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Canadian Rheumatology Association Recommendations for the Screening, Monitoring, and Treatment of Juvenile Idiopathic Arthritis-associated Uveitis

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ABSTRACT. ***Objectives.*** To develop Canadian recommendations for the screening, monitoring, and treatment of uveitis associated with juvenile idiopathic arthritis (JIA).

Methods. Recommendations were developed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE)-ADOLOPMENT approach. A working group of 14 pediatric rheumatologists, 6 ophthalmologists, 2 methodologists, and 3 caregiver/patient representatives reviewed recent American College of Rheumatology (ACR)/Arthritis Foundation (AF) recommendations and worked in pairs to develop evidence-to-decision (EtD) tables. A survey to assess agreement and recommendations requiring group discussion was completed. EtD tables were presented, discussed, and voted upon at a virtual meeting, to produce the final recommendations. A health equity framework was applied to all aspects of the adolopment process including the EtD tables, survey responses, and virtual meeting discussion.

Results. The survey identified that 7 of the 19 recommendations required rigorous discussion. Seventy-five percent of working group members attended the virtual meeting to discuss controversial topics as they pertained to the Canadian environment, including timing to first eye exam, frequency of screening, escalation criteria for systemic and biologic therapy, and the role of nonbiologic therapies. Equity issues related to access to care and advanced therapeutics across Canadian provinces and territories were highlighted. Following the virtual meeting, 5 recommendations were adapted, 2 recommendations were removed, and 1 was developed de novo.

Conclusion. Recommendations for JIA-associated uveitis were adapted to the Canadian context by a working group of pediatric rheumatologists, ophthalmologists with expertise in the management of uveitis, and parent/patient input, taking into consideration cost, equity, and access.

Key Indexing Terms: chronic anterior uveitis, evidence-to-decision framework, GRADE-ADOLOPMENT, guidelines, juvenile idiopathic arthritis

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Chronic, asymptomatic anterior uveitis occurs in up to 20% of children with juvenile idiopathic arthritis (JIA) and can be associated with significant morbidity, including permanent vision loss.[1] However, early detection of ocular inflammation through regular ophthalmic screening with prompt and appropriate treatment can maintain good vision and prevent complications despite the diagnosis of a potentially sight-threatening uveitis. Female sex, young age at onset of JIA (age < 7), and antinuclear antibody (ANA) positivity are risk factors for JIA-associated uveitis.[2,3] The cumulative incidence of new-onset uveitis during the first 5 years after JIA diagnosis was 13.9%, which supports the need for vigilant uveitis screening during this time frame.[3] Care for patients with JIA-associated uveitis requires a collaborative approach between rheumatology and ophthalmology, and in some cases, other eye care providers for screening. Treatment for uveitis can be complex and may require combinations of topical and/or systemic therapies, with frequent healthcare visits and treatment changes.

In 2019, the American College of Rheumatology (ACR) and the Arthritis Foundation (AF) collaborated to develop and publish guidelines for the screening, monitoring, and treatment of JIA-associated uveitis.[4] These were the first North American guidelines to address JIA-associated uveitis and to propose an approach to using systemic immunosuppressive therapy for uveitis that is dependent on or refractory to topical glucocorticoids (GCs). Long-term use of topical GCs should be avoided to reduce their potential side effects, including increased intraocular pressure and cataract formation.[5,6] Despite a relatively uniform approach to treatment, only 3 published controlled trials specifically examined systemic therapies in JIA-associated uveitis.[7-9] Regulatory body approval for therapeutics is challenging and lacking because of the paucity of evidence. The ACR/AF guidelines provide an opportunity for education and advocacy to local, provincial, and national regulatory bodies and payers to improve access to advanced therapies. In Canada, where health care is a provincial rather than federal jurisdiction, there is variation in access to rheumatologists and ophthalmologists with expertise in uveitis and to biologic therapies. The availability of Canadian-specific, expert consensus guidelines for monitoring and managing JIA-associated uveitis will help ensure optimal care is standardized nationwide.

The ACR/AF guidelines used the rigorous Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) methodology, informed by a consensus process with rheumatology and ophthalmology experts, current literature, and patient/parent preferences and values. These guidelines were the first to address screening, monitoring, and treatment and the only to use GRADE methodology, and were therefore selected as a baseline framework. We used the GRADE-ADOLOPMENT method[10] to consider Canadian contextual differences, including patient preferences, cost/resource considerations, and feasibility of implementation. The adolopment method provides an efficient framework to capitalize on previous work and reduce redundancy. The development of evidence-to-decision (EtD) tables for each recommendation provide a transparent process for judgement of the evidence and context-specific considerations, and is then followed by adoption, adaptation, or de novo development of recommendations. Adoption is the use of an existing, trustworthy recommendation without modification of the original recommendation; adaptation involves identifying the pertinent healthcare questions, searching for existing guidelines that addressed those questions, critically appraising them, and deciding whether to accept or modify selected recommendations; and de novo development of recommendations involves formulating new questions and seeking to answer them in a recommendation not included in original guidelines.[10]

This work represents the first set of Canadian JIA-associated uveitis guidelines, and the first Canadian Rheumatology Association (CRA) guideline to apply the GRADE-ADOLOPMENT framework. Using this methodology allowed us to develop guidelines applicable to the Canadian context considering cost, equity, and access.

METHODS

A Canadian JIA-associated uveitis working group was assembled, including 14 pediatric rheumatologists representing 13 of 14 Canadian academic centers plus 1 community-based pediatric rheumatologist and 1 trainee. Six geographically diverse ophthalmologists with a special interest and/or subspecialty training in uveitis joined the working group in addition to 3 uveitis parent/patient champions. The CRA guidelines committee chair, a Cochrane Musculoskeletal representative, and a research associate were nonvoting members of the working group. All working group members completed the International Committee of Medical Journal Editors conflict of interest form prior to the start of the project.

Following the GRADE-ADOLOPMENT stages:

1. An updated systematic literature review was completed using the same search terms as the ACR/AF guidelines (further referred to as the source guideline). The systematic review was conducted by an electronic search of OVID MEDLINE, Embase, PubMed, and the Cochrane Library from October 13, 2017 (end date of the ACR/AF search), to February 6, 2020. In addition, literature reviews for equity, patient preferences, and economics were completed for this patient population. For each article, 2 working group members were assigned for data extraction and summary-of-finding (SoF) tables were completed (Supplementary File S1, available with the online version of this article). The quality of evidence was rated as high, moderate, low, or very low, accounting for risk of bias, inconsistency, indirectness, imprecision, and other considerations as per the GRADE recommendations.[11]
2. The recommendations from the source guidelines were reviewed by 2 members of the working group. Member pairs were selected to ensure geographic diversity and pairing of a rheumatologist with an ophthalmologist, 2 rheumatologists, or 2 ophthalmologists, depending on the context

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of each recommendation. Each pair reviewed the source guideline PICO (Population – Intervention – Control – Outcomes) question, selected articles, SoF tables, and the recommendation. Each recommendation also was considered using a Table of Equity Filters developed by the Quality Care Committee of the CRA that included the following data: Indigenous, rural/remote location, refugee, and low socioeconomic status/homelessness.[12,13] Using these sources, an EtD table[14] was developed for each recommendation (Supplementary File S2, available with the online version of this article) by the pair. EtD tables included the Summary of Evidence about the benefits and harms of the interventions being considered, in addition to information about the importance of the problem (eg, baseline risk), patients' values and preferences, resource use and costs, feasibility, acceptability, and potential impact on health equity of recommending specific intervention options in the context of the healthcare setting and affected stakeholders.

EtDs were reviewed (RB and DML) and discussed with the methodologists (GSH and JPP), with feedback and edits performed by each member pair.

3. A web survey was completed by all working group members to assess agreement on the source guideline recommendations in a Canadian context. Questions for each recommendation included the following: (1) Do you agree to adopt this recommendation as presented? (2) Do you agree to adopt this recommendation with a change in wording based on evidence/additional considerations as presented by the EtD table? (3) Are there any other considerations to add for this recommendation, such as a Canadian context of cost, access, or vulnerable populations? (4) Does this recommendation need to be discussed at the webinar? All respondents were provided with the accompanying finalized EtD (Supplementary File S2, available with the online version of this article) for review with the equity filters to be incorporated into their survey responses. All recommendations with > 50% of survey respondents indicating disagreement/discussion required were reviewed at a virtual meeting.

4. The virtual meeting held in August 2020 was facilitated by nonvoting advisors (GSH and JPP). An in-person consensus meeting was not possible because of the coronavirus disease 2019 (COVID-19) pandemic. EtDs with recommendations were presented, discussed, and voted upon at the meeting. Then, the decision was made for each recommendation to be adopted, adapted, or developed de novo in order to reach the final set of recommendations. Consensus was set a priori at 80% agreement of voting panel members. However, there was 100% agreement on all adapted and newly developed recommendations.

Ethics. Research Ethics Board approval was not required for this project.

RESULTS

The literature searches retrieved 410 citations for JIA-associated uveitis and 554 articles for equity, patient preferences, and economics after removing duplicates (Figure). Full-length articles were reviewed, data abstracted, and evidence graded using the 19 PICO questions from the source guideline. The screening process was done by 2 independent reviewers (DP and HYN) and disagreements were resolved by a third reviewer (RB or DML). Twenty-two additional articles were identified. From these, SoF tables (n = 26) for observational studies and GRADE tables (n= 2) for clinical trials were developed and updates to the ACR tables were produced (Supplementary File S1, available with the online version of this article). The available evidence was of 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 low quality by the GRADE system. Implementation in rural and remote areas, Indigenous populations, low socioeconomic status, and access to treatments were considerations applied to all recommendations.

The terms, definitions, medication interventions, and critical/important outcomes as defined by the ACR/AF guidelines[4] were used during the development of the CRA-GRADE-ADOLOPMENT recommendations.

How to interpret the recommendations. The strength of a recommendation is expressed as either strong ("the guideline panel strongly recommends...") or conditional ("the guideline panel conditionally recommends..."); the interpretations are outlined in Table 1.

Results from the web survey identified agreement to adopt 13 of the source recommendations by the Canadian Uveitis Working Group as presented (Table 2). The remaining 6 were discussed in detail at the virtual meeting attended by 75% (15/20) of the working group, 3 parent/patient representatives, and 2 nonvoting advisors (GSH and JPP). The 7 recommendations requiring significant revision pertained to screening (n = 1 recommendation adapted) and treatment (n = 6; Table 2). Following the virtual working group discussion, 5 recommendations were adapted (ACR/AF recommendations 1, 8, 9, 13, and 15), 2 recommendations were removed (ACR/AF recommendations 10 and 11), and 1 was developed de novo (new recommendation 4). For the working group members who could not attend the virtual meeting, feedback and comments were incorporated, and 100% consensus was achieved from the group discussion for the 7 recommendations discussed below. The revised recommendations are as follows:

Recommendation 1 (ACR/AF recommendation 1 adapted). In children and adolescents with JIA at high risk of developing chronic anterior uveitis (CAU), ophthalmic screening at least every 3 months for the first 4 years is conditionally recommended over screening at a different frequency. Patients with newly diagnosed disease should be screened as early as possible after diagnosis, within the first 1 to 3 months if asymptomatic (conditional recommendation, very low certainty of evidence).

Remarks: When deciding on the frequency of ophthalmic monitoring, close collaboration and communication between rheumatologists and ophthalmologists is crucial. The addition of "at least every 3 months" encompasses those with vision-threatening disease. The group also discussed adding "for at least the first 4 years of disease" to be reflective of risk for development of uveitis based on significant risk factors. These are well described and include young age at onset of JIA (< 7 years), oligoarticular subtype, female sex, and a positive ANA test.[3,15] The group agreed that the recommendation should include timing to first eye examination and that this information be shared with caregivers. This was not addressed in the ACR/AF recommendations. Caregiver/patient understanding of the importance of timing of examination was noted to be critical given the asymptomatic nature of uveitis that can lead to a delay in diagnosis if initial and ongoing regular screening is delayed.[16] The expert consensus discussion agreed the time to first examination to be within 1 to 3 months of diagnosis regardless of the geographic location of the patient. The working group acknowledged that this may be challenging for patients living in rural/remote areas who must travel to access eye care, and for those requiring funding for travel to eye care. A detailed discussion occurred

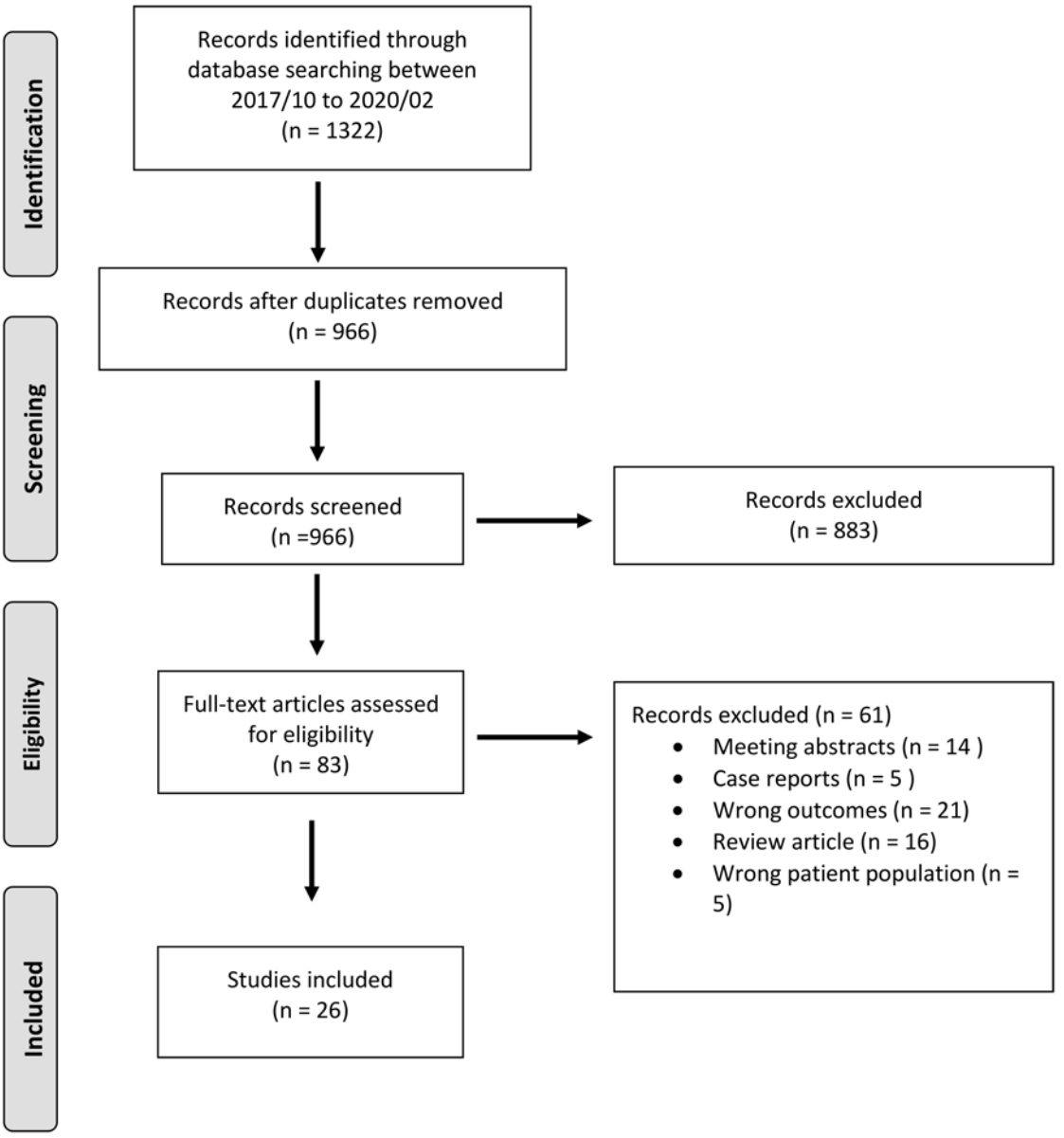

Figure. Summary of search strategies to identify key articles.

around who can and should perform ophthalmic screening, with differing opinions and additional considerations put forth from geographically diverse centers. Given the large geographic area that pediatric rheumatology/ophthalmology centers serve and the lack of a sufficient number of ophthalmologists in many urban centers, timely access can be a concern. Ophthalmic screening is optimally completed by an ophthalmologist but could include another eyecare provider if timely access is otherwise not possible. Eye examination should be verified by an ophthalmologist with uveitis expertise when the opportunity comes available.

Recommendations 2 and 3 (ACR/AF recommendation 8 and 9 adapted). For recommendation 2, in children and adolescents with JIA and CAU requiring more than 2 drops per day of prednisolone acetate 1% (or equivalent) at 3 months after the start of uveitis treatment, and not on systemic therapy, adding systemic therapy to taper topical GCs is conditionally recommended over not adding systemic therapy and maintaining on topical GCs only (conditional recommendation, very low certainty of evidence).

For recommendation 3, in children and adolescents with JIA and CAU requiring more than 2 drops per 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 (conditional recommendation, very low certainty of evidence).

Remarks: The adapted recommendations differ from the ACR/AF guidelines, which indicate a threshold of 1 to 2 drops per day for the addition/change/escalation of systemic therapy.

Table 1. Interpretation of strong and conditional recommendations.

Implications for	Strong Recommendation	Conditional Recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.
Clinicians	Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.
Policy makers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Policy making will require substantial debate and involvement of various stakeholders. Performance measures should assess if decision making is appropriate.
Researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty of the evidence. In such instances, further research may provide important information that alters the recommendations.	The recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps.

Review of the evidence for this recommendation revealed published data showing that there is a risk of ocular complications when more than 2 drops of topical GCs are used per day.[17,18] A robust discussion occurred regarding the threshold for escalation to systemic therapy, and while evidence is limited, both rheumatologists and ophthalmologists agreed the risk for complications related to topical GC therapy is increased with long-term use of 3 or more drops per day.[17] This recommendation is also in agreement with the Australia- and New Zealand–based expert consensus JIA-Uveitis Working Group recommendations, which support the threshold of greater than 2 drops per day.[19] The decision to escalate therapy should be individualized and done using a shared decision-making framework; in some cases where noncompliance or significant burden is associated with topical drops, escalation may be considered when 1 to 2 drops per day is required.

The group unanimously agreed upon a maximum 3-month interval of monitoring uveitis, at which point adding systemic therapy should be considered. The group discussed the term "active" to which the group agreed also includes "steroid dependent." Active uveitis includes steroid-dependent uveitis that appears controlled on more than 2 drops of topical steroid per day.

Recommendation 4 (developed de novo). In children and adolescents with JIA and CAU who are initiating systemic treatment for CAU, methotrexate (MTX) is conditionally recommended as the first-line disease-modifying antirheumatic drug (DMARD; conditional recommendation, very low certainty of evidence).

Remarks: The working group developed a conditional recommendation for MTX use as the first-line DMARD. The ACR/AF guidelines did not have a specific recommendation for a first-line systemic therapy although it is implied in recommendation 10, which conditionally recommends subcutaneous over oral MTX in patients starting systemic therapy. Both the expert consensus-based Single Hub and Access Point for Paediatric Rheumatology in Europe (SHARE),[20] and Australia/New Zealand[19] groups have a specific recommendation for MTX as the first-line systemic therapy. MTX has demonstrated safety and efficacy for the treatment of JIA-associated uveitis in several retrospective studies in doses of 15 mg/m^2 (alternatively up to 1 mg/kg) to a maximum of 25 mg weekly.[21-27] These results have been confirmed in subsequent systematic reviews.[28-30] Two other consensus treatment guidelines also support MTX as the first-line systemic therapy for JIA-associated uveitis.[20,31] Other nonbiologic DMARD (nbDMARD) therapies, including mycophenolate mofetil (MMF), azathioprine, and cyclosporine, have been used in uveitis with variable success,[32-36] and these drugs are most often tried in MTX-refractory cases. The studies include very small numbers of patients, restricting the quality of evidence and the evidence of efficacy. Overall, the evidence for MTX is more robust than for other conventional DMARDs, despite the generally limited quality of studies available. Thus, MTX is conditionally recommended as the first-line systemic therapy for JIA-associated uveitis.

The source guidelines conditionally recommend subcutaneous over oral MTX (ACR/AF recommendation 10) because of data suggesting increased bioavailability of the subcutaneous formulation at doses greater than 15 mg/m^2.[37,38] The Methotrexate Advice and Recommendations on Juvenile Idiopathic Arthritis[31] consensus recommendations align with this recommendation, as do the Childhood Arthritis and Rheumatology Research Alliance Consensus Treatment Plans for Juvenile Idiopathic Arthritis–Associated and Idiopathic Chronic Anterior Uveitis.[39] However, there is a lack of high-quality evidence demonstrating clinical superiority of subcutaneous over oral MTX in JIA-associated uveitis. The dose,

Table 2. Recommendations for ophthalmic screening, ophthalmic monitoring, and treatment of children with JIA-associated uveitis, including modifications by the CRA Uveitis Working Group.

	Recommendation(s)
Ophthalmic screening	In children and adolescents with JIA at high risk of developing uveitis:[a] · Ophthalmic screening at least every 3 months in high-risk patients for at least the first 4 years of disease is conditionally recommended over screening at a different frequency. Patients with newly diagnosed disease should be screened as early as possible after diagnosis (within the first 1-3 months if asymptomatic) (**adapted**).
Ophthalmic monitoring	In children and adolescents with JIA and controlled uveitis who are: · Tapering or discontinuing topical GC, ophthalmic monitoring within 1 month after each change of topical GC is strongly recommended over monitoring less frequently (**adopted**). · On stable therapy, ophthalmic monitoring no less frequently than every 3 months is strongly recommended over monitoring less frequently (**adopted**). · Tapering or discontinuing systemic therapy, ophthalmic monitoring within 2 months of changing systemic therapy is strongly recommended over monitoring less frequently (**adopted**).
GC use	In children and adolescents with JIA and active CAU: · Using PSL acetate 1% topical drops is conditionally recommended over difluprednate topical drops (**adopted**). · Adding or increasing topical GCs for short-term control is conditionally recommended over adding systemic GCs (**adopted**). In children and adolescents with JIA and CAU requiring > 2 drops/day of PSL acetate 1% for uveitis control: · If not on systemic therapy, adding systemic therapy in order to taper topical GCs is conditionally recommended over not adding systemic therapy and maintaining topical GCs only (**adapted**). · If requiring > 2 drops/day of PSL 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 (**adapted**). In children and adolescents with JIA who develop new CAU activity[b] despite stable systemic therapy: · Topical GCs prior to changing/escalating systemic therapy is conditionally recommended over changing/escalating systemic therapy immediately (**adopted**).
DMARDs and biologics	In children and adolescents with JIA and active CAU who are/have: · Started systemic treatment for uveitis, MTX is conditionally recommended as first-line DMARD (**developed *de novo***). · Started a TNFi, starting a monoclonal antibody TNFi is conditionally recommended over ETN (**adopted**). · Inadequate response to one monoclonal TNFi, optimizing the dose and/or frequency is conditionally recommended over switching to another monoclonal antibody TNFi (**adapted**). · 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 a different class (**adopted**). · Failed MTX and 2 monoclonal antibody TNFis at optimized dose, the use of ABA or tocilizumab as biologic DMARD options are conditionally recommended over nonbiologic DMARD options (mycophenolate, leflunomide, cyclosporine) (**adapted**).
Education about treatment of AAU	In children and adolescents with SpA: · Education is *strongly* recommended regarding the warning signs of AAU for the purpose of decreasing delay in treatment, duration of symptoms, or complications of uveitis (**adopted**). · 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 treatment with topical GCs first (**adopted**).
Taper 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 GCs first is *strongly* recommended over tapering systemic therapy (**adopted**). 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 (**adopted**).

Adapted from ACR/AF guidelines.[4] Each recommendation had very low quality of evidence. AAU: acute anterior uveitis; ABA: abatacept; ACR: American College of Rheumatology; AF: Arthritis Foundation; CAU: chronic anterior uveitis; CRA: Canadian Rheumatology Association; DMARD: disease-modifying antirheumatic drug; ETN: etanercept; GC: glucocorticoid; JIA: juvenile idiopathic arthritis; MTX: methotrexate; PSL: prednisolone; SpA: spondyloarthritis; TNFi: tumor necrosis factor inhibitor. [a] Children at high risk are those with oligoarthritis, polyarthritis (rheumatoid factor negative), psoriatic arthritis, or undifferentiated arthritis who are also antinuclear antibody positive, aged < 7 years at JIA onset, and have JIA duration of ≤ 4 years. [b] Definition of new CAU activity; no prior uveitis or loss of control of previously controlled uveitis.

presence of or potential for complications, patient/caregiver preference, patient/caregiver comfort level with injections, and provincial health authority criteria for funding biologics following MTX failure (so as not to delay escalation of therapy) should be considered when deciding on the initial route of administration of MTX for children with JIA-associated uveitis.

Recommendation 11 from the ACR/AF guidelines provides a conditional recommendation for starting dual therapy over MTX alone, but the working group favored monotherapy with MTX. There is no direct evidence for one approach over the other, and no evidence about the risk of complications and safety of dual therapy compared to the safety of MTX monotherapy. The working group had concerns about the lack of access to

tumor necrosis factor inhibitors (TNFis) as a first-line therapy in Canada for treatment of JIA-associated uveitis.

The ophthalmologists noted that there are no standardized definitions for severe or sight-threatening complications. The ACR/AF defines severe as "the presence of ocular structural complications due to uveitis, or complications of topical steroid therapy." It was noted that severe uveitis is not necessarily more difficult to treat than mild uveitis because disease severity does not equal disease chronicity; however, presence of complications of uveitis, such as posterior synechiae or cataracts are indicators of a poor visual outcome for patients with JIA-associated uveitis.[1] The group, therefore, decided to remove the term "severe." Thus, recommendation 11 from the source guidelines was removed from the current guidelines.

Recommendation 5 (ACR/AF recommendation 13 adapted). In children and adolescents with JIA and active CAU who have an inadequate response to one monoclonal antibody TNFi at standard JIA dosing, optimizing the dose and/or frequency of the current TNFi is conditionally recommended over switching to another monoclonal antibody TNFi (conditional recommendation, very low certainty of evidence).

Remarks: There are no randomized controlled trials for comparisons of one monoclonal TNFi vs another for the treatment of JIA-associated CAU. The working group considered that the ACR/AF wording of "above standard" dosing may have equity implications with access to "above standard" dosing potentially differing by treating site or based on reimbursement issues, both of which can cause anxiety for patients/caregivers. Product monograph dosing for adalimumab (ADA) includes dosing of 40 mg subcutaneously every 2 weeks for patients weighing more than 30 kg; however, to achieve maximal clinical benefit patients may be treated with 40 mg subcutaneously weekly, with no significant increase in reported adverse effects.[40,41] Decreasing the interval of infliximab to less than every 4 weeks and/or increasing the dose to more than 10 mg/kg can be considered. Older case series literature supports its safety.[42] Patient/caregiver advisors also note that adjustments to current medication regimens would be preferred rather than introducing a new medication unless there are clear benefits to doing so (conditional recommendation, very low certainty of evidence).

Recommendation 6 (ACR/AF recommendation 15 adapted). In children and adolescents with JIA and active CAU who have failed MTX and 2 monoclonal antibody TNFis at optimized doses, the use of abatacept (ABA) or tocilizumab (TCZ) as biologic DMARD (bDMARD) options are conditionally recommended over nbDMARD options (MMF, leflunomide, or cyclosporine; conditional recommendation, very low certainty of evidence).

Remarks: There is no evidence to guide treatment of CAU in patients who have failed 2 monoclonal TNFis. The ACR/AF recommendations do not specify a preference of bDMARD vs nbDMARD options. The working group's expert opinion with review of observational data conditionally recommended a bDMARD such as TCZ or ABA[9,43-47] over a nbDMARD in patients with refractory CAU. Other biologic agents investigated include daclizumab and rituximab[48,49] and an alternative monoclonal TNFi (golimumab).[50,51] All studied biologic therapies do demonstrate some benefit in patients refractory to conventional therapy. Of note, in patients refractory to monoclonal TNFi, literature review reveals no direct evidence of the effects of low drug trough levels or the development of antidrug antibodies on the clinical efficacy of biological agents in patients with uveitis. The SHARE[20] group based their recommendations on findings in other clinical settings, concluding that in cases of loss of efficacy over time, consideration should be given to testing for antidrug antibodies and drug trough levels.[52-54] If the patient has no antibodies, but has low trough levels, increasing the dose or shortening the interval may be an option.[41]

DISCUSSION

Results from our CRA Uveitis Working Group differed from the ACR/AF recommendations in some aspects of screening and treatment for JIA-associated CAU when considered in the Canadian context. These differences include: (1) the timing to first ophthalmic screening, (2) threshold of topical GC for escalation to systemic treatment (> 2 drops/day of prednisolone acetate 1% for > 3 months), (3) initial use of biologics favoring a step-up approach (with MTX conditionally recommended as a first-line DMARD) because of a lack of evidence but also because of access concerns to bDMARDs as a first-line therapy, (4) removal of the recommendation for use of subcutaneous vs oral MTX because of a lack of evidence, (5) modification of the recommendation for increasing the TNFi from "above standard dose and/or frequency" to "optimize" dose over TNFi switching, and (6) recommendation for the use of biologic over nonbiologic therapies for patients failing MTX and TNFi therapies.

The 2019 ACR/AF guidelines provide guidance on the screening, monitoring, and treatment with GC, nbDMARDs, and bDMARDs for CAU, as well as the education and treatment of children with or at risk of developing acute anterior uveitis. The guidelines were conducted using a rigorous GRADE methodology and the voting panel included pediatric rheumatologists, ophthalmologists, and adult patients with JIA. A caregiver and patient panel reviewed the collated evidence and provided input on their values and preferences in a separate voting meeting. Overall, the quality of evidence was very low, and most recommendations were conditional; however, the guidelines fill an important clinical gap in the care of children with JIA-associated uveitis.

Given the rigorous nature of the development of the ACR guidelines, recency of publication, and similarities in our medical systems, the GRADE-ADOLOPMENT approach was chosen over duplication of a GRADE methodology framework for the current project. Across the United States and Canada, we have similar challenges with access to medications, rheumatologists, and ophthalmologists. Thus, the ACR/AF guidelines are largely applicable to the Canadian context. However, a few important differences exist, including the 10 provincially regulated and 3 territorially regulated public and private payment models for medication, and hence there is varying access to biologic agents for the treatment of JIA-associated CAU.[55] Also

differing from the US is federally regulated coverage by the Non-Insured Health Benefits program for First Nations and Inuit populations. Further, access to pediatric rheumatology and ophthalmology care with expertise in uveitis varies greatly across the country. There is approximately 1 rheumatologist per 75,000 children in Canada[56] but there are only 3 ophthalmologists per 100,000 population[34] in Canada, with a far smaller number having expertise in uveitis in the pediatric patient population.[57] Additionally, the density of pediatric rheumatologists and ophthalmologists is much higher in certain urban centers than in many other parts of Canada. Equitable access to the optimal shared care model for JIA-associated CAU can be affected by distance to an urban center, with some patients living in remote areas having to travel more than 2000 km to their treating center. In some instances, this may require involvement of other eyecare providers for screening.

The GRADE-ADOLOPMENT approach provides a structured means to selectively combine adoption, adaptation, and de novo development of guideline recommendations. The most important first step of this process was to conduct an updated systematic review that was used by the guideline panel. Further, efficiency was optimized by using the EtD framework, which provides transparency in the decision-making process and in the considerations made by the guideline panel when formulating recommendations.

In Canada, we do not have national pharmacare and thus significant provincial differences in access to biologics remain. Off-label use of biologics can be challenging to access because of high cost and lack of compassionate drug supply. The introduction of biosimilars may improve equitable access to therapies. Across the country, biosimilar drugs and availability is changing rapidly; for example, as of May 2021 there are 4 new ADA biosimilars available with Health Canada indications for pediatric uveitis. In some provinces, private insurance plans follow guidance from the public reimbursement standards and uniquely cover biosimilar drugs. Over the past 2 years some provinces have moved to nonmedical switching from the originator biologic to the biosimilar to promote savings of healthcare dollars.

The CRA Uveitis Working Group, comprising pediatric rheumatologists, ophthalmologists with expertise in uveitis, patient/caregiver representatives, and methodology advisors, completed adolopment of the ACR/AF recommendations in a relatively short time, less than 1 year of effective time spent, and at low cost. An additional strength of this work is the incorporation of updated evidence. Judgments of the Canadian Uveitis Working Group did not markedly differ in the strength and direction of the recommendations, and as such, the majority of the source recommendations were adopted with minor alterations. Moving forward, we recommend the GRADE-ADOLOPMENT approach, especially if a credible set of guidelines with all supporting materials that were developed using a transparent process is available. The CRA JIA-associated CAU guidelines provide Canadian contextual considerations for optimal shared uveitis care, supporting equitable access to care and treatment.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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