis	5	0.15	2 (40.0)	3 (60.0)	2 (40.0)	3 (60.0)
Eales' disease	4	0.12	2 (50.0)	2 (50.0)	2 (50.0)	2 (50.0)
TINU	4	0.12	3 (75.0)	1 (25.0)	3 (75.0)	1 (25.0)
Birdshot chorioretinopathy	3	0.09	3 (100.0)	0	2 (66.7)	1 (33.3)
Cytomegalovirus – anterior segment infection	3	(0.09)	0	3 (100.0)	1 (33.3)	2 (66.7)
Endophthalmitis (chronic)	3	0.09	1 (33.3)	2 (66.7)	3 (100.0)	0
Histoplasmosis suspected	3	0.09	2 (66.7)	1 (33.3)	1 (33.3)	2 (66.7)
Idiopathic multifocal choroiditis	3	0.09	3 (100.0)	0	2 (66.7)	1 (33.3)
MEWDS	3	0.06	2 (66.7)	1 (33.3)	3 (100.0)	0
Primary intraocular lymphoma	3	0.09	2 (66.7)	1 (33.3)	1 (33.3)	2 (66.7)
Epstein Barr-Virus	2	0.06	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)
Multifocal Choroiditis and Panuveitis	2	0.06	2 (100.0)	0	1 (50.0)	1 (50.0)
Psoriasis	2	0.06	1 (50.0)	1 (50.0)	0	2 (100.0)

Table 3 (continued)

Diagnosis	*N* 3404	%	Affected eye		Gender distribution	
			Bilateral *n* (%)	Unilateral *n* (%)	Female *n* (%)	Male *n* (%)
Relapsing polychondritis	2	0.06	1 (50.0)	1 (50.0)	2 (100.0)	0
UGH syndrome	2	0.06	0	2 (100.0)	0	2 (100.0)
AZOOR	1	0.03	1 (100.0)	0	1 (100.0)	0
Blau syndrome	1	0.03	1 (100.0)	0	0	1 (100.0)
Brucellosis suspected	1	0.03	0	1 (100.0)	0	1 (100.0)
CREST Syndrome	1	0.03	0	1 (100.0)	1 (100.0)	0
Crohn's disease	1	0.03	1 (100.0)	0	1 (100.0)	0
Cryoglobulinemic vasculitis	1	0.03	0	1 (100.0)	1 (100.0)	0
Cysticercosis	1	0.03	0	1 (100.0)	0	1 (100.0)
IRVAN syndrome	1	0.03	1 (100.0)	0	0	1
Leptospirosis (confirmed)	1	0.03	0	1 (100.0)	0	1 (100.0)
Leptospirosis (suspected)	1	0.03	1 (100.0)	0	0	1 (100.0)
Reactive arthritis	1	0.03	0	1 (100.0)	0	1 (100.0)
Takayasu arteritis	1	0.03	1 (100.0)	0	1 (100.0)	0
Undifferentiated vasculitis	1	0.03	0	1 (100.0)	1 (100.0)	0

AZOOR Acute zonal occult outer retinopathy, *IPICS* idiopathic persistent iritis after cataract surgery, *SLE* Systemic lupus erythematosus, *MEWDS* Multiple evanescent white dot syndrome, *TINU syndrome* Tubulointerstitial nephritis and *uveitis syndrome*, *UGH Uveitis-Glaucoma-Hyphema* syndrome, *VKH* Vogt-Koyanagi-Harada disease

Pars planitis accounts for most of the cases; this was also observed in this study [49, 50]. Conversely, in older populations (> 70 years old), suspicion of other etiologies like Primary intraocular lymphoma (PIOL) must be considered; [51] the setting of molecular and pathological diagnosis greatly influences the rate of lymphoma detection, in this cohort, PIOL presents as posterior inflammation (1 case) or panuveitis (2 cases). However, we acknowledge the setting of molecular and pathological diagnosis greatly influences the rate of lymphoma detection [52].

Regarding regional variances, anterior uveitis prevailed as the primary localization in Bucaramanga, Cali, and Medellín, in line with global literature [53–55]. However, in Bogotá, posterior uveitis was the most frequently observed, accounting for 29.7% of cases. This divergence can be attributed to the specialization of one of the Bogotá centers in treating toxoplasmosis.

In patients under 16 years, posterior uveitis was the most frequent localization, a pattern attributed to toxoplasmosis being the primary etiology in this age group. As age increased, the frequency of anterior uveitis rose, reaching a peak in the age group between 40 and 60 years, after which it decreased. In the 2009 Colombian study, panuveitis was the most common localization in young and middle-aged adults (16–50 years) [24]. However, the study of Polanía et al. also evidences a change to anterior uveitis [9]. This may be attributed to an increase in idiopathic cases where anterior uveitis was the most common localization and a greater capacity to perform the test for HLA-B27 + identification.

In patients over 50 years old, anterior uveitis remained the predominant localization [9]. This could be associated with increased idiopathic cases and virus-associated uveitis, where anterior uveitis was more commonly observed. Specifically, the incidence of Herpes zoster ophthalmicus in Colombia increased from 0.85 to 1.35 per 100,000 persons between 2015 and 2019, with people over 50 most affected [45].

Compared with other multicenter, population-based studies worldwide, our findings align with the observation that working-age females are predominantly affected, especially for non-infectious conditions. In a study encompassing 3,000 patients in the UK, Jones identified a clear preference for the female gender in cases of Juvenile idiopathic arthritis-associated uveitis (78%), Punctate Inner Choroidopathy (76%), and Chronic Anterior Uveitis (62%) [56]. In our analysis, females significantly outnumbered males in conditions such as Multiple evanescent white dot syndrome (100%), Vogt-Koyanagi-Harada syndrome (82.2%), Multiple Sclerosis (75%), and idiopathic etiology (60%). Conversely, males showed a higher prevalence of trauma iritis (81.6%), IPICS (66%), and infectious causes like Human Immunodeficiency Virus (89.6%) and Acute Retinal Necrosis (78.8%). Different factors could contribute to these differences, including genetics, sex hormones, and social factors [57–59].

Anterior uveitis is the more prevalent localization in both the Western [53, 56] and Eastern world, [54, 55], with idiopathic etiology leading the list, trailed by

173

Table 4 Causes of uveitis according to the anatomical site of inflammation

Diagnosis	*N* (%)	Anterior *N* = 1, 687 (%)	Intermediate *N* = 178 (%)	Posterior *N* = 780 (%)	Panuveitis *N* = 759 (%)
Idiopathic	944 (27.73)	684 (40.8)	*	77 (9.9)	183 (24.1)
Toxoplasmosis	858 (25.34)	42 (2.5)	3 (1.7)	548 (70.3)	266 (35.0)
Virus-associated uveitis (confirmed)	217 (6.41)	199 (11.9)	3 (1.7)	0	15 (2.0)
HLA-B27 Associated Acute Anterior Uveitis	165 (4.87)	153 (9.1)	7 (3.9)	0	5
Undetermined	152 (4.5)	89 (58.6)	8 (5.3)	18 (11.8)	37 (24.3)
Pars planitis	130 (3.82)	0	130 (73.0)	0	7 (0.9)
Traumatic iritis	114 (3.37)	100 (5.9)	2 (1.1)	4 (0.5)	8 (1.1)
Spondyloarthropathies	83 (2.42)	73 (4.4)	1 (0.6)	0	9 (1.2)
VKH	73 (2.16)	4 (0.2)	1 (0.6)	5 (0.6)	63 (8.3)
Toxocariasis	72 (2.13)	2 (0.1)	3 (1.7)	55 (7.1)	12 (1.6)
Undifferentiated autoinflammatory disease	67 (1.98)	47 (2.8)	2 (1.1)	1 (0.1)	17 (2.2)
Fuchs uveitis syndrome	52 (1.54)	49 (2.9)	2 (1.1)	0	1 (0.1)
Rheumatoid arthritis	44 (1.30)	34 (2.0)	1 (0.6)	0	9 (1.2)
Lens induced uveitis	39 (1.15)	34 (2.0)	0	0	5
Juvenile Idiopathic Arthritis	37 (1.09)	26 (1.6)	2 (1.1)	1 (0.1)	8 (1.0)
Syphilis	28 (0.83)	8 (0.5)	3 (1.7)	5 (0.6)	12 (1.6)
Cytomegalovirus – posterior segment infection	21 (0.6)	0	0	13 (61.9)	8 (38.1)
Presumed Ocular Tuberculosis	21 (0.62)	5 (0.3)	4 (2.2)	2 (0.3)	10 (1.3)
Granulomatous polyangiitis	19 (0.56)	15 (0.9)	0	0	4 (0.5)
SLE	15 (0.44)	11	1 (0.6)	1 (0.1)	2 (0.3)
Retinitis pigmentosa	15 (0.44)	0	0	13 (1.7)	2 (0.3)
Sarcoidosis (presumed)	15 (0.44)	6 (0.4)	3 (1.7)	1 (0.1)	5 (0.7)
Sarcoidosis (definite)	13 (0.38)	1 (0.1)	2 (1.1)	0	10 (1.3)
Drug-induced uveitis	13 (0.38)	10 (0.6)	1 (0.6)	1 (0.1)	1 (0.1)
HIV associated	13 (0.38)	6 (0.4)	0	3 (0.4)	4
Sjögren syndrome	13 (0.38)	10 (0.6)	0	0	3 (0.4)
Posner-Schlossman Syndrome	12 (0.35)	12 (0.7)	0	0	0
Behçet's disease	9 (0.27)	5 (0.3)	0	1 (0.1)	3 (0.4)
Endophthalmitis (acute)	9 (0.27)	4 (0.2)	0	1 (0.1)	4 (0.5)
Serpiginous Choroidopathy	9 (0.24)	0	0	7	2 (0.3)
Sympathetic ophthalmia	9 (0.27)	0	0	2 (0.3)	7 (0.9)
Ulcerative colitis	9 (0.27)	9 (0.5)	0	0	0
Multiple sclerosis	8 (0.24)	2 (0.1)	2 (1.1)	2 (0.3)	2 (0.3)
Virus-associated uveitis (suspected)	7 (0.21)	5 (0.3)	0	0	2 (0.3)
IPICS	6 (0.17)	6 (0.3)	0	0	0
Immune recovery uveitis	5 (0.15)	3 (0.2)	1 (0.6)	0	1 (0.1)
Eales' disease	4 (0.12)	1 (0.1)	0	3 (0.4)	0
TINU	4 (0.12)	2 (0.1)	0	0	2 (0.3)
Birdshot chorioretinopathy	3 (0.09)	0	0	0	3 (0.4)
Cytomegalovirus – anterior segment infection	3 (0.09)	3 (0.2)	0	0	0
Endophthalmitis (chronic)	3 (0.09)	0	0	1 (0.1)	2 (0.3)
Histoplasmosis suspected	3 (0.09)	1 (0.1)	0	1 (0.1)	1 (0.1)
Idiopathic multifocal choroiditis	3 (0.09)	0	0	0	3 (0.4)
MEWDS	3 (0.06)	0	0	3 (0.4)	0
Primary intraocular lymphoma	3 (0.09)	0	0	1 (0.1)	2 (0.3)
Epstein Barr-Virus	2 (0.06)	0	0	0	2 (0.3)
Multifocal Choroiditis and Panuveitis	2 (0.06)	0	0	0	2 (0.3)
Psoriasis	2 (0.06)	0	0	1 (0.1)	1 (0.1)

Table 4 (continued)

Diagnosis	*N* (%)	Anterior *N* = 1,687 (%)	Intermediate *N* = 178 (%)	Posterior *N* = 780 (%)	Panuveitis *N* = 759 (%)
Relapsing polychondritis	2 (0.06)	2 (0.1)	0	0	0
UGH syndrome	2 (0.06)	2 (0.1)	0	0	0
AZOOR	1 (0.03)	0	0	1 (0.1)	0
Blau syndrome	1 (0.03)	0	0	0	1 (0.1)
Brucellosis suspected	1 (0.03)	1 (0.1)	0	0	0
CREST Syndrome	1 (0.03)	1 (0.1)	0	0	0
Crohn's disease	1 (0.03)	1 (0.1)	0	0	0
Cryoglobulinemic vasculitis	1 (0.03)	1 (0.1)	0	0	0
Cysticercosis	1 (0.03)	0	0	1 (0.1)	0
IRVAN syndrome	1 (0.03)	0	0	1 (0.1)	0
Leptospirosis (confirmed)	1 (0.03)	1 (0.1)	0	0	0
Leptospirosis (suspected)	1 (0.03)	0	1 (0.6)	0	0
Reactive arthritis	1 (0.03)	1 (0.1)	0	0	0
Undifferentiated vasculitis	1 (0.03)	1 (0.1)	0	0	0

AZOOR Acute zonal occult outer retinopathy, *IPICS* idiopathic persistent iritis after cataract surgery, *SLE* Systemic lupus erythematosus, *MEWDS* Multiple evanescent white dot syndrome, *TINU syndrome* Tubulointerstitial nephritis and *uveitis syndrome*, *UGH syndrome Uveitis-Glaucoma-Hyphema*-syndrome, *VKH* Vogt-Koyanagi-Harada disease, *HIV* Human immunodeficiency virus, *HLA-B27* Human leukocyte antigen B27 *see pars planitis

infectious and non-infectious [54]. However, distinct patterns emerge in certain developing countries. For instance, Brazil reported a deviation from this trend, with posterior uveitis accounting for most cases (43.1%); [26], although this was observed in 1,053 patients, they were all from a single center. Similarly, in Colombia, posterior uveitis was the most common localization decades ago [24]. Nevertheless, this study noted a recent increase in cases of anterior uveitis. This shift is explained by the increase in idiopathic cases, which were commonly anterior.

To rule out an infectious etiology is a pivotal step of uveitis diagnosis and treatment, then it is essential to know the main etiologies according to the geographical prevalence. In South America, toxoplasmosis remains the predominant infectious cause, with viral anterior uveitis following closely. This aligns with other South American countries where toxoplasmosis accounts for 24.03% of all uveitis cases [26]. However, it differs from Asian countries where ocular tuberculosis is more prevalent compared to our population (19.6% vs. 0.3%) [54]. Other infections, such as syphilis, although not the most common, must always be ruled out [55].

The main strength of this study is the multicenter methodology across different cities in Colombia, providing a comprehensive description of uveitis. Prior research has often relied on small samples from tertiary centers or focused solely on specific causes, limiting their

Table 5 Uveitis anatomical distribution regarding age groups

Age group	Anterior *N* = 1,687	Intermediate *N* = 178	Posterior *N* = 780	Panuveitis *N* = 759
0–9	12 (14.5)	12 (14.5)	37 (44.6)	22 (26.5)
10.-19	64 (24.2)	51 (19.2)	94 (35.5)	56 (21.1)
20–29	143 (31.8)	22 (4.9)	167 (37.1)	118 (26.2)
30–39	252 (43.9)	23 (4.0)	147 (25.6)	152 (26.5)
40–49	337 (56.4)	24 (4.2)	105 (18.2)	123 (21.3)
50–59	348 (59.8)	17 (3.0)	91 (16.1)	119 (21.1)
60–69	269 (60.7)	19 (4.3)	71 (16.0)	84 (19.0)
70–79	185 (65.6)	6 (2.1)	43 (15.2)	48 (17.0)
> 80	77 (68.8)	1 (0.9)	16 (14.3)	18 (16.1)

*48 patients had not reported their age in the clinical record

175

Table 6 Causes of uveitis by age in Colombia

Diagnosis	0–9 *N* = 83	10–19 *N* = 265	20–29 *N* = 450	30–39 *N* = 574	40–49 *N* = 589	50–59 *N* = 575	60–69 *N* = 443	70–79 *N* = 282	> 80 *N* = 112
Idiopathic	15 (1.6)	47 (5.0)	99 (10.5)	139 (14.7)	160 (17.0)	160 (17.0)	143 (15.1)	118 (12.5)	54 (5.7)
Toxoplasmosis	22 (26.5)	88 (33.2)	198 (44.0)	197 (34.3)	119 (20.6)	102 (18.1)	74 (16.7)	40 (14.2)	12 (10.7)
Virus-associated uveitis (confirmed)	1 (1.2)	8 (3.0)	20 (4.4)	34 (5.9)	36 (6.2)	39 (6.9)	42 (9.5)	24 (8.5)	11 (9.8)
HLA-B27 Associated Acute Anterior Uveitis	2 (2.4)	4 (1.5)	15 (3.3)	30 (5.2)	42 (7.3)	40 (7.1)	19 (4.3)	9 (3.2)	2 (1.8)
Undetermined	2 (2.4)	7 (2.6)	7 (1.6)	24 (4.2)	25 (4.2)	29 (5.0)	24 (5.4)	22 (7.8)	4 (3.5)
Pars planitis	10 (13.0)	42 (32.3)	19 (14.6)	18 (13.8)	17 (13.1)	8 (6.2)	11 (8.5)	3 (2.3)	1 (0.8)
Traumatic iritis	1 (1.2)	6 (2.3)	19 (4.2)	26 (4.5)	33 (5.6)	14 (2.5)	8 (1.8)	4 (1.4)	3 (2.7)
Spondyloarthropathies	0	0	7 (1.6)	11 (1.9)	26 (4.5)	17 (3.0)	16 (3.6)	6 (2.1)	0
VKH	0	3 (1.1)	10 (2.2)	10 (1.7)	19 (3.3)	19 (3.4)	7 (1.6)	3 (1.1)	0
Toxocariasis	12 (14.5)	26 (9.8)	17 (3.8)	8 (1.4)	5 (0.9)	3 (0.5)	0	1 (0.4)	0
Undifferentiated autoinflammatory disease	1 (1.2)	6 (2.3)	1 (0.2)	13 (2.3)	12 (2.1)	18 (3.2)	13 (2.9)	3 (1.1)	0
Fuchs uveitis syndrome	0	0	1 (0.2)	11	11 (1.9)	16 (2.8)	6 (1.4)	4 (1.4)	3 (2.7)
Rheumatoid arthritis	0	0	1 (0.2)	1 (0.2)	2 (0.3)	3 (0.5)	3 (0.7)	3 (1.1)	2 (1.8)
Lens induced uveitis	0	0	0	3 (0.5)	4 (0.7)	7 (1.2)	9 (2.0)	13 (4.6)	3 (2.7)
Juvenile Idiopathic Arthritis	10 (12.0)	17 (6.4)	7 (1.6)	0	2 (0.3)	1 (0.2)	0	0	0
Syphilis	0	0	3 (0.7)	3 (0.5)	5 (0.9)	8 (1.4)	4 (0.9)	3 (1.1)	2 (1.8)
Cytomegalovirus – posterior segment infection	1 (1.2)	0	1 (0.2)	7 (1.2)	8 (1.4)	4 (0.7)	0	0	0
Presumed Ocular Tuberculosis	2 (2.4)	0	3 (0.7)	2 (0.3)	4 (0.7)	3 (0.5)	6 (1.4)	1 (0.4)	0
Granulomatous polyangiitis	0	0	0	2 (0.3)	3 (0.5)	5 (0.9)	4 (0.9)	2 (0.7)	3 (2.7)
SLE	0	0	0	0	2 (0.3)	2 (0.4)	5 (1.1)	3 (1.1)	0
Retinitis pigmentosa	0	0	0	0	0	1 (0.2)	1 (0.2)	0	0
Sarcoidosis (presumed)	1 (1.2)	2 (0.8)	0	2 (0.3)	1 (0.2)	3 (0.5)	3 (0.7)	0	1 (0.9)
Sarcoidosis (definite)	0	0	0	4 (0.7)	9 (1.6)	12 (2.1)	14 (3.2)	4 (1.4)	1 (0.9)
Drug-induced uveitis	0	0	0	2 (0.3)	0	7 (1.2)	4 (0.9)	0	0
HIV associated	0	0	2 (0.4)	3 (0.5)	2 (0.3)	4 (0.7)	2 (0.5)	0	0
Sjögren syndrome	0	0	1 (0.2)	1 (0.2)	0	3 (0.5)	3 (0.7)	0	1 (0.9)
Posner-Schlossman Syndrome	0	0	0	0	1 (0.2)	0	0	2 (0.7)	1 (0.9)
Behçet's disease	0	0	2 (0.4)	3 (0.5)	0	4 (0.7)	0	0	0
Endophthalmitis (acute)	0	0	1 (0.2)	0	0	2 (0.4)	2 (0.5)	2 (0.7)	2 (1.8)
Serpiginous Choroidopathy	1 (1.2)	3 (1.1)	1 (0.2)	1 (0.2)	3 (0.5)	1 (0.2)	2 (0.5)	2 (0.7)	1 (0.9)
Sympathetic ophthalmia	0	0	0	1 (0.2)	2 (0.3)	4 (0.7)	1 (0.2)	1 (0.4)	0
Ulcerative colitis	0	0	0	2 (0.3)	2 (0.3)	1 (0.2)	2 (0.5)	1 (0.4)	1 (0.9)
Multiple sclerosis	0	0	1 (0.2)	1 (0.2)	0	0	0	0	0
Virus-associated uveitis (suspected)	0	1 (0.4)	1 (0.2)	0	1 (0.2)	2 (0.4)	1 (0.2)	0	0
IPICS	0	2 (0.5)	0	0	0	0	2 (0.5)	0	2 (0.5)
Immune recovery uveitis	0	0	0	1 (0.2)	3 (0.5)	1 (0.2)	0	0	0
Eales' disease	0	0	1 (0.2)	0	1 (0.2)	1 (0.2)	1 (0.2)	0	0
TINU	1 (1.2)	1 (0.4)	0	0	1 (0.2)	0	1 (0.2)	0	0
Birdshot chorioretinopathy	0	0	0	0	1 (0.2)	0	0	2 (0.7)	0
Cytomegalovirus – anterior segment infection	0	0	0	2 (0.3)	0	0	0	1 (0.4)	0
Endophthalmitis (chronic)	0	0	0	0	0	1 (0.2)	1 (0.2)	1 (0.4)	0
Histoplasmosis suspected	0	0	1 (0.2)	0	1 (0.2)	0	0	0	1 (0.9)
Idiopathic multifocal choroiditis	0	0	0	1 (0.2)	0	2 (0.4)	0	0	0
MEWDS	0	1 (0.4)	0	2 (0.3)	3 (0.5)	5 (0.9)	2 (0.5)	1 (0.4)	1 (0.9)
Primary intraocular lymphoma	0	0	1 (0.2)	1 (0.2)	3 (0.5)	6 (1.1)	1 (0.2)	0	0

Table 6 (continued)

Diagnosis	0–9 *N* = 83	10–19 *N* = 265	20–29 *N* = 450	30–39 *N* = 574	40–49 *N* = 589	50–59 *N* = 575	60–69 *N* = 443	70–79 *N* = 282	> 80 *N* = 112
Epstein Barr-Virus	0	0	0	1	0	0	1 (0.2)	0	0
Multifocal Choroiditis and Panuveitis	0	0	1 (0.2)	1 (0.2)	0	0	1 (0.2)	0	0
Psoriasis	0	0	0	0	1 (0.2)	1 (0.2)	0	1 (0.4)	0
Relapsing polychondritis	0	0	0	0	1 (0.2)	0	0	0	0
UGH syndrome	0	0	0	0	0	1 (0.2)	0	1 (0.4)	0
AZOOR	0	0	0	0	0	1 (0.2)	0	0	0
Blau syndrome	1 (1.2)	0	0	0	0	0	0	0	0
Brucellosis suspected	0	0	1 (0.2)	0	0	0	0	0	0
CREST Syndrome	0	0	0	0	0	0	1 (0.2)	0	0
Crohn's disease	0	0	0	0	0	1 (0.2)	0	0	0
Cryoglobulinemic vasculitis	0	0	0	1	0	0	0	0	0
Cysticercosis	0	1 (0.4)	0	0	0	0	0	0	0
IRVAN syndrome	0	0	1 (0.2)	0	0	0	0	0	0
Leptospirosis (confirmed)	0	0	1 (0.2)	0	0	0	0	0	0
Leptospirosis (suspected)	0	1 (0.4)	0	0	0	0	0	0	0
Reactive arthritis	0	0	1 (0.2)	0	0	0	0	1 (0.4)	0
Takayasu arteritis	0	0	0	0	1 (0.2)	0	0	0	0
Undifferentiated vasculitis	0	0	0	1 (0.2)	0	0	0	0	0

AZOOR Acute zonal occult outer retinopathy, *IPICS* idiopathic persistent iritis after cataract surgery, *SLE* Systemic lupus erythematosus, *MEWDS* Multiple evanescent white dot syndrome, *TINU syndrome* Tubulointerstitial nephritis and *uveitis syndrome*, *UGH syndrome Uveitis-Glaucoma-Hyphema*-syndrome, *VKH* Vogt-Koyanagi-Harada disease, *HIV* Human immunodeficiency virus, *HLA-B27* Human leukocyte antigen B27

generalizability. Our study includes seven referral centers from four main cities in Colombia, providing a comprehensive representation of patients from the central regions of the country (where most of the population is located) (Fig. 2). Uveitis is generally an alarming entity that forces patients to consult and in most cases general ophthalmologists refer patients to the uveitis specialist, so we estimate that many of the patients who live in cities other than the evaluated surely consulted in one of these centers, which reduces the potential loss of cases.

Our study has some limitations. Due to economic and accessibility disparities among the country's regions, the potential for selection bias cannot be entirely ruled out. Nonetheless, by encompassing private and public centers in our study, we aimed to reduce this risk, considering the extensive coverage reported by the Colombian health system (97.78%). Furthermore, as our data was gathered from tertiary referral centers, there is a potential for overestimating rarer etiologies and underestimating cases of uveitis that are easily treatable. Moreover, previous Colombian studies reported the prevalence of an undetermined etiology at around 16.5% and 21.6%, but in our study, it was only 4.5% [9, 24]. Therefore, we acknowledge the possibility that some undetermined cases could have been mistakenly categorized as idiopathic. However, given that experienced uveitis specialists conducted most diagnoses, and the data was meticulously recorded by knowledgeable personnel following the SUN criteria, the likelihood of this risk is minimized. Moreover, we report diagnoses like rheumatoid arthritis, systemic lupus erythematosus, and antiphospholipid syndrome. However, these diseases should be understood as possible systemic associated conditions to uveitis and not as a direct cause [9, 60–63].

In conclusion, this is the most extensive multicenter study conducted in South America, focusing on the epidemiology of uveitis. Infectious uveitis remains the most common etiology, with ocular toxoplasmosis as the most frequent cause. However, compared to previous studies, an increase in non-infectious conditions was also observed. This study emphasizes the importance of conducting multicenter research to identify changes in the patterns of uveitis and keep updated the epidemiological knowledge of these group of diseases.

Abbreviations *JIA*: Juvenile idiopathic arthritis; *AZOOR*: Acute zonal occult outer retinopathy; *BCVA*: Best-corrected visual acuity; *HIV*: Human Immunodeficiency Virus; *HLA-B27*: Human leukocyte antigen B27; *IOL*: Intra-ocular lens; *IPICS*: Idiopathic persistent iritis after cataract surgery; *MEWDS*: Multiple evanescent white dot syndrome; *PIOL*: Primary intraocular lymphoma; *SUN*: Standardization of uveitis nomenclature; *STROBE*: Strengthening the reporting of observational studies in epidemiology; *SLE*: Systemic lupus erythematosus; *TINU syndrome*: Tubulointerstitial nephritis and uveitis syndrome; *UGH*: Uveitis-Glaucoma-Hyphema syndrome; *VKH*: Vogt-Koyanagi-Harada disease

177

Author contribution All authors attest that they meet the current ICMJE criteria for Authorship.

Funding Open Access funding provided by Colombia Consortium. This research has not received specific aid from public sector agencies, the commercial sector, or non-profit entities.

Data availability The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval This study was approved by the Ethics Committee of Universidad del Rosario under the reference DVO005 2101—CV1615. Additionally, this study adheres to the ethical principles for human research established by the Helsinki Declaration, the Belmont Report, and Colombian Resolution 008430 of 1993.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Luca C, Raffaella A, Sylvia M et al (2017) Changes in patterns of uveitis at a tertiary referral center in Northern Italy: analysis of 990 consecutive cases. Int Ophthalmol. https://doi.org/10.1007/s10792-016-0434-x
2. Rathinam S, Babu M (2013) Algorithmic approach in the diagnosis of uveitis. Indian J Ophthalmol 61:255. https://doi.org/10.4103/0301-4738.114092
3. Albini TA, Rice JB, White AG et al (2020) Economic burden of Non-Infectious Inflammatory Eye Disease (NIIED) in a commercially-insured population in the United States. Ocul Immunol Inflamm 28:164–174. https://doi.org/10.1080/09273948.2018.1560476
4. Tsirouki T, Dastiridou A, Symeonidis C et al (2018) A focus on the epidemiology of uveitis. Ocul Immunol Inflamm 26:2–16. https://doi.org/10.1080/09273948.2016.1196713
5. Gritz D (2004) Incidence and prevalence of uveitis in Northern California The Northern California Epidemiology of Uveitis Study. Ophthalmology 111:491–500. https://doi.org/10.1016/j.ophtha.2003.06.014
6. Mezei G, Chang ET, Mowat FS, Moolgavkar SH (2021) Comments on a recent case-control study of malignant mesothelioma of the pericardium and the tunica vaginalis testis. Scand J Work Environ Health 47:85–86. https://doi.org/10.5271/sjweh.3909
7. Acharya NR, Tham VM, Esterberg E et al (2013) Incidence and prevalence of uveitis: results from the pacific ocular inflammation study. JAMA Ophthalmol 131:1405. https://doi.org/10.1001/jamaophthalmol.2013.4237
8. Hart CT, Zhu EY, Crock C et al (2019) Epidemiology of uveitis in urban Australia. Clin Exp Ophthalmol ceo.13517. https://doi.org/10.1111/ceo.13517
9. Polanía D, Reyes-Guanes J, Rojas-Carabali W et al (2023) A new look into uveitis in Colombia: changes in distribution patterns and clinical characteristics over the last 25 years. Graefes Arch Clin Exp Ophthalmol 261:561–573. https://doi.org/10.1007/s00417-022-05796-2
10. (2005) Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop. Am J Ophthalmol 140:509–516. https://doi.org/10.1016/j.ajo.2005.03.057
11. Davis JL, Madow B, Cornett J et al (2010) Scale for photographic grading of vitreous haze in uveitis. Am J Ophthalmol 150:637-641.e1. https://doi.org/10.1016/j.ajo.2010.05.036
12. The Standardization of Uveitis Nomenclature (Sun) Working Group (2021) Classification criteria for sarcoidosis-associated uveitis. Am J Ophthalmol 228:220–230.https://doi.org/10.1016/j.ajo.2021.03.047
13. Mochizuki M, Smith JR, Takase H et al (2019) Revised criteria of International Workshop on Ocular Sarcoidosis (IWOS) for the diagnosis of ocular sarcoidosis. Br J Ophthalmol 103:1418–1422. https://doi.org/10.1136/bjophthalmol-2018-313356
14. Baarsma GS, La Hey E, Glasius E et al (1987) The predictive value of serum angiotensin converting enzyme and lysozyme levels in the diagnosis of ocular sarcoidosis. Am J Ophthalmol 104:211–217. https://doi.org/10.1016/0002-9394(87)90406-5
15. Borciuch C, El-Jammal T, Kodjikian L et al (2024) Value of chest x-ray and chest computed tomography for systemic sarcoidosis diagnosis in undifferentiated uveitis. Ocul Immunol Inflamm 32:161–167. https://doi.org/10.1080/09273948.2023.2226203
16. Mao L, Dhar A, Meng G et al (2022) Blau syndrome NOD2 mutations result in loss of NOD2 cross-regulatory function. Front Immunol 13:988862. https://doi.org/10.3389/fimmu.2022.988862
17. Agrawal R, Agarwal A, Jabs DA et al (2020) Standardization of nomenclature for ocular tuberculosis – Results of Collaborative Ocular Tuberculosis Study (COTS) Workshop. Ocul Immunol Inflamm 28:74–84. https://doi.org/10.1080/09273948.2019.1653933
18. Soifer M, Mousa HM, Jammal AA et al (2022) Diagnosis and management of Idiopathic Persistent Iritis after Cataract Surgery (IPICS). Am J Ophthalmol 234:250–258. https://doi.org/10.1016/j.ajo.2021.10.004
19. Fekri S, Barzanouni E, Samiee S, Soheilian M (2023) Polymerase chain reaction test for diagnosis of infectious uveitis. Int J Retin Vitr 9:26. https://doi.org/10.1186/s40942-023-00465-w
20. Rangel CM, Restrepo-Arango M, Mejía-Salgado G et al (2023) Acute retinal necrosis: experience in a reference center in Santander – Colombia. Ocul Immunol Inflamm 1–9. https://doi.org/10.1080/09273948.2023.2244076
21. Goh EJH, Putera I, La Distia NR et al (2023) Ocular toxoplasmosis. Ocul Immunol Inflamm 31:1342–1361. https://doi.org/10.1080/09273948.2022.2117705
22. (2021) Classification criteria for pars planitis. Am J Ophthalmol 228:268–274. https://doi.org/10.1016/j.ajo.2021.03.045
23. McGonagle D, McDermott MF (2006) A Proposed Classification of the Immunological Diseases. PLoS Med 3:e297. https://doi.org/10.1371/journal.pmed.0030297
24. de-la-Torre A, López-Castillo CA, Rueda JC et al (2009) Clinical patterns of uveitis in two ophthalmology centres in Bogota, Colombia. Clin Exp Ophthalmol 37:458–466.https://doi.org/10.1111/j.1442-9071.2009.02082.x
25. Liberman P, Gauro F, Berger O, Urzua CA (2015) Causes of uveitis in a tertiary center in Chile: a cross-sectional retrospective review. Ocul Immunol Inflamm 23:339–345. https://doi.org/10.3109/09273948.2014.981548

26. Gonzalez Fernandez D, Nascimento H, Nascimento C et al (2017) Uveitis in São Paulo, Brazil: 1053 new patients in 15 months. Ocul Immunol Inflamm 25:382–387. https://doi.org/10.3109/09273948.2015.1132741
27. Amaya J, Beltrán A, Chavarro D et al (2013) Estudio de disponibilidad y distribución de la oferta de médicos especialistas, en servicios de alta y mediana complejidad en Colombia. https://www.minsalud.gov.co/salud/Documents/Observatorio%20Talento%20Humano%20en%20Salud/DisponibilidadDistribución-MdEspecialistasCendex.pdf. Accessed 20 Oct 2023
28. Miserocchi E, Fogliato G, Modorati G, Bandello F (2013) Review on the worldwide epidemiology of uveitis. Eur J Ophthalmol 23:705–717. https://doi.org/10.5301/ejo.5000278
29. Heiligenhaus A, Minden K, Föll D, Pleyer U (2015) Uveitis in juvenile idiopathic arthritis. Dtsch Arztebl Int. https://doi.org/10.3238/arztebl.2015.0092
30. Rothova A, Buitenhuis HJ, Meenken C et al (1992) Uveitis and systemic disease. Br J Ophthalmol 76:137–141. https://doi.org/10.1136/bjo.76.3.137
31. Yeung IYL, Popp NA, Chan C-C (2015) The role of sex in uveitis and ocular inflammation. Int Ophthalmol Clin 55:111–131. https://doi.org/10.1097/IIO.0000000000000072
32. ÇakarÖzdal MP, Yazici A, Tüfek M, Öztürk F (2014) Epidemiology of uveitis in a referral hospital in Turkey. Turk J Med Sci 44:337–342. https://doi.org/10.3906/sag-1302-132
33. Silpa-archa S, Noonpradej S, Amphornphruet A (2015) Pattern of uveitis in a referral ophthalmology center in the central district of Thailand. Ocul Immunol Inflamm 23:320–328. https://doi.org/10.3109/09273948.2014.943773
34. Zheng Y, Zhang L-X, Meng Q-L et al (2015) Clinical patterns and characteristics of uveitis in a secondary hospital in southern China. Int J Ophthalmol 8:337–341. https://doi.org/10.3980/j.issn.2222-3959.2015.02.22
35. Dogra M, Singh R, Agarwal A et al (2017) Epidemiology of uveitis in a tertiary-care Referral Institute in North India. Ocul Immunol Inflamm 25:S46–S53. https://doi.org/10.1080/09273948.2016.1255761
36. Siak J, Kumaradas M, Chee S-P (2017) The pattern of uveitis in Sri Lanka. Ocul Immunol Inflamm 25:S63–S68. https://doi.org/10.1080/09273948.2017.1313991
37. Abaño JM, Galvante PR, Siopongco P et al (2017) Review of epidemiology of uveitis in Asia: pattern of uveitis in a tertiary hospital in the Philippines. Ocul Immunol Inflamm 25:S75–S80. https://doi.org/10.1080/09273948.2017.1335755
38. Nguyen M, Siak J, Chee S-P, Diem VQH (2017) The spectrum of uveitis in southern Vietnam. Ocul Immunol Inflamm 25:S100–S106. https://doi.org/10.1080/09273948.2016.1231826
39. Bigna JJ, Tochie JN, Tounouga DN et al (2020) Global, regional, and country seroprevalence of Toxoplasma gondii in pregnant women: a systematic review, modelling and meta-analysis. Sci Rep 10:12102. https://doi.org/10.1038/s41598-020-69078-9
40. Alvarez C, de-la-Torre A, Vargas M et al (2015) Striking divergence in *Toxoplasma ROP16* nucleotide sequences from human and meat samples. J Infect Dis 211:2006–2013.https://doi.org/10.1093/infdis/jiu833
41. Sánchez V, de-la-Torre A, Gómez-Marín JE (2014) Characterization of ROP18 alleles in human toxoplasmosis. Parasitol Int 63:463–469.https://doi.org/10.1016/j.parint.2013.10.012
42. Gómez-Marín JE, Muñoz-Ortiz J, Mejía-Oquendo M et al (2021) High frequency of ocular toxoplasmosis in Quindío, Colombia and risk factors related to the infection. Heliyon 7:e06659. https://doi.org/10.1016/j.heliyon.2021.e06659
43. Cifuentes-González C, Zapata-Bravo E, Sierra-Cote MC et al (2022) Colombian Ocular Infectious Epidemiology Study (COIES): ocular toxoplasmosis incidence and sociodemographic characterization, 2015–2019. Int J Infect Dis 117:349–355. https://doi.org/10.1016/j.ijid.2022.02.028
44. Ministerio de Salud y Protección Social (2013) Guías de Práctica Clínica para la prevención, detección temprana y tratamiento de las complicaciones del em- barazo, parto o puerperio. Bogotá
45. Cifuentes-González C, Rojas-Carabali W, Fonseca-Mora MA et al (2022) Colombian Ocular Infectious Epidemiology Study (COIES): herpes zoster ophthalmicus prevalence and sociodemographic characterization, 2015–2019. Int J Infect Dis 116:27–33. https://doi.org/10.1016/j.ijid.2021.12.332
46. Boada-Robayo L, Cruz-Reyes DL, Cifuentes-González C et al (2022) Exploring the association between precipitation and population cases of ocular toxoplasmosis in Colombia. PLoS Negl Trop Dis 16:e0010742. https://doi.org/10.1371/journal.pntd.0010742
47. Chen S-C, Chuang C-T, Chu M-Y, Sheu S-J (2017) Patterns and etiologies of uveitis at a tertiary referral center in Taiwan. Ocul Immunol Inflamm 25:S31–S38. https://doi.org/10.1080/09273948.2016.1189577
48. Birnbaum AD, French DD, Mirsaeidi M, Wehrli S (2015) Sarcoidosis in the national veteran population. Ophthalmology 122:934–938. https://doi.org/10.1016/j.ophtha.2015.01.003
49. Smith JA, Mackensen F, Sen HN et al (2009) Epidemiology and course of disease in childhood uveitis. Ophthalmology 116:1544-1551.e1. https://doi.org/10.1016/j.ophtha.2009.05.002
50. Ozdal PÇ, Sen E, Yazici A, Ozturk F (2012) Patterns of childhood-onset uveitis in a referral center in Turkey. J Ophthal Inflamm Infect 2:13–19. https://doi.org/10.1007/s12348-011-0044-8
51. Sagoo MS, Mehta H, Swampillai AJ et al (2014) Primary intraocular lymphoma. Surv Ophthalmol 59:503–516. https://doi.org/10.1016/j.survophthal.2013.12.001
52. Heiferman MJ, Yu MD, Mruthyunjaya P (2022) Update in molecular testing for intraocular lymphoma. Cancers 14:4546. https://doi.org/10.3390/cancers14194546
53. García-Aparicio A, Alonso Martín L, LópezLancho R et al (2021) Epidemiology of uveitis in a Spanish Region: prevalence and etiology. Ophthalmic Epidemiol 28:227–236. https://doi.org/10.1080/09286586.2020.1815802
54. Sabhapandit S, Murthy SI, Singh VM et al (2017) Epidemiology and clinical features of uveitis from urban populations in South India. Ocul Immunol Inflamm 25:S39–S45. https://doi.org/10.1080/09273948.2016.1236971
55. Yang P, Zhong Z, Du L et al (2021) Prevalence and clinical features of systemic diseases in Chinese patients with uveitis. Br J Ophthalmol 105:75–82. https://doi.org/10.1136/bjophthalmol-2020-315960
56. Jones NP (2015) The manchester uveitis clinic: the first 3000 patients—epidemiology and casemix. Ocul Immunol Inflamm 23:118–126. https://doi.org/10.3109/09273948.2013.855799
57. Anaya J-M, Rojas-Villarraga A, García-Carrasco M (2012) The autoimmune tautology: from polyautoimmunity and familial autoimmunity to the autoimmune genes. Autoimmune Dis 2012:1–2. https://doi.org/10.1155/2012/297193
58. Mathew RG, Goh BT, Westcott MC (2014) British Ocular Syphilis Study (BOSS): 2-year national surveillance study of intraocular inflammation secondary to ocular syphilis. Invest Ophthalmol Vis Sci 55:5394. https://doi.org/10.1167/iovs.14-14559
59. Yurkovetskiy L, Burrows M, Khan AA et al (2013) Gender bias in autoimmunity is influenced by microbiota. Immunity 39:400–412. https://doi.org/10.1016/j.immuni.2013.08.013
60. Hogan MJ, Thygeson P, Kimura SJ (1956) Uveitis in association with rheumatism. Trans Am Ophthalmol Soc 54:93–114; discussion, 114–120
61. Gallagher K, Viswanathan A, Okhravi N (2015) Association of systemic lupus erythematosus with uveitis. JAMA Ophthalmol 133:1190. https://doi.org/10.1001/jamaophthalmol.2015.2249
62. Uribe-Reina P, Muñoz-Ortiz J, Cifuentes-Gonzalez C et al (2021) Ocular manifestations in colombian patients with systemic rheumatologic diseases. OPTH 15:2787–2802. https://doi.org/10.2147/OPTH.S306621

63. Shapira Y, Ben-Arie-Weintrob Y, Gilburd B et al (2021) Antiphospholipid antibodies may be associated with uveitis. Eur J Ophthalmol 31:2446–2450. https://doi.org/10.1177/1120672120968729

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Authors and Affiliations

Alejandra de-la-Torre[1] · Germán Mejía-Salgado[1] · Carlos Cifuentes-González[1] · William Rojas-Carabali[1] · Miguel Cuevas[2] · Sandra García[3] · Carlos M. Rangel[4] · Claudia Durán[5] · Diana Isabel Pachón-Suárez[1] · Andrés Bustamante-Arias[6]

1 Neuroscience Research Group (NEUROS), Neurovitae Center for Neuroscience, Institute of Translational Medicine (IMT), School of Medicine and Health Sciences, Universidad del Rosario, Carrera 24 # 63C 69, Bogotá, Colombia

2 Department of Ophthalmology, School of Medicine and Health Sciences, Universidad de Antioquia, Medellín, Colombia

3 Department of Ophthalmology, School of Medicine and Health Sciences, Universidad Pontificia Javeriana, Cali, Colombia

4 Department of Ophthalmology, School of Medicine and Health Sciences, FOSCAL, Centro Oftalmológico Virgilio Galvis, Universidad Industrial de Santander, Universidad Autónoma de Bucaramanga, Floridablanca, Santander, Colombia

5 Ocular Immunology and Uveitis Department, School of Medicine and Health Sciences, Universidad CES, Medellín, Colombia

6 Clínica de Oftalmología Sandiego, Medellín, Colombia

PERSPECTIVES

Standardization of Uveitis Nomenclature for Reporting Clinical Data. Results of the First International Workshop

THE STANDARDIZATION OF UVEITIS NOMENCLATURE (SUN) WORKING GROUP

• PURPOSE: **To begin a process of standardizing the methods for reporting clinical data in the field of uveitis.**
• DESIGN: **Consensus workshop.**
• METHODS: **Members of an international working group were surveyed about diagnostic terminology, inflammation grading schema, and outcome measures, and the results used to develop a series of proposals to better standardize the use of these entities. Small groups employed nominal group techniques to achieve consensus on several of these issues.**
• RESULTS: **The group affirmed that an anatomic classification of uveitis should be used as a framework for subsequent work on diagnostic criteria for specific uveitic syndromes and that the classification of uveitis entities should be on the basis of the location of the inflammation and not on the presence of structural complications. Issues regarding the use of the terms "intermediate uveitis," "pars planitis," "panuveitis," and descriptors of the onset and course of the uveitis were addressed. The following were adopted: standardized grading schema for anterior chamber cells, anterior chamber flare, and for vitreous haze; standardized methods of recording structural complications of uveitis; standardized definitions of outcomes, including "inactive" inflammation, "improvement" and "worsening" of the inflammation, and "corticosteroid sparing," and standardized guidelines for reporting visual acuity outcomes.**
• CONCLUSIONS: **A process of standardizing the approach to reporting clinical data in uveitis research has begun, and several terms have been standardized. (Am J Ophthalmol 2005;140:509–516. © 2005 by Elsevier Inc. All rights reserved.)**

Accepted for publication Mar 17, 2005.

A listing of members of The Standardization of Uveitis Nomenclature (SUN) Working Group appears in the Appendix.

Supported by the American Uveitis Society and by an unrestricted grant from Centocor, Inc, Malvern, Pennsylvania, USA.

Inquiries to Douglas A. Jabs, MD, MBA, The Wilmer Eye Institute, 550 North Broadway, Suite 700, Baltimore, MD 21205; fax: 410-955-0629djabs@jhmi.edu

THE FIELD OF UVEITIS DEALS WITH MULTIPLE DISEASE entities, some of which are caused directly by infectious agents and others of which appear to be immune-mediated. Many uveitic entities are associated with systemic immune-mediated diseases, such as sarcoidosis, the HLA-B27-associated spondyloarthropathies, and Behçet's disease, whereas others are limited to the eye. Although attempts have been made to standardize some aspects of uveitis,[1] in general there is limited standardization of classification criteria, inflammation grading schema, and outcomes.[2] Standardization would enhance greatly the comparability of clinical research from different centers, permit meta-analyses, and assist in the development of a more complete and meaningful picture of the clinical course of these diseases and their response to treatment.

The American College of Rheumatology (ACR) has developed classification criteria for many of the rheumatic diseases such as rheumatoid arthritis and systemic lupus erythematosus.[3,4] These criteria have been developed through a standard process and validated against large databases, in an effort to maximize sensitivity and specificity. In the field of uveitis, provisional criteria have been developed for a limited number of disorders (acute retinal necrosis, progressive outer retinal necrosis, Vogt-Koyanagi-Harada disease, and tubulointerstitial nephritis with uveitis),[5–8] and they still await validation. Additionally, there are criteria for the systemic portion of three diseases in which uveitis is an important feature (ankylosing spondylitis, juvenile idiopathic arthritis, and Behçet's disease),[9–11] but not for the uveitis in these diseases. Like the ACR classifications of arthritis and vasculitis, which are on the basis of the anatomic pattern of the disease, the most widely used classification of uveitis is the one devised by

0002-9394/05/$30.00
doi:10.1016/j.ajo.2005.03.057

© 2005 BY ELSEVIER INC. ALL RIGHTS RESERVED.

the International Uveitis Study Group (IUSG),[1] and is based on the anatomic location of the inflammation. Nevertheless, there are ambiguities in its use, and it does not provide criteria for the diagnosis of specific uveitic entities. Although the establishment of criteria for specific uveitic entities is a major undertaking, resolution of some of the ambiguities can be addressed more easily.

Grading schema for intraocular inflammation typically uses an ordinal scale ranging from 0 to 4+. However, there are at least four systems for anterior chamber cells,[12–15] three for anterior chamber flare,[12–15] two for vitreous cells,[14,15] and three for vitreous haze or debris.[15–17] Although these systems generally are similar, there are differences, and the number of ordinal grades ranges from six to nine. Therefore, data from different groups are difficult to compare, and concepts, such as a two-step increase in the inflammation, are difficult to apply. A standardized set of criteria for grading the four aspects of intraocular inflammation (anterior chamber cells, anterior chamber flare, vitreous cells, and vitreous haze or debris) would enable the data from different groups and different studies to be compared directly. Although disease-specific scoring systems may require more complicated grading schema (for example, for the multifocal choroidopathies), these four grading schema form the building blocks of more complicated systems, and for some types of uveitis (for example, anterior uveitis) they may suffice.

The choice of outcomes for a clinical study depends on the goals of the study, and for many studies, multiple outcomes are appropriate. Nevertheless, for many clinical studies, particularly therapeutic studies, a primary outcome is needed, and for randomized clinical trials, one outcome typically is chosen as the basis for the sample size calculation. In rheumatology, composite scoring systems, such as the ACR scoring systems for improvement in rheumatoid arthritis (ACR 20, 50, and 70), are used.[18] However, in ophthalmology the ability to observe directly the amount of inflammation and measure directly the eye's ability to function (visual acuity and visual field) may allow simpler systems to be used. For long-term studies of visual impairment in uveitis, loss of visual function, such as visual acuity or visual field,[19] may be appropriate outcomes. For short-term studies of the effect of a new treatment on active uveitis, control of the inflammation is an appropriate outcome. For studies of corticosteroid-sparing agents, such as immunosuppressive drugs or biologic agents, in patients on chronic corticosteroid treatment with quiet disease, the ability to taper the prednisone dose below a clinically meaningful threshold[20] while maintaining inactive disease is an appropriate outcome. Although the outcome of choice will vary with the type of study, standardized terminology and standardized definitions are needed.

To begin the process of addressing these issues, the First International Workshop on Standardization of Uveitis Nomenclature was held on November 8 to 9, 2004 in Baltimore, Maryland, USA. Attendees included individuals invited to ensure a diverse group from leading centers around the world. Additionally, the meeting was announced and opened to all interested parties, although attendance was capped at 50 participants in order for the breakout sessions to be a manageable size. Fifty individuals from 35 centers in 13 countries participated in some part of the process, and 45 individuals from 33 of the 35 centers in these countries attended the meeting. The leaderships of American Uveitis Society (AUS) and of the International Uveitis Study Group (IUSG) endorsed the workshop, the process involved, and its conclusions, and members of both organizations participated in the workshop.

TABLE 1. The SUN* Working Group Anatomic Classification of Uveitis

Type	Primary Site of Inflammation†	Includes
Anterior uveitis	Anterior chamber	Iritis
		Iridocyclitis
		Anterior cyclitis
Intermediate uveitis	Vitreous	Pars planitis
		Posterior cyclitis
		Hyalitis
Posterior uveitis	Retina or choroid	Focal, multifocal, or diffuse choroiditis
		Chorioretinitis
		Retinochoroiditis
		Retinitis
		Neuroretinitis
Panuveitis	Anterior chamber, vitreous, and retina or choroid	

*SUN = Standardization of uveitis nomenclature.
†As determined clinically. Adapted from the International Uveitis Study Group anatomic classification in reference 1.

METHODS

BEFORE THE WORKSHOP, THE MEETING ORGANIZERS DISCUSSED possible areas to be addressed by the working group. A survey was developed to determine where there were areas of agreement and where there was a diversity of opinions. The survey instrument was pilot-tested on a small group of participants and revised. It then was sent to the members of the working group, and the responses compiled.

The working group then met for the workshop. At the meeting, the first one-half day was devoted to prepared presentations detailing the issues involved, and the results of the survey were presented. The 45 attendees were assigned to one of three groups for the afternoon sessions,

each of which addressed one of the three following subjects: (1) terminology; (2) grading inflammation and documenting complications; and (3) outcomes and results reporting. The small group sessions used nominal group techniques to achieve consensus when possible.[21] Items for which consensus could not be reached were tabled for future work. On the second day, the results of the small group sessions were presented to the entire group for review and acceptance (or tabling if there was substantial disagreement from the other groups). Issues related to the definitions of glaucoma and elevated intraocular pressure were tabled at the workshop and were addressed further by Delphi techniques[21] after consultation with glaucoma experts outside the group.

RESULTS

• **TERMINOLOGY:** There was consensus that an anatomic classification of uveitis should be used and should serve as a framework for subsequent work on diagnostic criteria for specific uveitic diagnoses. The IUSG anatomic classification scheme[1] (Table 1) was endorsed. Furthermore, it was agreed that the classification of the anatomic location of the uveitis should be on the basis of the site(s) of inflammation and not on the presence of structural complications.

Ambiguities in the IUSG system were addressed. There was consensus that the term *intermediate uveitis* should be used for that subset of uveitis where the vitreous is the major site of the inflammation, and that the presence of peripheral vascular sheathing and macular edema should not change the classification. The diagnostic term *pars planitis* should be used only for that subset of intermediate uveitis where there is snowbank or snowball formation occurring in the absence of an associated infection or systemic disease (that is, "idiopathic"). If there is an associated infection (for example, Lyme disease) or systemic disease (for example, sarcoidosis), then the term intermediate uveitis should be used. The term *panuveitis* should be reserved for those situations in which there is no predominant site of inflammation, but inflammation is observed in the anterior chamber, vitreous, and retina and/or choroid (that is, retinitis, choroiditis, or retinal vasculitis). For the definition of panuveitis, structural complications such as macular edema or neovascularization should not be considered in classifying the anatomic location of the uveitis. Inflammation in the anterior chamber and vitreous (that is, more vitritis than in an iridocyclitis and more anterior chamber inflammation than in intermediate uveitis) should be referred to as anterior and intermediate uveitis and not as panuveitis.

The term *retinal vasculitis* was addressed. There was consensus that it is a descriptive term for those situations in which there is evidence of ocular inflammation and retinal vascular changes. The presence of occlusive retinal vasculopathy, in the absence of visible inflammation such as in the antiphospholipid antibody syndrome, should not be considered retinal vasculitis. Achieving consensus on which retinal vascular changes constituted retinal vasculitis was more problematic. Although the group provisionally agreed to consider perivascular sheathing and vascular leakage or occlusion on fluorescein angiogram as evidence of retinal vascular disease for the classification of retinal vasculitis, there was consensus that the definition of retinal vasculitis required more work. For example, it was unresolved as to how to distinguish between retinal vasculitis and the peripheral vascular sheathing sometimes seen in intermediate uveitis.

TABLE 2. The SUN* Working Group Descriptors of Uveitis

Category	Descriptor	Comment
Onset	Sudden	
	Insidious	
Duration	Limited	≤3 months duration
	Persistent	>3 months duration
Course	Acute	Episode characterized by sudden onset and limited duration
	Recurrent	Repeated episodes separated by periods of inactivity without treatment ≥3 months in duration
	Chronic	Persistent uveitis with relapse in <3 months after discontinuing treatment

*SUN = Standardization of uveitis nomenclature.

The terms "acute" and "chronic" have been used inconsistently in the literature and have been used variably to refer to the onset of the uveitis, the duration of an attack of uveitis, or to the course of uveitis. Consensus was obtained that the use of these terms should be reserved for the description of the clinical course of the uveitis, and that other terms should be used to describe the onset of the uveitis and the duration of an attack of uveitis (Table 2). The onset of uveitis should be described either as *sudden* or *insidious*. The duration of an attack of uveitis should be described as either *limited*, if it is 3 months or less in duration or as *persistent*, if it is greater than 3 months in duration. The term *acute* should be used to describe the course of specific uveitic syndromes characterized by sudden onset and limited duration, such as HLA-B27-associated "acute anterior uveitis."[22] The term *recurrent* should be used to describe repeated episodes of uveitis separated by periods of inactivity without treatment, in which these periods of inactivity without treatment are at least 3 months in duration. The term *chronic* should be used to describe persistent uveitis characterized by prompt relapse (in less than 3 months) after discontinuation of therapy. It was agreed that the appearance of the keratic precipitates potentially conveys useful clinical information and may have diagnostic implications. However, keratic pre-

TABLE 3. The SUN* Working Group Grading Scheme for Anterior Chamber Cells

Grade	Cells in Field†
0	<1
0.5+	1–5
1+	6–15
2+	16–25
3+	26–50
4+	>50

*SUN = Standardization of uveitis nomenclature.
†Field size is a 1 mm by 1 mm slit beam.

TABLE 4. The SUN* Working Group Grading Scheme for Anterior Chamber Flare

Grade	Description
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

Adapted from reference 12.
*SUN = Standardization of uveitis nomenclature.

cipitates are not described in a universally standardized fashion. Although no consensus could be reached either on how to describe keratic precipitates or on the use of the term "granulomatous" as a descriptor for keratic precipitates, there was consensus that a series of standardized photographs should be used by a panel of experts to develop appropriate descriptive terms and then published as a standard reference.

• **GRADING INFLAMMATION AND DOCUMENTING COMPLICATIONS:** Consensus was achieved regarding standard methods for grading anterior chamber cells (Table 3) and anterior chamber flare (Table 4). Additionally, there was consensus that a set of standardized photographs should be developed to assist in grading anterior chamber flare. Although the level 0.5+ was selected over the term "trace," the system is an ordinal one, in which the levels represent a nonlinear hierarchy of increasing magnitude, but do not have a numerical relationship to the amount of inflammation. For the grading of anterior chamber cells, the presence or absence of a hypopyon should be recorded separately. Although it was agreed that the presence of vitreous cells was an important clinical feature, no consensus could be reached on a standard grading system for vitreous cells. The National Eye Institute system for grading vitreous haze was adopted with the proviso that the designation "trace" be recorded as 0.5+.[17]

The level of evidence required for reporting structural complications of uveitis depended on the complication being reported. It was agreed that macular edema could be reported as present or absent as determined clinically. However, ancillary testing can provide a greater level of sensitivity and specificity, and macular edema may be confirmed or excluded by either fluorescein angiography or optical coherence tomography. Similarly it was agreed that epiretinal membrane formation could be reported as present or absent as determined clinically and may be confirmed or excluded by either fundus photography or optical coherence tomography. It was expected that retrospective studies might report both levels of evidence, particularly if there was a variable use of ancillary studies, but that for clinical trials and epidemiologic studies in which there is prospective data collection, reporting results on the basis ancillary studies is preferable.

For reporting purposes, it was agreed that subretinal neovascularization should be reported only if confirmed by either fluorescein angiography or fluorescein angiography and indocyanine green angiography. Disk and retinal neovascularization should be reported if confirmed by fundus photography and fluorescein angiography. Although clinical grading of these outcomes may be acceptable in the setting of other retinal diseases, for uveitis, in which these complications are less common, the group decided that reporting was appropriate only if based on the appropriate ancillary testing. Although there was consensus that ancillary tests that document retinal dysfunction, such as perimetry or electroretinography, should be used for those diseases that cause diffuse retinal dysfunction (for example, birdshot chorioretinitis), there was no consensus on which tests are most appropriate for which disease.

There was consensus that the term *glaucoma* should not be considered synonymous with elevated intraocular pressure in a patient with uveitis, but that it should be reserved for those situations where there is either observed glaucomatous disk damage or demonstrated visual field loss. The term *elevated intraocular pressure* should be used for those situations where there is an intraocular pressure above a defined normal range or when there is an increase in intraocular pressure from baseline during a study with longitudinal data. The threshold for considering a rise in intraocular pressure substantial (for example, as in a rise in intraocular pressure attributable to corticosteroid use) was 10 mm Hg or greater. Although consensus was not achieved on the threshold for considering an intraocular pressure as elevated, the choices were narrowed to two. The first was to report at two levels: above 21 mm Hg (the traditional "upper limit of normal") and above 30 mm Hg (a level above which many practitioners would initiate treatment even without evidence of glaucomatous damage). The second option was to report intraocular pressure above the 24 mm Hg as elevated, as the risk of glaucoma appears to increase substantially as the intraocular pressure increases beyond this level.[23–25] The use of antiglaucoma

TABLE 5. The SUN* Working Group Activity of Uveitis Terminology

Term	Definition
Inactive	Grade 0 cells†
Worsening activity	Two step increase in level of inflammation (e.g. anterior chamber cells, vitreous haze) or increase from grade 3+ to 4+
Improved activity	Two step decrease in level of inflammation (e.g. anterior chamber cells, vitreous haze) or decrease to grade 0
Remission	Inactive disease for ≥3 months after discontinuing all treatments for eye disease

*SUN = Standardization of uveitis nomenclature.
†Applies to anterior chamber inflammation.

treatment can be reported, but because of the variability among practitioners in indications for treatment, it should not be used as the only criterion for reporting elevated intraocular pressure.

• **OUTCOMES AND RESULTS REPORTING:** The activity of anterior chamber inflammation should be on the basis of the cells in the anterior chamber. High-speed optical coherence tomography of the anterior chamber has demonstrated that a rare cell (but less than 1 per field on standard slit-lamp examination) may be present in the anterior chamber of normal individuals.[26] Therefore, it was agreed that for reporting purposes, *inactive* anterior uveitis should be defined as rare cells or less. The presence of one cell in every field is indicative of 0.5+ cells (or in some systems "trace cells") and, for reporting purposes, should not be considered inactive uveitis. As with the inability to reach consensus on a grading system for vitreous cells, no consensus could be reached on a definition of inactive vitritis on the basis of vitreous cells.

Although the goal of treatment of uveitis is to suppress the inflammation completely ("inactive" disease), for the short-term evaluation of new therapies, it may be appropriate to determine whether the inflammation has improved or worsened (Table 5). Given the semiquantitative nature of the grading systems (for example, for anterior chamber cells, vitreous haze), it was agreed that at least a two-step decrease in the level of inflammation for improvement and at least a two-step increase in the level of inflammation for worsening were better criteria than one-step changes. However, because of floor and ceiling effects (that is, 3+ only can increase by one step and 0.5+ only can decrease by one step), the definition of improvement should include a decrease in inflammation from 0.5+ to inactive, and the definition of worsening should include an increase from 3+ to the maximum grade. Hence, *improvement* in the inflammation will be defined as either a two-step decrease in the level of inflammation or a decrease to "inactive," and *worsening* of the inflammation will be defined as either a two-step increase in the level of inflammation or an increase to the maximum grade. The group considered several definitions of the term *remission*, including inactive disease on treatment, inactive disease after discontinuing treatment, and inactive disease for a specified duration after discontinuing treatment. Because chronic uveitis may be a life-long problem, which can be controlled by treatment but relapses promptly after discontinuing treatment, there was consensus that the term *remission* should be reserved for inactive disease for at least 3 months after discontinuing all treatments for eye disease. Clinical studies of immunosuppressive drugs and biologic agents for severe uveitis can evaluate either the response of active uveitis to the drug being evaluated or the ability of the drug being evaluated to maintain inactive disease in the face of tapering other drugs, such as systemic corticosteroids. Although global scoring systems for a reduction in the total corticosteroid and immunosuppressive drug regimen may be a desirable goal for research studies, in clinical practice a reduction in the prednisone dose for adults to 10 mg per day or less is a primary goal of immunosuppressive drug therapy.[20] Therefore, there was consensus that for reporting purposes in studies of adult patients, reduction in the dose of prednisone to 10 mg per day or less (or its equivalent for other corticosteroids) while maintaining inactive uveitis be considered the primary outcome for successful *corticosteroid sparing*. Although other outcomes also may be reported (for example, discontinuation of prednisone), in studies where corticosteroid sparing is an outcome, reduction in the dose of prednisone to 10 mg per day or less should be reported and should be the primary measure of this outcome.

Data from clinical series should use accepted statistical methods and should not report events or outcomes as the proportion of a population when there is variable follow-up.[27] Instead, the proportion with the outcome at presentation (or study entry) should be reported and the event rate during follow-up should be reported for longitudinal studies. In those series with complete or nearly complete follow-up, the distribution of outcomes at defined time point(s) after presentation (or study entry) can be reported. "Final visual acuity," defined as the last measured acuity in a series of patients with variable follow-up, should not be reported, because it is a flawed concept that may introduce uncontrolled bias

into the study.[27,28] Instead, rates of visual acuity loss or gain either below or above specified thresholds or the rate of acuity change (for example, doubling of the visual angle), should be reported. Alternatively, when there is complete or nearly complete follow-up, the distribution of visual acuities at a specified time after presentation (or study entry), also known as "interval visual acuity results,"[28] may be reported. There was consensus that key visual acuity thresholds that should form the basis for reporting results of uveitis studies include 6/15 or worse (20/50 or worse) and 6/60 or worse (20/200 or worse), and that key acuity changes include a doubling of the visual angle (or for improvement, a halving of the angle). The latter measurement is the basis for the widely used "three lines on an ETDRS visual acuity chart."[29] In situations where logarithmic visual acuity charts, such as the ETDRS charts, are not available, other acuity measurements (for example, Snellen acuities) should be converted to logMAR format to evaluate doubling of the visual angle. The formula for logMAR is:

$$\text{logMAR} = -\log_{10}(\text{visual acuity fraction})$$

Although logMAR reporting is superior to the number of lines on a Snellen chart approach, there remain problems introduced by the limitations of Snellen Charts, particularly in the poorer ranges of visual acuity (that is, 20/100 or worse), where a line may be represented by one or two letters. Therefore, the use of logarithmic charts, especially in prospective studies, is encouraged.

CONCLUSIONS

THE FIRST INTERNATIONAL WORKSHOP ON STANDARDIZATION of Uveitis Nomenclature (SUN) has produced consensus on several items, beginning the process of developing international standards for reporting clinical data in the field of uveitis. Standardization should provide greater precision and enhance comparability among reports from different groups. Long term, a set of classification criteria for specific uveitic entities, completion of the process of standardizing the grading of inflammation, and the development of disease-specific outcomes are needed. The SUN Working Group advocates that the standards herein be applied in all studies of uveitis begun after publication of this manuscript.

REFERENCES

1. Bloch-Michel E, Nussenblatt RB. International Uveitis Study Group recommendations for the evaluation of intraocular inflammatory disease. Am J Ophthalmol 1987;103:234–235.
2. Rosenbaum JT, Holland GN. Uveitis and the Tower of Babel. Arch Ophthalmol 1996;114:604–605.
3. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–324.
4. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271–1277.
5. Holland GN. The Executive Committee of the American Uveitis Society. Standard diagnostic criteria for the acute retinal necrosis syndrome. Am J Ophthalmol 1994;117:663–666.
6. Engstrom RE Jr., Holland GN, Margolis TP, et al. The progressive outer retinal necrosis syndrome. A variant of necrotizing herpetic retinopathy in patients with AIDS. Ophthalmology 1994;101:1488–1502.
7. Read RW, Holland GN, Rao NA, et al. Revised diagnostic criteria for Vogt-Koyanagi-Harada disease: report of an international committee on nomenclature. Am J Ophthalmol 2001;131:647–652.
8. Mandeville JT, Levinson RD, Holland GN. The tubulointerstitial nephritis and uveitis syndrome. Surv Ophthalmol 2001;46:195–208.
9. Goie The HS, Steven MM, van der Linden SM, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis: a comparison of the Rome, New York and modified New York criteria in patients with a positive clinical history screening test for ankylosing spondylitis. Br J Rheumatol 1985;24:242–249.
10. Petty RE, Southwood TR, Manners P, Baum J, et al. International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31:390–392.
11. International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease. Lancet 1990;335:1078–1080.
12. Hogan MJ, Kimura SJ, Thygeson P. Signs and symptoms of uveitis: I. Anterior uveitis. Am J Ophthalmol 1964;47:155–170.
13. Schlaegel T. Essentials of uveitis. Boston: Little, Brown, Inc, 1967.
14. Nussenblatt RB, Whitcup SM. Uveitis: fundamentals and clinical practice, 3rd ed. Philadelphia: Mosby, 2004.
15. Foster CS, Vitale AT. Diagnosis and treatment of uveitis. Philadelphia: W.B. Saunders Company, 2002.
16. Kimura SJ, Hogan MJ. Signs and symptoms of uveitis: II. Classification of the posterior manifestations of uveitis. Am J Ophthalmol 1964;47:171–176.
17. Nussenblatt RB, Palestine AG, Chan CC, Roberge F. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. Ophthalmology 1985;92:467–471.
18. Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727–735.
19. Oh KT, Christmas NJ, Folk JC. Birdshot retinochoroiditis. Long-term follow-up of a chronically progressive disease. Am J Ophthalmol 2002;133:622–629.
20. Jabs DA, Rosenbaum JT, Foster CS, et al. Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders. Am J Ophthalmol 2000;130:492–513.

21. Delbecq AL, Van de Ven AH, Gustafson DH. Group techniques for program planning. A guide to nominal group and Delphi processes. Glenview: Scott Foresman and Company, 1975.
22. Tay-Kearney ML, Schwam BL, Lowder C, et al. Clinical features and associated systemic disease of HLA-B27 uveitis. Am J Ophthalmol 1996;121:47–56.
23. Sommer A, Tielsch JM, Katz J, et al. Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. Arch Ophthalmol 1991;109:1090–1095.
24. Mitchell P, Smith W, Attebo K, Healey PR. Prevalence of open-angle glaucoma in Australia. The Blue Mountains Eye Study. Ophthalmology 1996;103:1661–1669.
25. Buhrmann RR, Quigley HA, Barron Y, West SK, Oliva MS, Mmbaga BB. Prevalence of glaucoma in a rural East African population. Invest Ophthalmol Vis Sci 2000;41:40–48.
26. Lowder CY, Li Y, Perez VL, Huang D. Anterior chamber cell grading with high-speed optical coherence tomography. ARVO Abstracts 2004. Available at http://abstracts.iovs.org/cgi/content/abstract/45/5/3372. Accessed 1 December 2004.
27. Jabs DA. Improving the reporting of clinical case series. Am J Ophthalmol. 2005;139:900–905.
28. DiLoreto DA Jr, Bressler NM, Bressler SB, Schachat AP. Use of best and final visual acuity outcomes in ophthalmologic research. Arch Ophthalmol 2003;121:1586–1590.
29. Ferris FL III, Kassoff A, Bresnick GH, Bailey I. New visual acuity charts for clinical research. Am J Ophthalmol 1982; 94:91–96.

APPENDIX

STANDARDIZATION OF UVEITIS NOMENCLATURE WORKING Group.

Workshop Organizers and Writing Committee. Douglas A. Jabs, MD, MBA, The Wilmer Eye Institute, The Departments of Ophthalmology and Medicine, The Johns Hopkins University School of Medicine, and The Department of Epidemiology, The Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, USA; Robert B. Nussenblatt, MD, The National Eye Institute, The National Institutes of Health, Bethesda, Maryland, USA; James T. Rosenbaum, MD, Casey Eye Institute, The Departments of Ophthalmology and Medicine, Oregon Health Sciences University, Portland, Oregon, USA.

Workshop Attendees. Leyla S. Atmaca, MD, The Department of Ophthalmology, Gazi Mustafa Kemal Bulvari, Ankara, Turkey; Matthias D. Becker, MD, PhD, FEBO, Interdisciplinary Uveitis Center, University of Heidelberg, Heidelberg, Germany; Antoine P. Brezin, MD, PhD, Ophtalmologie, Université Paris and Hôpital Cochin, Paris, France; Soon-Phaik Chee, MD, Ocular Inflammation and Immunology, Singapore National Eye Centre, Singapore; Janet L. Davis, MD, The Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami, Miami, Florida, USA; Jean Deschenes, MD, Department of Ophthalmology, McGill University Health Center, Montreal, Quebec, Canada; Marc de Smet, MD, PhD, Department of Ophthalmology, University of Amsterdam, Amsterdam, The Netherlands; Andrew Dick, MD, Research Clinical Sciences, University of Bristol, Bristol Eye Hospital, Bristol, United Kingdom; James P. Dunn, MD, The Wilmer Eye Institute, The Department of Ophthalmology, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; John V. Forrester, MD, Department of Ophthalmology, University of Aberdeen, Aberdeen, United Kingdom; Rudolph M. Franklin, MD, New Orleans, Louisiana, USA; William A. Godfrey, MD, University of Kansas School of Medicine and Hunkeler Eye Institute, Kansas City, Missouri, USA; Debra A. Goldstein, MD, University of Illinois at Chicago Eye and Ear Infirmary, Chicago, Illinois, USA; Elizabeth M. Graham, FRCP, DO, FRCOphth, St. Thomas Hospital, London, United Kingdom; Carl P. Herbort, MD, PD, MER, La Source Eye Centre and University of Lausanne, Lausanne, Switzerland; Gary N. Holland, MD, Jules Stein Eye Institute, David Geffen School of Medicine at UCLA, Los Angeles, California, USA; Henry J. Kaplan, MD, The Department of Ophthalmology and Visual Science, University of Louisville, Louisville, Kentucky, USA; John H. Kempen, MD, PhD, The Wilmer Eye Institute, The Department of Ophthalmology, The Johns Hopkins University, and The Department of Epidemiology, The Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, USA; David L. Knox, MD, The Wilmer Eye Institute, The Department of Ophthalmology, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; Paul A. Latkany, MD, New York Eye and Ear Infirmary, New York, New York, USA; Phuc LeHoang, MD, PhD, Department of Ophthalmology, La Pitíe-Salpêtriere School of Medicine, Paris, France; Ralph D. Levinson, MD, Jules Stein Eye Institute, David Geffen School of Medicine at UCLA, Los Angeles, California, USA; Grace Levy-Clarke, MD, The National Eye Institute, The National Institutes of Health, Bethesda, Maryland, USA; Careen Y. Lowder, MD, PhD, Cleveland Clinic, Cleveland, Ohio, USA; Peter J. McCluskey, MD, FRACO, FRACS, University of New South Wales, School of Medical Sciences, Sydney, New South Wales, Australia; Manabu Mochizuki, MD, Department of Ophthalmology and Visual Sciences, Tokyo Medical and Dental University, Tokyo, Japan; Cristina Muccioli, MD, São Paulo Medical School, Federal University of São Paulo, São Paulo, Brazil; Philip I. Murray, MD, Academic Unit Ophthalmology, University of Birmingham, Birmingham, United Kingdom; Quan Dong Nguyen, MD, MSc, The Wilmer Eye Institute, The Department of Ophthalmology, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; Narsing A. Rao, MD, Doheny Eye Institute, University of Southern California, Los Angeles, California, USA; Russell W. Read, MD, Department of Ophthalmology and Pathology, University of Alabama at

Birmingham, Birmingham, Alabama, USA; Antonio G. Secchi, MD, Department of Ophthalmology, University of Padua, Padua, Italy; Janine A. Smith, MD, The National Eye Institute, The National Institutes of Health, Bethesda, Maryland, USA; Justine R. Smith, MBBS, PhD, Casey Eye Institute, Department of Ophthalmology, Oregon Health Sciences University, Portland, Oregon, USA; Ronald E. Smith, MD, Doheny Eye Institute, University of Southern California, Los Angeles, California, USA; Eric B. Suhler, MD, The Department of Ophthalmology, Casey Eye Institute, Oregon Health Sciences University, Portland, Oregon, USA; Jennifer E. Thorne, MD, The Wilmer Eye Institute, The Department of Ophthalmology, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; Russell N. Van Gelder, MD, PhD, The Department of Ophthalmology and Visual Sciences, Washington University, St. Louis, Missouri, USA; Albert T. Vitale, MD, The Department of Ophthalmology and Visual Sciences; University of Utah, Salt Lake City, Utah, USA; Denis Wakefield, MD, University of New South Wales, Randwick, New South Wales, Australia; Robert S. Weinberg, MD, The Department of Ophthalmology, The Wilmer Eye Institute, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; Manfred Zierhut, MD, The Department of Ophthalmology, University of Tuebingen, Tuebingen, Germany.

Members not in Attendance. Rubens Belfort, Jr, MD, Department of Ophthalmology, EPM Federal University of São Paulo, São Paulo, Brazil; C. Stephen Foster, MD, Massachusetts Eye and Ear Infirmary, Department of Ophthalmology, Harvard University, Boston, Massachusetts, USA; Susan Lightman, MD, Department of Clinical Ophthalmology, Institute of Ophthalmology and Moorfields Eye Hospital, London, United Kingdom; Shigeaki Ohno, MD, Department of Ophthalmology and Visual Sciences, Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido Japan; Aniki Rothova, MD, F.C. Donders Institute of Ophthalmology, Utrecht, Netherlands.

OPEN ACCESS

EXTENDED REPORT

Consensus-based recommendations for the management of uveitis associated with juvenile idiopathic arthritis: the SHARE initiative

Tamas Constantin,[1] Ivan Foeldvari,[2] Jordi Anton,[3] Joke de Boer,[4] Severine Czitrom-Guillaume,[5] Clive Edelsten,[6] Raz Gepstein,[7] Arnd Heiligenhaus,[8,9] Clarissa A Pilkington,[10] Gabriele Simonini,[11] Yosef Uziel,[12] Sebastian J Vastert,[13] Nico M Wulffraat,[13] Anne-Mieke Haasnoot,[4] Karoline Walscheid,[8] Annamária Pálinkás,[1] Reshma Pattani,[6] Zoltán Györgyi,[1] Richárd Kozma,[1] Victor Boom,[14] Andrea Ponyi,[1] Angelo Ravelli,[15] Athimalaipet V Ramanan[16]

Handling editor Josef S Smolen

For numbered affiliations see end of article.

Correspondence to
Prof Athimalaipet V Ramanan, University Hospitals Bristol NHS Foundation Trust & Bristol Medical School, University of Bristol, Bristol BS8 1TH, UK; avramanan@hotmail.com

Received 28 January 2018
Revised 7 March 2018
Accepted 11 March 2018
Published Online First 28 March 2018

ABSTRACT

Background In 2012, a European initiative called Single Hub and Access point for pediatric Rheumatology in Europe (SHARE) was launched to optimise and disseminate diagnostic and management regimens in Europe for children and young adults with rheumatic diseases. Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children and uveitis is possibly its most devastating extra-articular manifestation. Evidence-based guidelines are sparse and management is mostly based on physicians' experience. Consequently, treatment practices differ widely, within and between nations.

Objectives To provide recommendations for the diagnosis and treatment of JIA-associated uveitis.

Methods Recommendations were developed by an evidence-informed consensus process using the European League Against Rheumatism standard operating procedures. A committee was constituted, consisting of nine experienced paediatric rheumatologists and three experts in ophthalmology from Europe. Recommendations derived from a validated systematic literature review were evaluated by an Expert Committee and subsequently discussed at two consensus meetings using nominal group techniques. Recommendations were accepted if >80% agreement was reached (including all three ophthalmologists).

Results In total, 22 recommendations were accepted (with >80% agreement among experts): 3 on diagnosis, 5 on disease activity measurements, 12 on treatment and 2 on future recommendations.

Conclusions The SHARE initiative aims to identify best practices for treatment of patients suffering from JIA-associated uveitis. Within this remit, recommendations for the diagnosis and treatment of JIA-associated uveitis have been formulated by an evidence-informed consensus process to suggest a standard of care for JIA-associated uveitis patients throughout Europe.

Check for updates

To cite: Constantin T, Foeldvari I, Anton J, *et al*. *Ann Rheum Dis* 2018;**77**:1107–1117.

INTRODUCTION

In 2012, Single Hub and Access point for pediatric Rheumatology in Europe (SHARE) was launched with the aim of optimising and disseminating diagnostic and management regimens for children and adolescents with rheumatic diseases. The European League against Rheumatism (EULAR) has produced a number of recommendations in the area of paediatric rheumatology such as juvenile dermatomyositis[1] using a standardised procedure[2] and referring to a generalised instrument for guideline assessment: the Appraisal of Guidelines for Research & Evaluation.[3]

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children, and uveitis is the most frequent and potentially most devastating extra-articular manifestation. There are no international consensus statements specifically relating to the diagnosis and treatment of JIA-associated uveitis although there are national guidelines from Germany and Spain.[4 5] Management is therefore based on physicians' personal experience; and considerable variation in clinical practice, both in terms of investigation and management of JIA-associated uveitis, was found in an extensive survey of uveitis experts.[6]

With the rapid development of novel therapies for JIA, clear recommendations based on available best evidence and expert opinion (when trial evidence is lacking) will help physicians in the care of patients with JIA-associated uveitis. The uveitis seen with JIA is usually chronic anterior uveitis which is asymptomatic, but acute anterior uveitis can also be seen in the enthesitis-related arthritis subtype.[7 8] There is a clear need to regularly update those managing patients with JIA uveitis through expert opinion. While the majority of treatments available for the treatment of arthritis have a solid evidence base from clinical trials, corresponding data for patients with uveitis may not be known or the level of evidence may not be as strong at the time of their introduction into clinical practice.

The primary aims of the recommendations forwarded by the Expert Group were to develop agreed strategies to

- prevent or reduce the likelihood of JIA-associated uveitis from occurring and minimise the damage at the time of diagnosis
- recommend treatments and management strategies that would reduce inflammation and prevent the development of those ocular complications most likely to cause irreversible visual loss.

METHODS

A committee of 12 experts (AH, BV, CP, CE, SC-G, IF, JdB, JA, KW, RG, YU, NW) in paediatric rheumatology (n=9) or ophthalmology (n=3) was established to develop recommendations for JIA-associated uveitis based on consensus, but evidence informed, using EULAR standard operating procedures for developing best practice.[2 3]

Systematic literature search

The electronic databases PubMed/MEDLINE, Embase and Cochrane were searched independently by two researchers for eligible articles in February 2015. All synonyms of JIA were searched in Medical Subject Headings/Emtree terms, titles and abstracts (figure 1). Reference tracking was performed in all included studies (full search strategy is shown in figure 1). Experts (TC, AP, VB) selected papers relevant to uveitis associated with JIA investigations and/or treatment to be taken forward for validity assessment (inclusion and exclusion criteria shown in figure 1) by members of the expert committee.

Validity assessment

The selected articles were randomly allocated to the expert group, and two members per paper independently assessed the methodological quality of those papers meeting the inclusion

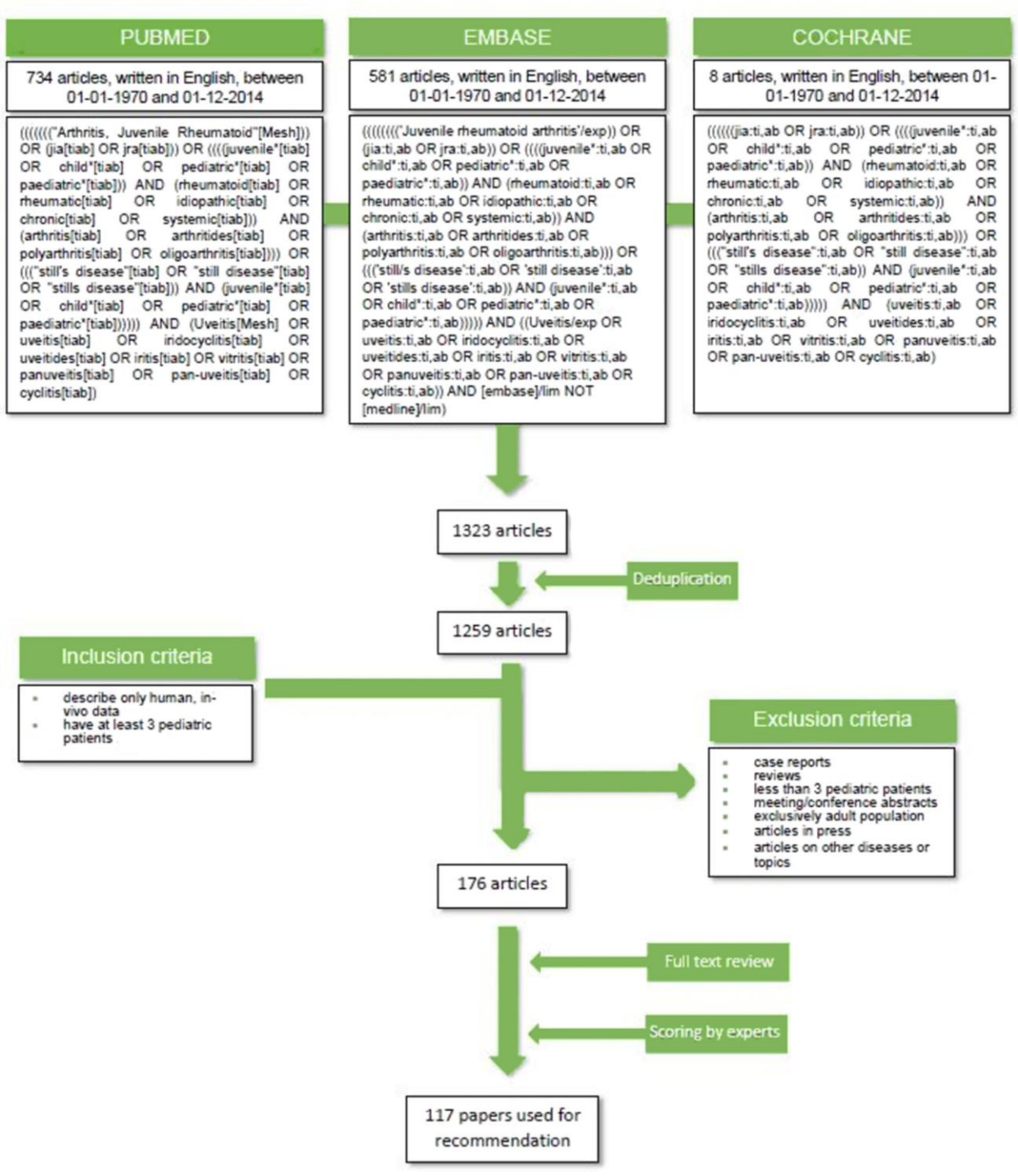


Figure 1 Summary of search strategy for identification of key articles.

Table 1 Recommendations for diagnosis and screening in juvenile idiopathic arthritis (JIA)-related uveitis

Recommendation	L	S	Agreement (%)	References
1. All patients in whom a diagnosis of JIA is being considered should be screened for uveitis according to a contemporary and audited protocol. Formal screening protocol should be administered in all centres, where patients with JIA are seen.	2A	B	100	13-32
2. Frequency of ophthalmological follow-up visits must be based on disease severity and needs to be decided in conjunction with an expert ophthalmologist.	4	D	100	13-27 33-66
3. Patients with JIA stopping any systemic immunosuppressant are at risk of developing new onset uveitis or recurrence of uveitis after a prolonged remission. After stopping systemic immunosuppression, it is recommended that all patients with JIA are screened by an ophthalmologist at least every three months for at least 1 year.	2B	B	100	67-70

Agreement indicates the % of experts that agreed on the recommendation during the final voting round of the consensus meeting.
1A, meta-analysis of cohort studies; 1B, meta-analysis of case-control studies; 2A, cohort studies; 2B, case-control studies; 3, non-comparative descriptive studies; 4, expert opinion; A, based on level 1 evidence; B, based on level 2 or extrapolated from level 1; C, based on level 3 or extrapolated from level 1 or 2; D, based on level 4 or extrapolated from level 3 or 4 expert opinion. L, level of evidence; S, strength of evidence.

criteria (figure 1). Data were extracted using predefined scoring forms for diagnostic and therapeutic studies. Disagreements were resolved by discussion or by the opinion of a third expert. Adapted classification tables for diagnostic, therapeutic and epidemiological studies were used to determine the level of evidence and strength of each recommendation.[9–11]

Establishment of recommendations

As part of the EULAR standard operating procedure, experts described the main results and conclusions of each paper, along with their validity and level of evidence. These descriptions were collated by five experts (TC, GS, YU, RG, JdB) and used to formulate provisional recommendations which were reviewed by a panel of three experts (IF, NW, JdB). A summary of the evidence was presented along with each provisional recommendation to the expert committee. The recommendations were revised and discussed at a face-to-face meeting in March 2014 (Genova: 12 participants), using a Nominal Group Technique to reach a consensus.[12] A non-voting expert (AR) facilitated the process. Recommendations were accepted when ≥80% (10 of 12) of the experts agreed (including all three ophthalmologists).

RESULTS

Literature review

The literature search yielded a total of 1323 papers which, after deduplication, left 1259 unique articles. Evaluation of inclusion/exclusion criteria in titles and/or abstracts resulted in a core reference database of 176 articles for which full-text copies were obtained for quality screening by the expert committee. Of these, 117 were selected to support the development of consensus-based recommendations by the expert group (figure 1).

Recommendations

The sections that follow report the recommendations of the expert committee based on the supporting literature.[13–128] Tables 1–4 summarise the recommendations, the level of evidence that they provide and the strength of the recommendation, and the percentage of experts who agreed with these assessments.

Background

JIA is the most common chronic rheumatic disease in children with an incidence of 8.2 (7.5–9.0)/100 000 of the population under 16 and an annual prevalence of approximately 70.2 [16 – 140]/100 000.[129 130] The wide prevalence range has been attributed to the different study designs employed, but the incidence is thought to vary little worldwide.[130] The incidence of JIA-associated uveitis is thought to be approximately 1/10 000 and there is some evidence that it is less frequent in oriental populations with JIA.[7 131]

Structural complications, some of them leading to irreversible visual loss, include cataracts, glaucoma, band keratopathy, macular oedema, retinal detachment and sequelae associated with chronic hypotony. The uveitis usually has an insidious time course and can be chronic or recurrent but, most frequently, JIA-associated uveitis is a chronic relapsing condition lasting several years. It almost universally starts as an anterior uveitis, but in rare instances can become a panuveitis. JIA-associated uveitis is usually asymptomatic in the age group in which it

Table 2 Recommendations for disease activity measurement in juvenile idiopathic arthritis (JIA)-related uveitis

	L	S	Agreement (%)	References
4. There should be good communication between the ophthalmologist and the paediatric rheumatologist concerning changes in disease activity treatment changes and responsibility for treatment monitoring.	3	C	100	71
5. There is a need to develop shared outcome measures to help guide decisions on systemic treatment.	4	D	100	
6. At present, there is no validated biomarker to follow the activity of uveitis.	2A	B	100	4 21 29 31 32 37 41 46 72-76
7. At present, no widely accepted definition of inactive disease for JIA-related uveitis is available. The goal of treating JIA-associated uveitis should be no cells in the anterior chamber. The presence of macular and/or disk oedema, ocular hypotony and rubeosis iridis may require anti-inflammatory treatment even in the absence of AC cells.	2B	B	100	4 69 78
8. We recommend 2 years of inactive disease off topical steroids before reducing systemic immunosuppression (both DMARDs and biological therapies).	3	C	92	67

Agreement indicates the % of experts that agreed on the recommendation during the final voting round of the consensus meeting.
1A, meta-analysis of cohort studies; 1B, meta-analysis of case-control studies; 2A, cohort studies; 2B, case-control studies; 3, non-comparative descriptive studies; 4, expert opinion; A, based on level 1 evidence; B, based on level 2 or extrapolated from level 1; C, based on level 3 or extrapolated from level 1 or 2; D, based on level 4 or extrapolated from level 3 or 4 expert opinion. DMARD, disease-modifying anti rheumatic drugs; L, level of evidence; S, strength of evidence.

Table 3 Recommendations for treatment in juvenile idiopathic arthritis (JIA)-related uveitis

	L	S	Agreement (%)	References
9. Active uveitis in JIA usually requires immediate treatment.	2B	B	100	69 71 78-80
10. Topical corticosteroids (preferably prednisolone acetate or dexamethasone) are the first-line treatment of anterior uveitis.	4	D	100	81
11. Topical and systemic NSAIDs have no demonstrable effect as monotherapy, but may be used as additional therapy.	3	C	92	79 81 82
12. Systemic immunosuppression in active uveitis is recommended if poor prognostic factors are present at the first visit. Poor prognostic factors including lack of remission later on during the disease course require systemic immunosuppression.	2A		100	4 19 22 29 55 56 65 78 83 84
13. Systemic immunosuppression is recommended if inactivity could not be reached within 3 months or inflammation is reactivating during steroid dose reduction.	2B	B	100	55 59 68 69 78 80 85-87
14. Methotrexate is the first choice as systemic immunosuppression.	4	D	100	68 84 88-95
15. In case of methotrexate inefficacy or intolerance, adding or switching to biological treatment is recommended.	3	C	92	91-104
16. The use of anti-TNF treatment strategies *(adalimumab>infliximab>golimumab)* is recommended in patients with uveitis refractory/resistant to DMARD therapy, principally methotrexate.	3	C	100	86 100 101 104-117 120-124 126 127
17. Based on the current evidence, etanercept should not be considered for JIA-associated uveitis.	1B	A	100	87 100 109 117-121
18. Switching between different anti-TNF treatments might be valuable if uveitis is refractory to the first anti-TNF, even though the present evidence comes from small case series or inception cohorts.	3	C	100	87 113 116 122
19. In case of lack of efficacy, consider testing for antidrug antibodies and drug trough level. If the patient has no antibodies but has low trough levels, consider increasing the dose or shortening the interval.	4	D	100	
20. Tocilizumab, rituximab and abatacept might be potential options for cases refractory to previous anti-TNF therapy.	3	C	100	123-125

Agreement indicates the % of experts that agreed on the recommendation during the final voting round of the consensus meeting.
1A, meta-analysis of cohort studies; 1B, meta-analysis of case-control studies; 2A, controlled study without randomisation; 2B, quasi-experimental study; 3, descriptive study; 4, expert opinion; A, based on level 1 evidence; B, based on level 2 or extrapolated from level 1; C, based on level 3 or extrapolated from level 1 or 2; D, based on level 4 or extrapolated from level 3 or 4 expert opinion.; DMARD, disease-modifying antirheumatic drugs; L, level of evidence; NSAIDs, non-steroidal anti-inflammatory drugs; S, strength of evidence; TNF, tumour necrosis factor.

most commonly develops (age 3–7 years), but severe inflammation may cause symptomatic pain and redness and these symptoms and signs, as well as pupil distortion, may be noticed by carers and lead to early referral. Reduced visual function is an uncommon cause of presentation in small children unless it is severe and usually secondary to irreversible structural damage. The presence of antinuclear antibodies (ANA), oligoarthritis and early onset of arthritis are predominant risk factors for chronic anterior uveitis in those with JIA, and improved identification of children at risk is a key priority for targeted screening programmes. This exercise only looked at chronic anterior uveitis associated with JIA and not at acute anterior uveitis seen in human leukocyte antigen (HLA) B27-positive children with enthesitis-related arthritis.

Table 4 Recommendations for future plans in juvenile idiopathic arthritis (JIA)-related uveitis

	L	S	Agreement (%)	References
21. Validated outcome measures for JIA-associated uveitis are needed	3	C	100	73 126-128
22. Controlled clinical trials are needed for JIA-associated uveitis	1B	A	100	119

Agreement indicates the % of experts that agreed on the recommendation during the final voting round of the consensus meeting.
1A, meta-analysis of cohort studies; 1B, meta-analysis of case-control studies; 2A, cohort studies; 2B, case-control studies; 3, non-comparative descriptive studies; 4, expert opinion (diagnostic studies); 1A, meta-analysis of randomised controlled trials; 1B, randomised controlled study; 2A, controlled study without randomisation; 2B, quasi-experimental study; 3, descriptive study; 4, expert opinion (therapeutic studies); A, based on level 1 evidence; B, based on level 2 or extrapolated from level 1; C, based on level 3 or extrapolated from level 1 or 2; D, based on level 4 or extrapolated from level 3 or 4 expert opinion. , level of evidence; S, strength of evidence .

Timely and aggressive treatment is clearly needed where there is significant damage at the time of diagnosis. However, the variable course of the disease means that some significant events may occur years after therapy commences and there remains considerable disagreement among expert practitioners about the timing and indications for treatment escalation.[132 133]

Recommendations for diagnosis and screening in JIA-related uveitis

Screening for JIA-associated uveitis

All patients with JIA should be screened for uveitis according to contemporary and audited screening protocols which should be implemented in all centres in which patients with JIA are being managed.[42 43] There is no necessity for the screening process to take place in the same institution as the rheumatological care. It is especially important, however, that all children in whom the diagnosis of JIA is being considered should have a timely check by a local ophthalmologist rather than wait for confirmation of the diagnosis from a paediatric rheumatology referral centre. It is the responsibility of paediatric rheumatologist to ensure children with JIA are referred for screening. Screening starts with all individuals with a 'suspected' diagnosis of JIA and the clinical responsibility for organising this service needs to be clear. This is independent of whether it is the remit of the ophthalmologist not specialised in uveitis, paediatrician or rheumatologist (table 1). The evidence published to suggest that the risk factors originally proposed for the development of chronic uveitis in the JIA population (early-onset arthritis, ANA positivity and oligoarticular subtype) is suboptimal: the expert group noted that despite the fact that a number of screening protocols have been published there is no evidence to suggest that any one of them is superior.[5 23 26 61 74]

Advances in genetics have not found any more specific diagnostic markers than the HLA types originally reported as being associated with both oligoarticular disease and uveitis.[14 15 30 32 38 48 50 56] There is no evidence, at present, that genotyping adds specificity to the established clinical risk factors on which contemporary screening programmes are based.

Despite the advances in subtyping ANAs in other rheumatic disorders, there has been little advance in our understanding of the association of ANAs with the risk of JIA-associated uveitis[28 34 35 41 60 67] although antibodies to nuclear structures such as histones and chromatin[16 21 41 52–54 64 77] and ocular antigens have been reported.[13 33 51 75] Two studies found that children with higher inflammatory activity (as determined by higher erythrocyte sedimentation rate (ESR) values) when oligoarthritis or polyarthritis was diagnosed had an increased risk of developing uveitis.[27 31]

There is a clear unmet need to adapt screening policies to the contemporary usage of early systemic immunosuppressant treatment of arthritis[57 61 62 64] and novel biomarkers and future genotyping may improve targeting of the population being screened.

Monitoring during follow-up

The risk of visual symptoms and potential for relapse in patients initially responding to treatment highlights the necessity for maintained regular close ophthalmological scrutiny. The expert group recommended that the frequency of ophthalmological follow-up should be based on ocular disease severity and decided upon in conjunction with an expert ophthalmologist.

Screening after stopping treatment of uveitis

Methotrexate (MTX) is the immunosuppressive therapy of choice in patients with JIA-related uveitis (see recommendation 14, table 3). Once long-lasting remission of uveitis is achieved, MTX is usually stopped, but the optimal period of disease control prior to withdrawal of both topical and systemic treatment remains unclear. Patients stopping MTX are at risk of developing new onset uveitis or recurrence of uveitis after prolonged remission in the first year. Indeed, the majority of patients in a recently reported series relapsed within 24 months of stopping therapy.[67–70] Consequently, after stopping immunosuppression with MTX (prescribed for arthritis or uveitis) it is recommended that all patients with JIA are screened by an ophthalmologist at least every three months for a minimum of 1 year.

It also remains unclear for those patients on multiple treatments, in which order treatments are best withdrawn. Relapse of uveitis after withdrawal of MTX appears to be delayed in older patients, those who have been on treatment for longer duration.[67] The authors recommended that the period of uveitis inactivity should be >2 years before MTX is withdrawn.[67] The expert group also recommend that patients should have 2 years of inactive disease while not using topical steroids before reducing systemic immunosuppression.

There is a clear need for continuing monitoring in the early period of remission after medications are stopped, especially in patients on long-term therapy, topical or systemic, which had maintained disease control. The expert group recommends that monitoring of disease in remission by an ophthalmologist should be at least every three months and should continue for at least 3 years off all forms of treatment. The length of remission best predicting lifetime remission remains unknown. More robust data on effective screening strategies are required.

Recommendations for disease activity measurement in JIA-associated uveitis

A pivotal goal in the management of JIA-associated uveitis is to minimise loss of vision through the early diagnosis of ocular morbidity. Early referral and appropriate treatment to eliminate ocular inflammation are seen to be crucial in preserving visual acuity. Visual loss is mainly caused by glaucoma, macular damage from inflammatory oedema, hypotony or amblyopia: structural damage can occur prior to diagnosis and also arise following years of poorly controlled inflammation.

Multiple studies have found delayed presentation with damage at diagnosis, surgery and length of follow-up to be the major risks for lifelong visual loss.[4 68 78] Male gender and non-Caucasian race may be additional risk factors for some complications.[18 19 37 56 65 71] Immunosuppressive treatment is therefore aimed at reducing agreed measures of active intraocular inflammation which include the level of cellular infiltrate, breakdown of vascular barriers (eg, flare) and macular oedema: few of these measures have been validated and different markers may be appropriate in eyes with different levels of structural damage or at different stages of disease.[134]

In one study, an increase in anterior chamber cell grade was associated with elevated rates of visual loss in a dose-dependent fashion, whereas immunotherapy was associated with a reduced risk of visual loss, particularly for the 20/50 or worse outcome (HR 0.40; P<0.01).[78] Others have found anterior chamber flare a better predictor of visual loss.[63]

There are no established biomarkers currently available for predicting disease activity or guiding treatment in JIA-associated uveitis and research efforts in this area need to be intensified (table 2).[24 32 34 35 40 44 49 75–80]

In a small group of children with JIA-related anterior uveitis, serum interleukin-2R levels were significantly increased,[72] while in a larger cohort of children there was a significant correlation between the presence of anterior uveitis and aqueous humour levels of transthyretin.[73] Until reliable biomarkers are found, management relies on frequent ophthalmic examination. Future opportunities might include gene expression and proteomic profiling of the serum, peripheral blood leucocytes and aqueous humour; measurement of acute-phase reactants; HLA typing and determination of ANAs.[74] Evidence-based guidelines by the German Ophthalmological Society, the Society for Childhood and Adolescent Rheumatology and the German Society for Rheumatology noted that macular oedema, ocular hypotony and rubeosis iridis are often associated with chronic inflammation and anti-inflammatory treatment should be initiated (or intensified) even in the absence of cells in the anterior chamber.[4] The expert group recommended that the goal of treating JIA-associated uveitis should be no cells in the anterior chamber although this may not be practically possible (table 2). With reference to the Standardization of Uveitis Nomenclature (SUN) Working Group, a multinational interdisciplinary group (MIWGUC) developed a set of core outcome measures for uveitis that may provide a framework for evaluating disease severity and its course, risk for structural impairment, levels of impairment in visual function and responses to treatment.[74] These would be invaluable in clinical studies involving patients with JIA-associated uveitis. However, these proposed outcome measures remain to be validated in children.[135] To best guide treatment decisions, there should be good communication between the ophthalmologist and the paediatric rheumatologist concerning changes in disease activity treatment changes and responsibility for treatment monitoring. Recently published guidance for management

of non-infectious uveitis in adults has some important principles for the management of panuveitis in all age groups.[136]

Recommendations for treatment in JIA-associated uveitis

Active uveitis in JIA usually requires immediate treatment. In a comparison of two cohorts of patients with new-onset JIA, separated by a 10-year interval, the more recently treated patients received early intensive treatment and close monitoring, and reported fewer complications and milder uveitis with visual loss avoided in most cases.[80] Treatment factors reported to be associated with improved outcomes included introduction of immunosuppressive therapy earlier in the course of the disease or at a younger age[69] and treatment with immunosuppressants generally.[71 78]

Based on past usage, the expert group recommend that topical corticosteroids (preferably prednisolone or dexamethasone) are the first-line treatments of choice for both acute and chronic anterior uveitis.[4 5 81 129] Children with JIA-related uveitis are frequently treated with topical corticosteroids over extended periods, and this increases the risk of cataract formation and glaucoma.

One study found that the increased risk of cataract formation with high-dose topical steroids was independent of active uveitis or presence of posterior synechiae.[81] The risk increased as the number of drops of topical corticosteroids instilled increased. The data suggested that patients may be treated with low doses of topical corticosteroids (≤3 drops daily) over moderate periods of follow-up (median 4 years; range 0.5–15 years) with a low risk of developing cataracts.[81] Among eyes receiving ≤2 drops daily, the incidence of cataract was 0/eye year. There appears to be no evidence to suggest that less potent topical steroids reduce adverse effects in this patient population (table 3). Systemic corticosteroids are not usually preferred in children due to risks of growth suppression and osteopenia; however, they are potentially helpful in individual cases for rapid control of severe uveitis or in the presence of macular oedema.

In a retrospective study, the adjunctive use of non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of chronic iridocyclitis was evaluated in 14 patients, 8 with JIA and 6 with idiopathic iridocyclitis.[82] In all patients, the activity of the iridocyclitis improved with the addition of NSAIDs to their treatment regimens, permitting reduction in the dose of corticosteroid drugs. These data suggest that NSAID therapy may have an adjunctive role in the treatment of chronic iridocyclitis in childhood, but not as monotherapy.

Systemic immunosuppression for active uveitis is recommended to reduce complications in those cases where topical steroids are insufficient to eliminate ocular inflammation short term, or such high doses are required that treatment risks outweigh the beneficial effects. However, the threshold for introducing systemic treatment is lower in those with multiple risks for visual loss as discussed earlier.[129] Immediate systemic immunosuppression in active uveitis is recommended if poor prognostic factors are present at the first visit. Studies suggest instituting aggressive immunosuppression in high-risk patients even before there is any clear evidence of complications developing.[27 39] Poor prognostic factors include uveitis antedating arthritis[19 22 74]; posterior synechia[55 68 74 75]; male gender[19 22 55]; band keratopathy, glaucoma and cataract[55]; poor initial vision, hypotony, macular oedema and dense vitreous body opacification[55]; and lack of remission later on during the disease course (table 3). Age at the time of uveitis onset does not appear to be a risk factor.[22 56]

Definition of treatment failure

Treatment failure should lead to a change in treatment dose, route or modality taking into consideration the fact that many of the drugs require different times to achieve their optimal effect and there are sometimes only a limited number of drugs available. Inappropriate drug changes may result from difficulties in achieving consensus on the definition of treatment failure. In a retrospective study, the clinical outcome of 23 patients with JIA-associated uveitis unresponsive to corticosteroids was ascertained. Uveitis was controlled using immunosuppressive therapy in all cases.[86] Patients treated within 4–30 months from onset of uveitis achieved better improvement of vision compared with patients who received immunosuppressive therapy after 3 years ($P<0.005$ for right and left eyes pooled; $P=0.0075$ for best eyes; $P=0.0375$ for worst eyes). These data are supported by findings from the SITE study which reported that among patients with JIA-associated uveitis receiving tertiary care use of immunosuppressants reduced the risk of vision loss by about 60%.[78] The expert group recommended that systemic immunosuppression should be used if inactivity cannot be achieved with topical steroids within 3 months or inflammation is reactivated during steroid dose reduction. The benefits of immunosuppressive therapy are now well recognised, and, in general, patients in remission received this treatment earlier in the course of disease compared with patients who relapsed.[55 59 68 78–87]

Based on findings of efficacy and tolerability/safety from a number of studies, the expert group recommended that MTX is the immunosuppressive therapy of choice in patients with JIA-related uveitis.[68 84 88–90] Other forms of immunosuppressive therapy such as azathioprine, sulfasalazine, mycophenolate mofetil, cyclosporine and leflunomide have been assessed in patients with uveitis, often in MTX-resistant cases.[91 95] The studies have generally included a small numbers of patients, and in the case of cyclosporine, the clinical efficacy was poor and the authors noted that it has limited value in this indication.[94] The results with other forms of immunosuppressive therapy were more encouraging, but were in fewer patients.[91–93 95] At this stage they may prove to be useful treatment options in patients not responding to, or who cannot tolerate, MTX and they also have a place accompanying biological treatment in those who are MTX-intolerant. There is also evidence of the greater effectiveness of MTX in controlling arthritis in JIA compared with other conventional immunosuppressants. It is not uncommon for treatment to fail when treatments other than MTX are used because of recurrent arthritis rather than failure to control the uveitis.

As noted above, the evidence with other forms of immunosuppressive therapy in patients with JIA-related uveitis is low,[91–95] whereas many conventional immunosuppressants are used in adult onset uveitis with no specific agent favoured as the first choice. In both adult and childhood patients who fail to respond to conventional immunosuppressants, expert groups recommend adding or switching to biological treatments. There is a growing number of studies supporting the use of biological therapy in MTX refractory uveitis.[93–108] A wide range of biological therapies have been investigated in JIA-related uveitis refractory to conventional therapy, with adalimumab being the most widely studied; other agents investigated include infliximab, daclizumab, etanercept, golimumab, abatacept, tocilizumab and rituximab.[96–108 123–125]

All of the biological therapies investigated produced some benefit in patients with uveitis refractory to conventional therapy.[86 100–127] There are very few comparative studies. One

study found infliximab to be significantly superior to etanercept in children with refractory JIA-associated chronic uveitis.[100] In another small study, adalimumab was more efficacious than infliximab when used as first-line anti-TNF treatment.[106] Adalimumab also produced higher remission rates versus infliximab in the medium-term treatment (at least 12 months) of patients with JIA-related uveitis[107] and in children with uveitis it was significantly superior to infliximab in maintaining remission over a 3-year treatment period.[102] The expert group recommends treatment with anti-tumour necrosis factor (TNF) agents (adalimumab>infliximab>golimumab) in patients with uveitis refractory/resistant to disease-modifying antirheumatic drug (DMARD) therapy, principally methotrexate.[86 100–127]

The use of TNF inhibitors in uveitis was hypothesised based on their proven efficacy in a range of systemic inflammatory disorders including JIA, rheumatoid arthritis and Crohn's disease.[109] Etanercept is a recombinant DNA dimeric fusion protein that antagonises TNF-α, and it has proven to be effective in children with polyarticular JIA.[118] Evidence for the clinical benefit of etanercept in uveitis has generally been disappointing; it was associated with a high relapse rate and a high risk for developing uveitis flares.[87 100 109 117–121] Based on these findings, the expert group recommend that etanercept should not be considered for JIA-associated uveitis.

Findings from studies including small numbers of patients provide evidence that if treatment with one anti-TNF agent becomes ineffective switching to a different anti-TNF agent could prove to be clinically beneficial.[87 113 116 122] The efficacy and safety of adalimumab was evaluated in in 26 children with JIA resistant to current therapy (disease-modifying drugs in 17 cases and anti-TNF agents in 9 cases). Switching to adalimumab had a beneficial impact on disease control in 17 (65.4%) of patients.[113] In total, 17 patients with severe recalcitrant uveitis (resistant to etanercept, infliximab, adalimumab, rituximab or abatacept) were switched to golimumab and 14 achieved a positive response, and in 12 of these the disease was inactive at the final visit (mean duration 22 months; range 6–29 months).[116] Dhingra *et al* reported preliminary evidence that in seven cases of refractory uveitis switching between biological agents (over a period of 5–24 months) helped to control intraocular inflammation.[122]

While the literature search revealed no direct evidence of the effects of low drug trough levels or the development of anti-drug antibodies (ADAs) on the clinical efficacy of biological agents in patients with uveitis, the expert group considered findings from other clinical settings. They concluded that in cases of loss of efficacy over time consideration should be given to testing for ADAs and drug trough levels.[137 138] If the patient has no antibodies, but has low trough levels, increasing the dose or shortening the interval may be an option.[139]

In keeping with an earlier recommendation (18, table 3), there are data from small studies that in patients with JIA-related uveitis

Table 5 Proposed domains and items for outcome measures of juvenile idiopathic arthritis (JIA)-associated uveitis (from the Multinational Working Group in JIA-related uveitis)[74]

Domains	Items
Grade of cells in anterior chamber	Slit-lamp examination (according to SUN criteria)
Grade of flare in anterior chamber*	Slit-lamp examination for routine clinical practice and prospective trials (according to SUN criteria) Laser flare photometry for prospective trials
Number of visits with active uveitis	Records of treating physician ► Duration of activity over a minimum of four visits/year
Visual acuity (appropriate test for age)	Best-corrected visual acuity Thresholds: ≤20/50, ≤20/200 and no light perception Estimate contribution of amblyopia, yes/no
Development of structural complications	Synechiae, yes/no ► Initial and additional Ocular hypotony, yes/no (<5 mm Hg) Ocular hypertension, yes/no (>21 mm Hg) Glaucoma, yes/no Cataract, yes/no Band keratopathy in the central cornea, yes/no Macular oedema by optical coherence tomography, yes/no ► Funduscopy and optical coherence tomography for routine clinical practice (for macula and optic disc) ► Funduscopy and optical coherence tomography for prospective trials Epiretinal membrane formation, yes/no ► Funduscopy for routine clinical practice ► Funduscopy and optical coherence tomography for prospective trials
Quality of life	Childhood Health Assessment Questionnaire Child Health Questionnaire Pediatric Quality of Life Inventory Uveitis-specific quality of life instrument (not yet available for non-English speaking countries)
Overall uveitis-related disability	Assessment by parents, visual analogue scale Assessment by children, visual analogue scale Assessment by treating ophthalmologist, visual analogue scale Assessment by treating paediatric rheumatologist, visual analogue scale
Social outcome	School/kindergarten absence
Anti-inflammatory medication*	Reduction of corticosteroid dose—topical dose—systemic dose
Surgery*	Yes/no
Biomarkers	Research tools (not currently available

*Not an outcome measure, but should be documented.
SUN, Standardization of Uveitis Nomenclature.

refractory to conventional therapy and at least one anti-TNF therapy switching to drugs such as abatacept, rituximab or tocilizumab may be beneficial.[123–125] This included patients in whom the main cause of poor visual acuity was macular oedema.[125] There is now growing evidence for the role of tocilizumab in macular oedema associated with uveitis.[140 141] There is also an ongoing trial of tocilizumab in children with anti-TNF refractory JIA-associated uveitis (http://www.aptitude-trial.org.uk/).

The optimum time for surgery in children with complications from refractory uveitis has not been addressed as a recommendation due to paucity of evidence. Recent literature does demonstrate that a significant number of children with uveitis still require surgery for complications.[142]

Recommendations for future plans in JIA-related uveitis

A MIWGUC identified the need for clinical trials and longitudinal studies to determine the benefits and costs of health interventions in this setting.[74] To achieve this the group proposed a core set of outcomes aimed at ensuring that changes in relevant outcomes were measured, and that standardisation of outcome measures would facilitate data pooling and comparisons between interventions (tables 4 and 5). The outcomes should be agreed on by both researchers and patients, and they will provide a common focus for interventional studies. Disease-specific and universally agreed on validated outcomes are likely to reduce selective reporting and reporting bias.[74] A limitation of this core set of outcomes is that, despite the fact that there was consensus by the Working Group regarding their utility, they still remain unvalidated. Visual impairment has a significant impact on the quality of life (QOL) of patients with JIA-related uveitis and vision-related QOL relates to the degree to which vision impacts the individual's ability to perform activities of daily living as well as social, emotional and economic well-being.[126–128] The Effects of Youngsters' Eyesight QOL is a useful instrument for measuring the effects of uveitis on QOL which is currently being validated.

The expert group indicated a need for more well-controlled clinical trials in children with JIA-related uveitis to provide the scientific best evidence in the areas of diagnosis, screening, disease activity and treatment to enable the optimal care of these patients.

DISCUSSION

Following a systematic review of the literature and Nominal Group Technique methodology, under the auspices of SHARE and EULAR operating procedures, 22 recommendations for the screening, diagnosis, disease activity monitoring, treatment and future plans for children with JIA-associated uveitis were accepted with at least 80% agreement. In a disease setting where the evidence base is limited by small numbers of patients, and which is developing rapidly, these expert recommendations should help specialists with the evidence-based advice to provide optimal care for their patients.

It should be noted that, in general, the level of evidence was quite low with 13 of 22 recommendations being level 3 or 4, seven level 2 and only two level 1. This highlights the need for more research in this clinical setting where a number of new therapies, particularly biological agents, have been introduced in recent years. At the time that the data search for this article took place, the expert group noted a need for more well-controlled clinical trials in children with JIA-related uveitis. The goal being to ensure that scientific best evidence is used to support optimal treatment. In the interim period, but clearly outside the search time frame of this review, a well-designed randomised controlled trial (RCT) has been published which compared adalimumab with placebo in children with JIA-related uveitis who were taking a stable dose of MTX.[135] Active treatment was shown to control inflammation and was associated with a lower rate of treatment failure compared with placebo. These results do not alter the recommendations of the expert group, but reinforce the intent of recommendation 15 in table 3: 'In case of methotrexate inefficacy or intolerance, adding or switching to biological treatment is recommended'. The only difference being that this recommendation is now supported by level 1 evidence, rather than level 3 evidence. More recently, another smaller RCT of adalimumab has also been published showing efficacy of adalimumab in JIA–uveitis although this study used flare as the primary outcome measure.[143] The utility of biological therapies is receiving wider attention, for example, a number of studies have reported the benefits of tocilizumab.[141 144] These findings from outside the systematic data search time period emphasise the need to regularly update the recommendations of the JIA-associated uveitis expert group so as to provide the highest levels of care in this clinical setting.

Author affiliations
[1]2nd Department of Pediatrics, Semmelweis University, Budapest, Hungary
[2]Klinikum Eilbek, Hamburger Zentrum für Kinder- und Jugendrheumatologie, Hamburg, Germany
[3]Department of Pediatric Rheumatology, Hospital Sant Joan de Déu, Universitat de Barcelona, Barcelona, Spain
[4]Department of Ophthalmology, University Hospital Utrecht, Utrecht, The Netherlands
[5]Service de médecine des adolescents, CHU Bicêtre, AP-HP, 78, rue du Général-Leclerc, Paris, France
[6]Department of Ophthalmology, Great Ormond Street Hospital, London, UK
[7]Department of Ophthalmology, Meir Medical Center, Kfar Sava, Israel
[8]Department of Ophthalmology, Uveitis-Center, and Ophtha Lab, at St. Franziskus Hospital, Muenster, Germany
[9]University of Duisburg-Essen, Duisburg, Germany
[10]Department of Rheumatology, Great Ormond Street Hospital, London, UK
[11]Department of Paediatrics, Rheumatology Unit, Anna Meyer Children's Hospital, University of Florence, Florence, Italy
[12]Department of Paediatrics, Meir Medical Center, Sackler School of Medicine, Tel-Aviv University, Tel Aviv, Israel
[13]Department of Pediatric Rheumatology and Immunology, Wilhelmina Children's Hospital, University Medical Center Utrecht and University of Utrecht, Utrecht, The Netherlands
[14]Department of Internal Medicine, St. Antonius Hospital, Nieuwegein, The Netherlands
[15]Università degli Studi di Genova and Istituto Giannina Gaslini, Genoa, Italy
[16]University Hospitals Bristol NHS Foundation Trust & Bristol Medical School, University of Bristol, Bristol, UK

Acknowledgements The SHARE initiative has been endorsed by the executive committee of the Paediatric Rheumatology European Society and the International Society of Systemic Auto-Inflammatory Diseases. Editorial assistance was provided by Steve Clissold PhD (Content Ed Net, Spain).

Contributors AVR is senior author. NMW and SJV designed the SHARE initiative. AP, VB, A-MH, ZG and RK performed the systematic literature review, supervised by SJV, JdB and NMW. Validity assessment of selected papers was done by TC, IF, JA, JdB, SC-G, CE, RG, AH, CAP, GS, YU, NMW, KW and SJV. Recommendations were formulated by TC, GS, YU, RG and JdB. Provisional recommendations were reviewed by a panel of three experts (IF, NMW and JdB). The expert committee consisted of IF, JA, JdB, SC-G, CE, RG, AH, CAP, GS, YU, SJV and NW; they completed the online surveys and/or participated in the subsequent consensus meeting. AR assisted in the preparation of the live consensus meeting and facilitated the consensus procedure using nominal group technique. TC and AVR wrote the manuscript, with contribution and approval of all coauthors.

Funding Literature search in the preparation of the manuscript was supported by an unrestricted grant from Abbvie. Prof Ramanan is Co-Chief Investigator of APTITUDE Study funded by Arthritis Research UK (Grant Ref 20659).

Competing interests AH: research grants from BMBF, Pfizer and Novartis and honoraria from AbbVie, Alimera Sciences, Allergan, MSD Sharp and Dohme, Pfizer,

Santen, and Xoma. JdB: lectures and advisory board sponsored by AbbVie. SC-G: Pfizer, occasional consulting and registration fees to EULAR/PReS congress and Novartis, registration fees for PReS. IF: advisory board: Abbvie, Novartis, Chugai, Lilly, Medac, Genentech, Bayer. CE: Abbvie: receipt of honoraria and travel expenses. JA has received research grants, speakers bureau or has participated in advisory groups for Abbvie, Pfizer, Roche and BMS. CAP, educational sponsorship from Abbvie. AVR, co-chief investigator of Sycamore Study (funded by NIHR and ARUK). Honoraria/speaker fees from Abbvie, Roche, Lily, UCB and SOBI.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

1 Enders FB, Bader-Meunier B, Baildam E, *et al*. Consensus-based recommendations for the management of juvenile dermatomyositis. *Ann Rheum Dis* 2017;76:329-40.
2 van der Heijde D, Aletaha D, Carmona L, *et al*. 2014 Update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. *Ann Rheum Dis* 2015;74:8-13.
3 Brouwers MC, Kho ME, Browman GP, *et al*. AGREE II: advancing guideline development, reporting and evaluation in health care. *Can Med Assoc J* 2010;182:E839-42.
4 Heiligenhaus A, Michels H, Schumacher C, *et al*. Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis. *Rheumatol Int* 2012;32:1121-33.
5 Bou R, Adán A, Borrás F, *et al*. Clinical management algorithm of uveitis associated with juvenile idiopathic arthritis: interdisciplinary panel consensus. *Rheumatol Int* 2015;35:777-85.
6 Zierhut M, Heiligenhaus A, deBoer J, *et al*. Controversies in juvenile idiopathic arthritis-associated uveitis. *Ocul Immunol Inflamm* 2013;21:167-79.
7 Clarke SLN, Sen ES, Ramanan AV. Juvenile idiopathic arthritis-associated uveitis. *Pediatric Rheumatology* 2016;14:27.
8 Sen ES, Dick AD, Ramanan AV. Uveitis associated with juvenile idiopathic arthritis. *Nat Rev Rheumatol* 2015;11:338-48.
9 Zhang W, *et al*. EULAR evidence based recommendations for gout. Part I: diagnosis. Report of a task force of the standing committee for international clinical studies including therapeutics (ESCISIT). *Ann Rheum Dis* 2006;65:1301-11.
10 Zhang W, Doherty M, Bardin T, *et al*. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2006;65:1312-24.
11 Dougados M, Betteridge N, Burmester GR, *et al*. EULAR standardised operating procedures for the elaboration, evaluation, dissemination, and implementation of recommendations endorsed by the EULAR standing committees. *Ann Rheum Dis* 2004;63:1172-6.
12 Van de Ven AH, Delbecq AL. The nominal group as a research instrument for exploratory health studies. *Am J Public Health* 1972;62:337-42.
13 Uchiyama RC, Osborn TG, Moore TL. Antibodies to iris and retina detected in sera from patients with juvenile rheumatoid arthritis with iridocyclitis by indirect immunofluorescence studies on human eye tissue. *J Rheumatol* 1989;16:1074-8.
14 Giannini EH, Malagon CN, Van Kerckhove C, *et al*. Longitudinal analysis of HLA associated risks for iridocyclitis in juvenile rheumatoid arthritis. *J Rheumatol* 1991;18:1394-7.
15 Malagon C, Van Kerckhove C, Giannini EH, *et al*. The iridocyclitis of early onset pauciarticular juvenile rheumatoid arthritis: outcome in immunogenetically characterized patients. *J Rheumatol* 1992;19:160-3.
16 Murray KJ, Szer W, Grom AA, *et al*. Antibodies to the 45 kDa DEK nuclear antigen in pauciarticular onset juvenile rheumatoid arthritis and iridocyclitis: selective association with MHC gene. *J Rheumatol* 1997;24:560-7.
17 Berk AT, Koçak N, Ünsal E. Uveitis in juvenile arthritis. *Ocul Immunol Inflamm* 2001;9:243-51.
18 Zulian F, Martini G, Falcini F, *et al*. Early predictors of severe course of uveitis in oligoarticular juvenile idiopathic arthritis. *J Rheumatol* 2002;29:2446-53.
19 Chia A, Lee V, Graham EM, *et al*. Factors related to severe uveitis at diagnosis in children with juvenile idiopathic arthritis in a screening program. *Am J Ophthalmol* 2003;135:757-62.
20 Chen CS, Roberton D, Hammerton ME. Juvenile arthritis-associated uveitis: visual outcomes and prognosis. *Can J Ophthalmol* 2004;39:614-20.
21 Nordal EB, Songstad NT, Berntson L, *et al*. Biomarkers of chronic uveitis in juvenile idiopathic arthritis: predictive value of antihistone antibodies and antinuclear antibodies. *J Rheumatol* 2009;36:1737-43.
22 Kalinina Ayuso V, Ten Cate HA, van der Does P, *et al*. Male gender as a risk factor for complications in uveitis associated with juvenile idiopathic arthritis. *Am J Ophthalmol* 2010;149:994-9.
23 Saurenmann RK, Levin AV, Feldman BM, *et al*. Risk factors for development of uveitis differ between girls and boys with juvenile idiopathic arthritis. *Arthritis Rheum* 2010;62:1824-8.
24 Angeles-Han ST, Pelajo CF, Vogler LB, *et al*. Risk markers of juvenile idiopathic arthritis-associated uveitis in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry. *J Rheumatol* 2013;40:2088-96.
25 Cole TS, Frankovich J, Iyer S, *et al*. Profiling risk factors for chronic uveitis in juvenile idiopathic arthritis: a new model for EHR-based research. *Pediatr Rheumatol Online J* 2013;11:45.
26 Calandra S, Gallo MC, Consolaro A, *et al*. Female sex and oligoarthritis category are not risk factors for uveitis in Italian children with juvenile idiopathic arthritis. *J Rheumatol* 2014;41:1416-25.
27 Pelegrín L, Casaroli-Marano R, Antón J, *et al*. Predictive value of selected biomarkers, polymorphisms, and clinical features for oligoarticular juvenile idiopathic arthritis-associated uveitis. *Ocul Immunol Inflamm* 2014;22:208-12.
28 Egeskjold EM, Johansen A, Permin H, *et al*. The significance of antinuclear antibodies in juvenile rheumatoid arthritis associated with chronic bilateral iridocyclitis. *Acta Paediatr Scand* 1982;71:615-20.
29 Cabral DA, Petty RE, Malleson PN, *et al*. Visual prognosis in children with chronic anterior uveitis and arthritis. *J Rheumatol* 1994;21:2370-5.
30 Haas JP, Truckenbrodt H, Paul C, *et al*. Subtypes of HLA-DRB1*03, *08, *11, *12, *13 and *14 in early onset pauciarticular juvenile chronic arthritis (EOPA) with and without iridocyclitis. *Clin Exp Rheumatol* 1994;12(Suppl 10):S7-14.
31 Kotaniemi K, Kotaniemi A, Savolainen A. Uveitis as a marker of active arthritis in 372 patients with juvenile idiopathic seronegative oligoarthritis or polyarthritis. *Clin Exp Rheumatol* 2002;20:109-12.
32 Zeggini E, Packham J, Donn R, *et al*. Association of HLA-DRB1*13 with susceptibility to uveitis in juvenile idiopathic arthritis in two independent data sets. *Rheumatology* 2006;45:972-4.
33 Bloom JN, Ni M, Moore TL, *et al*. Serum antiocular antibodies in patients with juvenile rheumatoid arthritis. *J Pediatr Ophthalmol Strabismus* 1993;30:243-8.
34 Campanilho-Marques R, Bogas M, Ramos F, *et al*. Prognostic value of antinuclear antibodies in juvenile idiopathic arthritis and anterior uveitis. Results from a systematic literature review. *Acta Reumatol Port* 2014;39:116-22.
35 de Boer J, Steijaert A, van den Bor R, *et al*. Development of macular edema and impact on visual acuity in uveitis associated with juvenile idiopathic arthritis. *Ocul Immunol Inflamm* 2015;23:67-73.
36 Ducos de Lahitte G, Terrada C, Tran TH, *et al*. Maculopathy in uveitis of juvenile idiopathic arthritis: an optical coherence tomography study. *Br J Ophthalmol* 2008;92:64-9.
37 Edelsten C, Lee V, Bentley CR, *et al*. An evaluation of baseline risk factors predicting severity in juvenile idiopathic arthritis associated uveitis and other chronic anterior uveitis in early childhood. *Br J Ophthalmol* 2002;86:51-6.
38 Glass D, Litvin D, Wallace K, *et al*. Early-onset pauciarticular juvenile rheumatoid arthritis associated with human leukocyte antigen-DRw5, iritis, and antinuclear antibody. *J Clin Invest* 1980;66:426-9.
39 Grassi A, Corona F, Casellato A, *et al*. Prevalence and outcome of juvenile idiopathic arthritis-associated uveitis and relation to articular disease. *J Rheumatol* 2007;34:1139-45.
40 Heiligenhaus A, Niewerth M, Ganser G, *et al*. Prevalence and complications of uveitis in juvenile idiopathic arthritis in a population-based nation-wide study in Germany: suggested modification of the current screening guidelines. *Rheumatology* 2007;46:1015-9.
41 Ingegnoli F, Del Papa N, Comina DP, *et al*. Autoantibodies to chromatin: prevalence and clinical significance in juvenile rheumatoid arthritis. *Clin Exp Rheumatol* 2004;22:499-501.
42 Kanski JJ. Screening for uveitis in juvenile chronic arthritis. *Br J Ophthalmol* 1989;73:225-8.
43 Kodsi SR, Rubin SE, Milojevic D, *et al*. Time of onset of uveitis in children with juvenile rheumatoid arthritis. *J Aapos* 2002;6:373-6.
44 Kotaniemi K, Sihto-Kauppi K. Occurrence and management of ocular hypertension and secondary glaucoma in juvenile idiopathic arthritis-associated uveitis: An observational series of 104 patients. *Clin Ophthalmol* 2007;1:455-9.
45 Marvillet I, Terrada C, Quartier P, *et al*. Ocular threat in juvenile idiopathic arthritis. *Joint Bone Spine* 2009;76:383-8.
46 Mathur G, Biswas J. Systemic associations of anterior uveitis in a tertiary care ophthalmic centre in south India. *Int Ophthalmol* 2012;32:417-21.
47 McGill NW, Gow PJ. Juvenile rheumatoid arthritis in Auckland: a long term follow-up study with particular reference to uveitis. *Aust N Z J Med* 1987;17:305-8.
48 Melin-Aldana H, Giannini EH, Taylor J, *et al*. Human leukocyte antigen-DRB1*1104 in the chronic iridocyclitis of pauciarticular juvenile rheumatoid arthritis. *J Pediatr* 1992;121:56-60.

49 Merayo-Lloves J, Power WJ, Rodriguez A, *et al*. Secondary glaucoma in patients with uveitis. *Ophthalmologica* 1999;213:300-4.
50 Miller ML, Fraser PA, Jackson JM, *et al*. Inherited predisposition to iridocyclitis with juvenile rheumatoid arthritis: selectivity among HLA-DR5 haplotypes. *Proc Natl Acad Sci U S A* 1984;81:3539-42.
51 Murray P. Serum autoantibodies and uveitis. *Br J Ophthalmol* 1986;70:266-8.
52 Neuteboom GH, Hertzberger-ten Cate R, de Jong J, *et al*. Antibodies to a 15 kD nuclear antigen in patients with juvenile chronic arthritis and uveitis. *Invest Ophthalmol Vis Sci* 1992;33:1657-60.
53 Ohno S, Char DH, Kimura SJ, *et al*. HLA antigens and antinuclear antibody titres in juvenile chronic iridocyclitis. *Br J Ophthalmol* 1977;61:59-61.
54 Ostensen M, Fredriksen K, Kass E, *et al*. Identification of antihistone antibodies in subsets of juvenile chronic arthritis. *Ann Rheum Dis* 1989;48:114-7.
55 Paroli MP, Abbouda A, Restivo L, *et al*. Juvenile idiopathic arthritis-associated uveitis at an Italian tertiary referral center: clinical features and complications. *Ocul Immunol Inflamm* 2015;23:74-81.
56 Paroli MP, Speranza S, Marino M, *et al*. Prognosis of juvenile rheumatoid arthritis-associated uveitis. *Eur J Ophthalmol* 2003;13:616-21.
57 Reininga JK, Los LI, Wulffraat NM, *et al*. The evaluation of uveitis in juvenile idiopathic arthritis (JIA) patients: are current ophthalmologic screening guidelines adequate? *Clin Exp Rheumatol* 2008;26:367-72.
58 Sabri K, Saurenmann RK, Silverman ED, *et al*. Course, complications, and outcome of juvenile arthritis-related uveitis. *J Aapos* 2008;12:539-45.
59 Saurenmann RK, Levin AV, Feldman BM, *et al*. Prevalence, risk factors, and outcome of uveitis in juvenile idiopathic arthritis: a long-term followup study. *Arthritis Rheum* 2007;56:647-57.
60 Schaller JG, Johnson GD, Holborow EJ, *et al*. The association of antinuclear antibodies with the chronic iridocyclitis of juvenile rheumatoid arthritis (Still's disease). *Arthritis Rheum* 1974;17:409-16.
61 Sim KT, Venning HE, Barrett S, *et al*. Extended oligoarthritis and other risk factors for developing JIA-associated uveitis under ILAR classification and its implication for current screening guideline. *Ocul Immunol Inflamm* 2006;14:353-7.
62 Southwood TR, Ryder CA. Ophthalmological screening in juvenile arthritis: should the frequency of screening be based on the risk of developing chronic iridocyclitis? *Br J Rheumatol* 1992;31:633-4.
63 Wakefield D, Herbort CP, Tugal-Tutkun I, *et al*. Controversies in ocular inflammation and immunology laser flare photometry. *Ocul Immunol Inflamm* 2010;18:334-40.
64 Wittemann B, Neuer G, Michels H, *et al*. Autoantibodies to nonhistone chromosomal proteins HMG-1 and HMG-2 in sera of patients with juvenile rheumatoid arthritis. *Arthritis Rheum* 1990;33:1378-83.
65 Woreta F, Thorne JE, Jabs DA, *et al*. Risk factors for ocular complications and poor visual acuity at presentation among patients with uveitis associated with juvenile idiopathic arthritis. *Am J Ophthalmol* 2007;143:647-55.
66 Zannin ME, Buscain I, Vittadello F, *et al*. Timing of uveitis onset in oligoarticular juvenile idiopathic arthritis (JIA) is the main predictor of severe course uveitis. *Acta Ophthalmol* 2012;90:91-5.
67 Kalinina Ayuso V, van de Winkel EL, Rothova A, *et al*. Relapse rate of uveitis post-methotrexate treatment in juvenile idiopathic arthritis. *Am J Ophthalmol* 2011;151:217-22.
68 Papadopoulou C, Kostik M, Böhm M, *et al*. Methotrexate therapy may prevent the onset of uveitis in juvenile idiopathic arthritis. *J Pediatr* 2013;163:879-84.
69 Saboo US, Metzinger JL, Radwan A, *et al*. Risk factors associated with the relapse of uveitis in patients with juvenile idiopathic arthritis: a preliminary report. *J Aapos* 2013;17:460-4.
70 Shakoor A, Esterberg E, Acharya NR. Recurrence of uveitis after discontinuation of infliximab. *Ocul Immunol Inflamm* 2014;22:96-101.
71 Dana MR, Merayo-Lloves J, Schaumberg DA, *et al*. Visual outcomes prognosticators in juvenile rheumatoid arthritis-associated uveitis. *Ophthalmology* 1997;104:236-44.
72 Arocker-Mettinger E, Asenbauer T, Ulbrich S, *et al*. Serum interleukin 2-receptor levels in uveitis. *Curr Eye Res* 1990;9(Suppl 1):25-9.
73 Kalinina Ayuso V, de Boer JH, Byers HL, *et al*. Intraocular biomarker identification in uveitis associated with juvenile idiopathic arthritis. *Invest Ophthalmol Vis Sci* 2013;54:3709-20.
74 Heiligenhaus A, Foeldvari I, Edelsten C, *et al*. Proposed outcome measures for prospective clinical trials in juvenile idiopathic arthritis-associated uveitis: a consensus effort from the multinational interdisciplinary working group for uveitis in childhood. *Arthritis Care Res* 2012;64:1365-72.
75 Walscheid K, Hennig M, Heinz C, *et al*. Correlation between disease severity and presence of ocular autoantibodies in juvenile idiopathic arthritis-associated uveitis. *Invest Ophthalmol Vis Sci* 2014;55:3447-53.
76 Manzotti F, Orsoni JG, Zavota L, *et al*. Autoimmune uveitis in children: clinical correlation between antinuclear antibody positivity and ocular recurrences. *Rheumatol Int* 2002;21:127-32.
77 Massa M, De Benedetti F, Pignatti P, *et al*. Lack of temporal association of iridocyclitis with IgG reactivities to core histones and nucleosome subparticles in pauciarticular juvenile chronic arthritis. *Br J Rheumatol* 1995;34:507-11.
78 Gregory AC, Kempen JH, Daniel E, *et al*. Risk factors for loss of visual acuity among patients with uveitis associated with juvenile idiopathic arthritis: the Systemic Immunosuppressive Therapy for Eye Diseases Study. *Ophthalmology* 2013;120:186-92.
79 Yuce BY, Yilmaz SG, Kose S, *et al*. Outcome of pediatric uveitis at an university clinic. *Turk J Ophthalmol* 2013;43:395-401.
80 Kotaniemi K, Sihto-Kauppi K, Salomaa P, *et al*. The frequency and outcome of uveitis in patients with newly diagnosed juvenile idiopathic arthritis in two 4-year cohorts from 1990-1993 and 2000-2003. *Clin Exp Rheumatol* 2014;32:143-7.
81 Thorne JE, Woreta FA, Dunn JP, *et al*. Risk of cataract development among children with juvenile idiopathic arthritis-related uveitis treated with topical corticosteroids. *Ophthalmology* 2010;117:1436-41.
82 Olson NY, Lindsley CB, Godfrey WA. Nonsteroidal anti-inflammatory drug therapy in chronic childhood iridocyclitis. *Am J Dis Child* 1988;142:1289-92.
83 Wolf MD, Lichter PR, Ragsdale CG. Prognostic factors in the uveitis of juvenile rheumatoid arthritis. *Ophthalmology* 1987;94:1242-8.
84 Sijssens KM, Rothova A, Van De Vijver DA, *et al*. Risk factors for the development of cataract requiring surgery in uveitis associated with juvenile idiopathic arthritis. *Am J Ophthalmol* 2007;144:574-9.
85 Foster CS, Barrett F. Cataract development and cataract surgery in patients with juvenile rheumatoid arthritis-associated iridocyclitis. *Ophthalmology* 1993;100:809-17.
86 Yu EN, Meniconi ME, Tufail F, *et al*. Outcomes of treatment with immunomodulatory therapy in patients with corticosteroid-resistant juvenile idiopathic arthritis-associated chronic iridocyclitis. *Ocul Immunol Inflamm* 2005;13:353-60.
87 Foeldvari I, Nielsen S, Kümmerle-Deschner J, *et al*. Tumor necrosis factor-alpha blocker in treatment of juvenile idiopathic arthritis-associated uveitis refractory to second-line agents: results of a multinational survey. *J Rheumatol* 2007;34:1146-50.
88 Shetty AK, Zganjar BE, Ellis GS, *et al*. Low-dose methotrexate in the treatment of severe juvenile rheumatoid arthritis and sarcoid iritis. *J Pediatr Ophthalmol Strabismus* 1999;36:125-8.
89 Foeldvari I, Wierk A. Methotrexate is an effective treatment for chronic uveitis associated with juvenile idiopathic arthritis. *J Rheumatol* 2005;32:362-5.
90 Heiligenhaus A, Mingels A, Heinz C, *et al*. Methotrexate for uveitis associated with juvenile idiopathic arthritis: value and requirement for additional anti-inflammatory medication. *Eur J Ophthalmol* 2007;17:743-8.
91 Goebel JC, Roesel M, Heinz C, *et al*. Azathioprine as a treatment option for uveitis in patients with juvenile idiopathic arthritis. *Br J Ophthalmol* 2011;95:209-13.
92 Huang JL, Hung IJ, Hsieh KH. Sulphasalazine therapy in chronic uveitis of children with chronic arthritis. *Asian Pac J Allergy Immunol* 1997;15:71-5.
93 Sobrin L, Christen W, Foster CS. Mycophenolate mofetil after methotrexate failure or intolerance in the treatment of scleritis and uveitis. *Ophthalmology* 2008;115:1416-21.
94 Tappeiner C, Roesel M, Heinz C, *et al*. Limited value of cyclosporine A for the treatment of patients with uveitis associated with juvenile idiopathic arthritis. *Eye* 2009;23:1192-8.
95 Molina C, Modesto C, Martín-Begué N, *et al*. Leflunomide, a valid and safe drug for the treatment of chronic anterior uveitis associated with juvenile idiopathic arthritis. *Clin Rheumatol* 2013;32:1673-5.
96 Rajaraman RT, Kimura Y, Li S, *et al*. Retrospective case review of pediatric patients with uveitis treated with infliximab. *Ophthalmology* 2006;113:308-14.
97 Vazquez-Cobian LB, Flynn T, Lehman TJA. Adalimumab therapy for childhood uveitis. *J Pediatr* 2006;149:572-5.
98 Biester S, Deuter C, Michels H, *et al*. Adalimumab in the therapy of uveitis in childhood. *Br J Ophthalmol* 2007;91:319-24.
99 Gallagher M, Quinones K, Cervantes-Castaneda RA, *et al*. Biological response modifier therapy for refractory childhood uveitis. *Br J Ophthalmol* 2007;91:1341-4.
100 Tynjala P, Lindahl P, Honkanen V, *et al*. Infliximab and etanercept in the treatment of chronic uveitis associated with refractory juvenile idiopathic arthritis. *Ann Rheum Dis* 2007;66:548-50.
101 Kotaniemi K, Säilä H, Kautiainen H. Long-term efficacy of adalimumab in the treatment of uveitis associated with juvenile idiopathic arthritis. *Clin Ophthalmol* 2011;5:1425-9.
102 García-De-Vicuña C, Díaz-Llopis M, Salom D, *et al*. Usefulness of adalimumab in the treatment of refractory uveitis associated with juvenile idiopathic arthritis. *Mediators Inflamm* 2013;2013:1-6.
103 Magli A, Forte R, Navarro P, *et al*. Adalimumab for juvenile idiopathic arthritis-associated uveitis. *Graefes Arch Clin Exp Ophthalmol* 2013;251:1601-6.
104 Zholobova E, Galstian L, Nikolaeva MN, *et al*. Effectiveness of adalimumab in the treatment of juvenile idiopathic arthritis associated with uveitis. *Pediatric Rheumatology* 2014;12(Suppl 1):O5.
105 Simonini G, Taddio A, Cattalini M, *et al*. Prevention of flare recurrences in childhood-refractory chronic uveitis: an open-label comparative study of adalimumab versus infliximab. *Arthritis Care Res* 2011;63:612-8.
106 Simonini G, Taddio A, Cattalini M, *et al*. Superior efficacy of Adalimumab in treating childhood refractory chronic uveitis when used as first biologic modifier drug:

Adalimumab as starting anti-TNF-α therapy in childhood chronic uveitis. *Pediatr Rheumatol Online J* 2013;11:16.
107 Zannin ME, Birolo C, Gerloni VM, *et al*. Safety and efficacy of infliximab and adalimumab for refractory uveitis in juvenile idiopathic arthritis: 1-year followup data from the Italian Registry. *J Rheumatol* 2013;40:74–9.
108 William M, Faez S, Papaliodis GN, *et al*. Golimumab for the treatment of refractory juvenile idiopathic arthritis-associated uveitis. *J Ophthalmic Inflamm Infect* 2012;2:231–3.
109 Smith JR, Levinson RD, Holland GN, *et al*. Differential efficacy of tumor necrosis factor inhibition in the management of inflammatory eye disease and associated rheumatic disease. *Arthritis Rheum* 2001;45:252–7.
110 Richards JC, Tay-Kearney ML, Murray K, *et al*. Infliximab for juvenile idiopathic arthritis-associated uveitis. *Clin Exp Ophthalmol* 2005;33:461–8.
111 Kahn P, Weiss M, Imundo LF, *et al*. Favorable response to high-dose infliximab for refractory childhood uveitis. *Ophthalmology* 2006;113:860–4.
112 Tynjälä P, Kotaniemi K, Lindahl P, *et al*. Adalimumab in juvenile idiopathic arthritis-associated chronic anterior uveitis. *Rheumatology* 2008;47:339–44.
113 Trachana M, Pratsidou-Gertsi P, Pardalos G, *et al*. Safety and efficacy of adalimumab treatment in Greek children with juvenile idiopathic arthritis. *Scand J Rheumatol* 2011;40:101–7.
114 Díaz-Llopis M, Salom D, Garcia-de-Vicuña C, *et al*. Treatment of refractory uveitis with adalimumab: a prospective multicenter study of 131 patients. *Ophthalmology* 2012;119:1575–81.
115 Lerman MA, Burnham JM, Chang PY, *et al*. Response of pediatric uveitis to tumor necrosis factor-α inhibitors. *J Rheumatol* 2013;40:1394–403.
116 Miserocchi E, Modorati G, Pontikaki I, *et al*. Long-term treatment with golimumab for severe uveitis. *Ocul Immunol Inflamm* 2014;22:90–5.
117 Saeed MU, Raza SH, Goyal S, *et al*. Etanercept in methotrexate-resistant JIA-related uveitis. *Semin Ophthalmol* 2014;29:1–3.
118 Schmeling H, Horneff G. Etanercept and uveitis in patients with juvenile idiopathic arthritis. *Rheumatology* 2005;44:1008–11.
119 Smith JA, Thompson DJ, Whitcup SM, *et al*. A randomized, placebo-controlled, double-masked clinical trial of etanercept for the treatment of uveitis associated with juvenile idiopathic arthritis. *Arthritis Rheum* 2005;53:18–23.
120 Saurenmann RK, Levin AV, Feldman BM, *et al*. Risk of new-onset uveitis in patients with juvenile idiopathic arthritis treated with anti-TNFalpha agents. *J Pediatr* 2006;149:833–6.
121 Kakkassery V, Mergler S, Pleyer U. Anti-TNF-alpha treatment: a possible promoter in endogenous uveitis? observational report on six patients: occurrence of uveitis following etanercept treatment. *Curr Eye Res* 2010;35:751–6.
122 Dhingra N, Morgan J, Dick AD. Switching biologic agents for uveitis. *Eye* 2009;23:1868–70.
123 Zulian F, Balzarin M, Falcini F, *et al*. Abatacept for severe anti-tumor necrosis factor alpha refractory juvenile idiopathic arthritis-related uveitis. *Arthritis Care Res* 2010;62:821–5.
124 Heiligenhaus A, Miserocchi E, Heinz C, *et al*. Treatment of severe uveitis associated with juvenile idiopathic arthritis with anti-CD20 monoclonal antibody (rituximab). *Rheumatology* 2011;50:1390–4.
125 Mesquida M, Molins B, Llorenç V, *et al*. Long-term effects of tocilizumab therapy for refractory uveitis-related macular edema. *Ophthalmology* 2014;121:2380–6.
126 Angeles-Han ST, Griffin KW, Lehman TJ, *et al*. The importance of visual function in the quality of life of children with uveitis. *J Aapos* 2010;14:163–8.
127 Angeles-Han ST, Griffin KW, Harrison MJ, *et al*. Development of a vision-related quality of life instrument for children ages 8-18 years for use in juvenile idiopathic arthritis-associated uveitis. *Arthritis Care Res* 2011;63:1254–61.
128 Ezzahri M, Amine B, Rostom S, *et al*. The uveitis and its relationship with disease activity and quality of life in Moroccan children with juvenile idiopathic arthritis. *Clin Rheumatol* 2013;32:1387–91.
129 Prakken B, Albani S, Martini A. Juvenile idiopathic arthritis. *Lancet* 2011;377:2138–49.
130 Thierry S, Fautrel B, Lemelle I, *et al*. Prevalence and incidence of juvenile idiopathic arthritis: a systematic review. *Joint Bone Spine* 2014;81:112–7.
131 Yu HH, Chen PC, Wang LC, *et al*. Juvenile idiopathic arthritis-associated uveitis: a nationwide population-based study in Taiwan. *PLoS One* 2013;8:e70625.
132 Shen CC, Yeh KW, Ou LS, *et al*. Clinical features of children with juvenile idiopathic arthritis using the ILAR classification criteria: a community-based cohort study in Taiwan. *J Microbiol Immunol Infect* 2013;46:288–94.
133 Heiligenhaus A, Heinz C, Edelsten C, *et al*. Review for disease of the year: epidemiology of juvenile idiopathic arthritis and its associated uveitis: the probable risk factors. *Ocul Immunol Inflamm* 2013;21:180–91.
134 Ramanan AV, Guly C. Adalimumab for childhood onset uveitis. *Ann Rheum Dis* 2018;77:961–2.
135 Ramanan AV, Dick AD, Jones AP, *et al*. Adalimumab plus Methotrexate for Uveitis in Juvenile Idiopathic Arthritis. *N Engl J Med* 2017;376:1637–46.
136 Dick AD, Rosenbaum JT, Al-Dhibi HA, *et al*. Guidance on Noncorticosteroid Systemic Immunomodulatory Therapy in Noninfectious Uveitis: Fundamentals Of Care for UveitiS (FOCUS) Initiative. *Ophthalmology* 2018;S0161-6420:32446–6.
137 Leinonen ST, Aalto K, Kotaniemi KM, *et al*. Anti-adalimumab antibodies in juvenile idiopathic arthritis-related uveitis. *Clin Exp Rheumatol* 2017;35:1043–6.
138 Skrabl-Baumgartner A, Erwa W, Muntean W, *et al*. Anti-adalimumab antibodies in juvenile idiopathic arthritis: frequent association with loss of response. *Scand J Rheumatol* 2015;44:359–62.
139 Correll CK, Bullock DR, Cafferty RM, *et al*. Safety of weekly adalimumab in the treatment of juvenile idiopathic arthritis and pediatric chronic uveitis. *Clin Rheumatol* 2018;37:549–53.
140 Mesquida M, Molins B, Llorenç V, *et al*. Twenty-four month follow-up of tocilizumab therapy for refractory uveitis-related macular edema. *Retina* 2017:1.
141 Calvo-Río V, Santos-Gómez M, Calvo I, *et al*. Anti-Interleukin-6 Receptor Tocilizumab for Severe Juvenile Idiopathic Arthritis-Associated Uveitis Refractory to Anti-Tumor Necrosis Factor Therapy: A Multicenter Study of Twenty-Five Patients. *Arthritis Rheumatol* 2017;69:668–75.
142 Ferrara M, Eggenschwiler L, Stephenson A, *et al*. The Challenge of Pediatric Uveitis: Tertiary Referral Center Experience in the United States. *Ocul Immunol Inflamm* 2018;15:1–8.
143 Quartier P, Baptiste A, Despert V, *et al*. ADJUVITE Study Group. ADJUVITE: a double-blind, randomised, placebo-controlled trial of adalimumab in early onset, chronic, juvenile idiopathic arthritis-associated anterior uveitis. *Ann Rheum Dis* 2018;77:1003–11.
144 Tappeiner C, Mesquida M, Adán A, *et al*. Evidence for Tocilizumab as a Treatment Option in Refractory Uveitis Associated with Juvenile Idiopathic Arthritis. *J Rheumatol* 2016;43:2183–8.