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Editorial

Screening, Monitoring, and Treating Children With Juvenile Idiopathic Arthritis–associated Uveitis: Visualizing Better Outcomes

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Noninfectious ocular inflammatory disease, or uveitis, is a common and devastating complication of juvenile idiopathic arthritis (JIA). As many as 20% of children with JIA develop JIA-associated uveitis (JIA-U), and 50% experience ocular complications that can lead to damage.[1,2] Ocular complications can be the beginning of a downward spiral toward permanent vision impairment due to the development of amblyopia, glaucoma, optic nerve disease, and hypotony. Because most children will not experience any symptoms of uveitis, scheduled screening of these high-risk children is critical. Previously, screening was guided by the American Academy of Pediatrics recommendations based on an older classification scheme for arthritis—juvenile rheumatoid arthritis.[3] New arthritis categories were later added based on the accepted International League of Associations for Rheumatology (ILAR) JIA classification. Children with several of this JIA categories such as oligoarticular, polyarticular rheumatoid factor negative, psoriatic, and undifferentiated JIA are at higher risk for uveitis.[4] Thus, international groups (eg, Europe, Australia, New Zealand, UK) developed recommendations for the screening of children with JIA using various consensus methodology.

In 2019, the American College of Rheumatology (ACR) and Arthritis Foundation (AF) developed the first recommendations from North America that included screening of JIA and monitoring and treatment of JIA-U using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.[5] These recommendations included not just screening guidelines for detection of uveitis in children with JIA but also, critically, monitoring and treatment recommendations for these at-risk children. The importance of gathering both ophthalmologists and pediatric rheumatologists to craft these guidelines cannot be understated, as there are often differences among providers on the choice, duration, dose, and frequency of treatment required to prevent vision-threatening complications. The ACR/AF treatment recommendations were based on the strongest evidence to prevent ocular morbidity and blindness.

In this issue of *The Journal of Rheumatology*, Berard et al present the Canadian Rheumatology Association (CRA) screening, monitoring, and treatment recommendations for JIA-U to consider Canadian contextual differences, as healthcare in Canada is provincial rather than federal jurisdiction, and there is varied access to rheumatologists, ophthalmologists, and biologic therapies.[6] Most importantly, we commend the authors as they ensured that equity was reflected in the CRA recommendations, wherein they considered implementation in rural and remote areas, Indigenous populations, low socioeconomic status, and those with difficulties accessing treatment. This is especially important as easy access to rheumatologists, uveitis specialists, or pediatric ophthalmologists for uveitis detection and monitoring as well as to costly biologic therapy is not always possible in every setting. Here they evaluated, discussed, and voted on each ACR/

See JIA-associated uveitis recommendations, *page 390*

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AF recommendation and used the GRADE-ADOLOPMENT method to reduce redundancy with previous work. We congratulate the authors on this important paper and acknowledge the significant amount of time and effort required to craft their recommendations. Our editorial focuses on contrasting the differences in the recommendations that were adapted by Berard et al,[6] and considering problems with current methods of ophthalmic screening and monitoring for uveitis.

Differences in the CRA and ACR/AF recommendations

Fourteen pediatric rheumatologists, 6 ophthalmologists, 2 methodologists, and 3 caregiver/patient representatives reviewed the 19 ACR/AF recommendations, and 13 were adopted, 5 adapted, 2 removed, and 1 developed de novo.[5] The Table contrasts recommendations that were not adopted. Although we agree with several of the excellent adapted recommendations, we discuss those that we believe have implications for patient care and outcomes, namely, recommendations on ophthalmic screening, acceptable number of drops of topical glucocorticoids (GCs), and treatment with methotrexate (MTX) in combination with tumor necrosis factor inhibitors (TNFi).

Of utmost importance and potential for affecting vision outcomes is the removal of the ACR/AF recommendation to initiate combination therapy with MTX and a monoclonal antibody TNFi in children with severe active JIA-U and sight-threatening complications. The CRA guidelines preferred MTX monotherapy in all cases due to a lack of direct evidence for one approach over the other, risk of complications, and safety data of dual therapy. Further, the ophthalmologists state that a standardized definition of severe or sight-threatening complications does not exist.[6] However, the ACR/AF guideline provides a definition, and we suggest that an experienced ophthalmologist should be able to determine whether a child's eye disease is severe or has sight-threatening complications. Severity of uveitis has been defined previously by a number of groups and include the presence of complications at baseline, the presence of posterior synechiae, visual acuity, grade of anterior chamber inflammation at baseline, or presence of anterior chamber flare. Each of these features has been associated with a greater risk of recurrence and development of future complications.[7-9] In a randomized controlled trial where children were randomized to MTX + placebo or MTX + adalimumab (ADA), the trial was stopped early due to overwhelming superiority of MTX + ADA.[10] Treatment failures occurred in 65% of those taking

Table. Comparison of the Canadian Rheumatology Association (CRA) and American College of Rheumatology/Arthritis Foundation (ACR/AF) JIA-associated uveitis guideline recommendations from tables.

CRA Recommendations[6]	ACR/AF Recommendations[5]
Recommendation for ophthalmic screening in children and adolescents with JIA at high risk for developing uveitis:	
· 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 screening every 3 months is conditionally recommended.
In children and adolescents with JIA and CAU requiring > 2 drops/day of prednisolone acetate 1% (or equivalent) for uveitis control:	In children and adolescents with JIA and CAU still requiring 1-2 drops/day of prednisolone acetate 1% (or equivalent) for uveitis control:
· If not on systemic therapy, adding systemic therapy in order to taper topical GCs is conditionally recommended over not adding systemic therapy and maintaining topical GCs only (**adapted**).	· 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.
· If requiring > 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 (**adapted**).	· 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.
Recommendations for DMARDs and biologics in children and adolescents with JIA and active CAU who are/have:	
· Starting systemic treatment for uveitis, MTX is conditionally recommended as first-line DMARD (**developed de novo as ACR/AF considered deleted**).	· Starting systemic treatment for uveitis, using subcutaneous MTX is conditionally recommended over oral MTX.
· Deleted.	· Severe active CAU and sight-threatening complications, starting MTX and a monoclonal antibody TNFi immediately is conditionally recommended over MTX as monotherapy.
· Inadequate response to one monoclonal TNFi, optimizing the dose and/or frequency, is conditionally recommended over switching to another monoclonal antibody TNFi (**adapted**).	· Inadequate response to 1 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.
· Failed MTX and 2 monoclonal antibody TNFis at optimized dose, the use of abatacept or tocilizumab as biologic DMARD options are conditionally recommended over nonbiologic DMARD options (mycophenolate, leflunomide, cyclosporine) (**adapted**).	· Failed MTX 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.

CAU: chronic anterior uveitis; DMARD: disease-modifying antirheumatic drug; GC: glucocorticoid; JIA: juvenile idiopathic arthritis; MTX: methotrexate; TNFi: tumor necrosis factor inhibitor.

MTX + placebo vs 27% in MTX + ADA ($P < 0.001$). As these children were already on MTX monotherapy for 3 months and had active uveitis at time of randomization, it is important that appropriate treatment is prescribed at onset. Further, the Childhood Arthritis and Rheumatology Research Alliance consensus treatment plans, which were generated by consensus from rheumatologists in North America and ophthalmologists from the United States, agree that MTX be started simultaneously with a TNFi at the provider's discretion.[11] Deletion of this recommendation may significantly affect timely access to combined treatment for children with uveitis as they may no longer have this early option available. Further, as the CRA guidelines recommend TNFi for children who are refractory to MTX and there is no recommendation to discontinue MTX with the initiation of TNFi, the authors likely combine treatment and consider it safe in their own practice. However, we understand that TNFi may not be accessible due to cost in a resource-limited system, and this population of children are likely at greatest risk for poor vision outcomes and in most need of dual therapy.

The majority of recommendations support initiation of systemic treatment if > 2 drops daily (> 1 to 2 drops for ACR/AF, > 2 drops for CRA) of prednisolone acetate 1% are required, based on studies that show that ≤ 3 drops does not increase risk for cataract or glaucoma.[12,13] However, we contend that if a patient continues to require topical GC to control inflammation, the duration of use that is acceptable and safe is unclear. One of the concerns should be the risk of undertreatment in those patients with persistent smoldering disease. In those requiring continued topical GC, Thorne et al report that low doses of topical GCs (≤ 3 drops/day) over a moderate period of time (median 4 yrs, range 6 months to 15 yrs) was low risk for cataract but could not assess the effect of longer treatment or the risk of cumulative dose.[12] Thus, when to attempt taper and whether discontinuation will be possible are uncertain. Studies are required on the long-term outcomes of children who remain on > 2 drops of topical GC.

MTX is regarded as the first-line systemic treatment for all patients with uveitis. The Canadian guidelines propose a de novo recommendation of MTX as the first-line disease-modifying antirheumatic drug (DMARD), which they agree was not specifically recommended but rather implied in the ACR/AF guideline. They also do not recommend a specific route of administration. However, the ACR/AF clearly recommend that in those starting systemic therapy for JIA-U, MTX should be used, but include a preference for subcutaneous injection: "in children and adolescents with JIA and chronic anterior uveitis who are starting systemic treatment for uveitis, using subcutaneous MTX is conditionally recommended over oral MTX."[5] However, we agree that there are no conclusive studies that route of administration is associated with improved treatment response.

Screening and monitoring of JIA and JIA-U

Both guidelines, similar to others, recommend that children at high risk for JIA-U development, (oligoarticular, polyarticular rheumatoid factor, psoriatic and undifferentiated subtypes, antinuclear antibody positivity, JIA age of onset < 7 yrs, and JIA duration ≤ 4 yrs) require regular screening every 3 months. Berard et al[6] modified this recommendation for ophthalmic screening "at least every 3 months" to encompass those with vision-threatening disease. We commend the authors and agree that screening intervals more frequently than every 3 months may be necessary in children who are at risk for poor vision. Additionally, once active uveitis or evidence of previous ocular inflammation is found, examination intervals should be shortened to identify active disease. Studies suggest that children with JIA-U who are at risk for a severe course include those with certain findings at the initial ophthalmic examination (eg, visual acuity of 20/40 or worse, 20/200 or worse, presence of ≥ 1+ anterior chamber (AC) flare, and complications), male sex, young age at uveitis diagnosis, and Black race.[2,7,9,14,15] Thus, studies are needed to further delineate whether more frequent screening intervals improve visual outcomes in certain JIA populations, if children who follow screening recommendations develop fewer complications, whether decreasing screening intervals after 4 years of JIA is appropriate, and how long screening should continue into adulthood.

Despite following scheduled screening, as many as 50% of children with JIA-U still develop cataract, glaucoma, posterior synechiae, and other complications. This implies that either ocular inflammation is identified too late or the severity of ocular inflammation is mischaracterized and thus undertreated. The challenge of obtaining a careful complete slit lamp examination of a young child by an experienced provider cannot be understated. Clinical ophthalmic examination by slit lamp biomicroscopy is subjective and can be difficult in young children who may be less cooperative, or when performed by providers not trained to evaluate children. Further, Kempen et al report low agreement between observers in quantifying AC cells.[16] Inaccurate assessment of ocular inflammation has significant consequences as ongoing or undetected inflammation leads to ocular damage. There is a critical need for objective and accurate measures to complement clinical ophthalmic examinations. As assessment of younger or uncooperative children can be challenging, anterior segment (AS) optical coherence tomography (OCT) has been successfully trialed in children with JIA[17-19] (ClinicalTrials.gov: (NCT01746537). Validation studies to standardize the use of AS-OCT are being conducted. As most children with JIA-U present with anterior eye involvement, imaging of the posterior segment of the eye by OCT or fluorescein angiography are not routinely performed. Importantly, studies have shown that in those with presumably anterior disease alone, inflammation in other sections of the eye can be missed.[20,21] These studies show that in children with presumed inactive JIA-U by clinical examination, vessel leakage and cystoid macular edema are actually present. Hence, although scheduled ophthalmic screening is critical, consideration must be given to routine imaging and complete dilated fundus examination to ensure that these eyes are not being undertreated and subsequently experience damage.

Currently, there are no validated biomarkers of ocular inflammation. Aqueous humor fluid is promising in several studies, but

this can only be collected by invasive methods.[22,23] Blood may not accurately reflect ocular inflammation. Biomarkers measured in tear fluid by Schirmer strip represent another novel method to detect and monitor ocular inflammation.[24,25]

Although there are some differences in these and other international guidelines, overall, the recommendations are similar. All agree with the importance of regular ophthalmic screening to detect uveitis early, ophthalmic monitoring to ensure that a child adequately responds to local and/or systemic therapy, and appropriate and effective treatment that is optimized to prevent ocular damage. As newly addressed by Berard et al,[6] it is critical that issues associated with equity are kept at the forefront, because recommendations may not be applicable or even possible in all patients, especially in areas without easy access to rheumatologists, uveitis specialists, pediatric ophthalmologists, slit lamp biomicroscopy, or imaging modalities that would affect the ability to detect JIA-U accurately and in a timely manner. Further, biologics to treat uveitis such as TNFi, abatacept, and tocilizumab may not be readily available, and DMARDs such as methotrexate, leflunomide, cyclosporine, and mycophenolate may be the only therapeutic options. The development of guidelines that are globally applicable and consider equity are critical. Ultimately, we must ensure that every child is afforded access to subspecialists skilled in the evaluation and treatment of uveitis and that the most effective therapy is available if we want to optimize vision outcomes for all children.

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