

SPECIAL ARTICLE

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

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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).

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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.

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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.

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

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.

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

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.

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.

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 ([21514658, 2019, 6, Downloaded from <https://onlinelibrary.wiley.com/doi/10.1002/acr.23871> by University Of Pittsburgh University Library System, Wiley Online Library on \[15/07/2023\]. 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](https://dis-</p>
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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-

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

Recommendation
<p>Recommendations for ophthalmic screening</p> <p>In children and adolescents with JIA at high risk of developing uveitis:†</p> <ul style="list-style-type: none"> • Ophthalmic screening every 3 months is conditionally recommended (Recommendation 1, PICO 1).
<p>Recommendations for ophthalmic monitoring</p> <p>In children and adolescents with JIA and controlled uveitis who are:</p> <ul style="list-style-type: none"> • 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).
<p>Recommendations for glucocorticoid use</p> <p>In children and adolescents with JIA and active CAU:</p> <ul style="list-style-type: none"> • 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). <p>In children and adolescents with JIA and CAU still requiring 1–2 drops/day of prednisolone acetate 1% (or equivalent) for uveitis control:</p> <ul style="list-style-type: none"> • 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). <p>In children and adolescents with JIA who develop new CAU activity despite stable systemic therapy:‡</p> <ul style="list-style-type: none"> • Topical glucocorticoids prior to changing/escalating systemic therapy is conditionally recommended over changing/escalating systemic therapy immediately (Recommendation 7, PICO 12).
<p>Recommendations for DMARDs and biologics</p> <p>In children and adolescents with JIA and active CAU who are/have:</p> <ul style="list-style-type: none"> • 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).
<p>Recommendations for education about and treatment of AAU</p> <p>In children and adolescents with spondyloarthritis:</p> <ul style="list-style-type: none"> • 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)

Table 3. (Cont'd)

Recommendation
<p>Recommendations for tapering therapy for uveitis</p> <p>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):</p> <ul style="list-style-type: none"> • Tapering topical glucocorticoids first is strongly recommended over systemic therapy (Recommendation 18, PICO 6). <p>In children and adolescents with JIA and uveitis that is well controlled on DMARD and biologic systemic therapy only:</p> <ul style="list-style-type: none"> • 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*

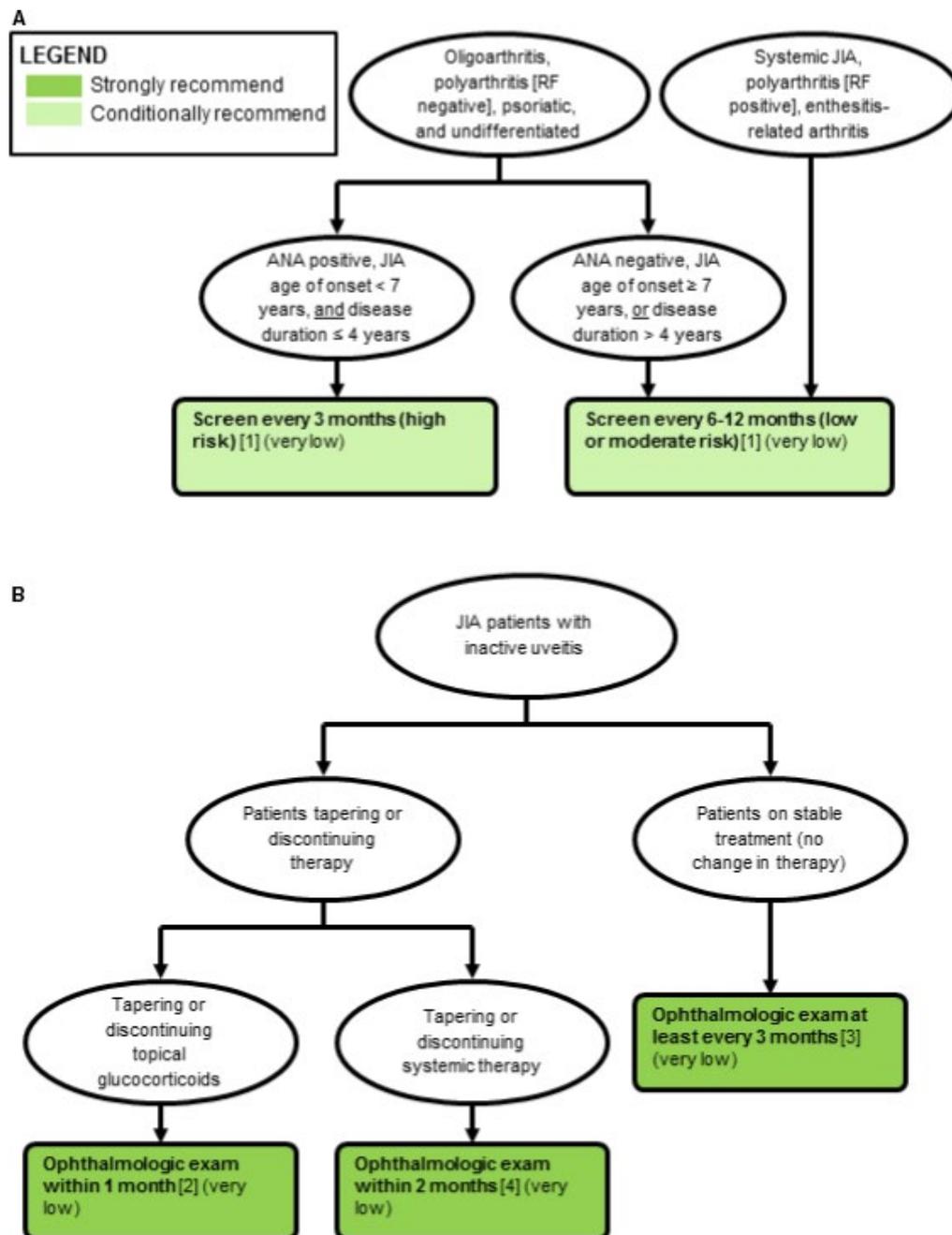


Figure 1. **A**, Ophthalmic screening examinations (see also Table 1). **B**, Ophthalmic monitoring examinations (see also Table 3). No recommendations were made for patients with uncontrolled chronic anterior uveitis. Patient/Population, Intervention, Comparison, and Outcomes (PICO) questions are shown 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

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

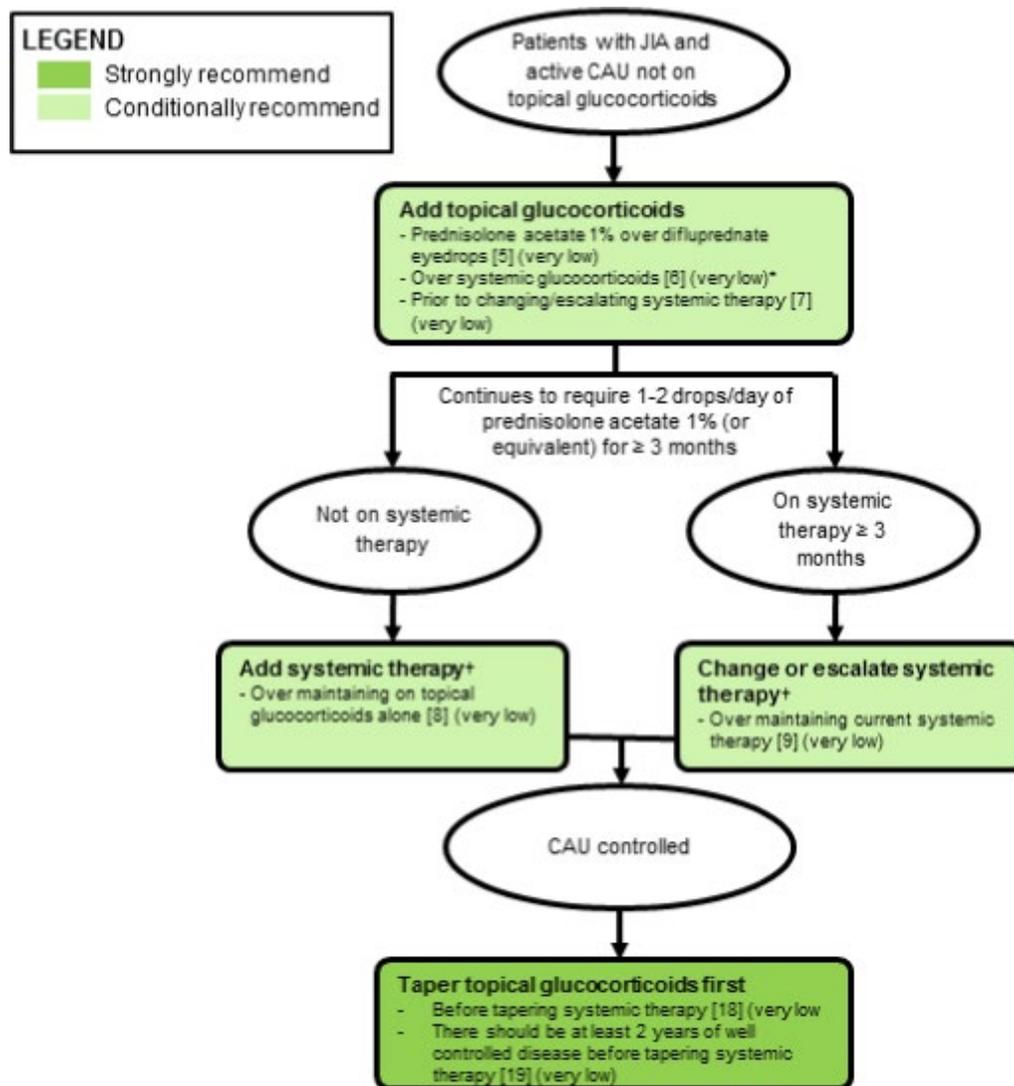


Figure 2. Recommendations for topical glucocorticoids in patients with juvenile idiopathic arthritis (JIA) and chronic anterior uveitis (CAU) (see also Table 3). Systemic therapy is defined as disease-modifying antirheumatic drugs and biologics. Topical glucocorticoids refer to prednisolone acetate 1% (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-threatening 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

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*

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

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 Kweicin, 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.

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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.

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