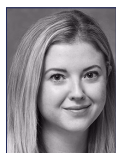


A PRIMER ON PEDIATRIC UVEITIS

Here's the latest on diagnosing, treating, and following these patients.

BY MONIQUE MUNRO MD, FRCSC; POOJA BHAT, MD; AND ANN-MARIE LOBO-CHAN, MD



Pediatric uveitis accounts for approximately 5% to 15% of all uveitis patients, and, while rare compared with adult uveitis, it presents

unique challenges.^{1,2} If ocular inflammation is not identified promptly and treated effectively, irreversible damage may occur.¹⁻⁸ Unfortunately, delayed presentations are more frequent in pediatric patients, given that patients may be asymptomatic, may be unaware symptoms are abnormal, or may be preverbal. Diagnosing and monitoring uveitis in a child requires an experienced examiner, and examination under anesthesia (EUA) is often necessary.^{6,9}

Treatment in these developing patients also carries significant weight beyond the already challenging side effects common in adults. Here, we discuss updates in the care for pediatric patients with uveitis.

CAUSES

As with its adult counterpart, pediatric uveitis may be secondary to infectious or noninfectious causes and is classified based on the location of ocular involvement. Anterior uveitis is the most common presentation for pediatric uveitis, and the differential diagnosis is slightly more focused compared with adult uveitis.

Noninfectious uveitis accounts for the majority of pediatric uveitis in Europe and the United States.³ Noninfectious causes include juvenile idiopathic arthritis (JIA)-associated uveitis (the most common cause in the United States and Northern Europe), juvenile-onset spondyloarthropathies, postinfectious autoimmune uveitis, tubulointerstitial nephritis and uveitis, systemic lupus erythematosus, Behçet disease, and sarcoidosis, including early-onset sarcoidosis and Blau syndrome.^{6,7,10,11}

Infectious uveitis is more common in children than in adults, and entities such as toxoplasmosis, toxocariasis, and viral infections (eg, herpes simplex virus) should be considered.^{6,7} While rare, masquerade syndromes also need to be considered, including retinoblastoma and other local tumors; leukemia and other systemic malignancies;

inherited retinal diseases such as retinitis pigmentosa; juvenile xanthogranuloma; chronic retinal detachment; and intraocular foreign bodies.^{5,12}

NEW DIAGNOSTICS

Genetic testing is more prevalent in medicine, and HLA class I and II gene polymorphisms have been observed in association with pediatric uveitis. For example, HLA-DRB1*11 and HLA-DRB1*13 are associated with JIA, and HLA-DR2 and HLA-DR15 are associated with pars planitis.¹³

Biomarkers would be a valuable tool to monitor pediatric patients and avoid repeat EUA. Various biomarkers have been studied for early diagnosis and classification of patients with JIA-associated uveitis. For example, research has shown that the Th1:Th2 ratio, anti-interleukin (IL)-10, and IL-13 are higher in JIA-associated uveitis patients compared with JIA patients without ocular inflammation.^{13,14}

TREATMENTS: NEW AND OLD

Evidence suggests that early and aggressive treatment improves visual outcomes in pediatric patients with uveitis. Physicians must be comfortable with systemic immunomodulating therapies because pediatric autoimmune uveitis

AT A GLANCE

- ▶ Evidence suggests that early and aggressive treatment improves visual outcomes in pediatric patients with uveitis.
- ▶ Noninfectious uveitis accounts for the majority of pediatric uveitis in Europe and the United States.
- ▶ Pediatric patients with uveitis should be frequently examined until remission is achieved, and frequent follow-up is necessary due to the increased risk for flares in these patients.

frequently has a chronic course with a high risk for relapse that can lead to significant ocular morbidity. Even low-grade residual inflammation can cause significant damage to a pediatric eye long-term.^{8,12} Due to this risk, the goal is to achieve inactive uveitis (defined as grade 0 cells in the anterior chamber according to the Standardization of Uveitis Nomenclature criteria) with steroid-sparing medications and to eventually reach drug-free remission.^{13,15} However, this goal is difficult to attain because the side effects of immunomodulating medications in developing pediatric patients are a significant concern.^{13,16} This is further complicated by the fact that few medications are approved for pediatric uveitis.

Corticosteroids

The current approach for treating acute pediatric uveitis includes topical and oral corticosteroids. While a stepwise approach is commonly used in adult uveitis patients, steroids must be used sparingly in pediatric patients because long-term systemic side effects, such as growth retardation, weight gain, and hyperglycemia, can have deleterious effects on children.^{9,16} If a corticosteroid therapy fails or if a patient has chronic uveitis, a systemic disease associated with a chronic uveitis, or frequent recurrent uveitis with ocular sequelae, early initiation of corticosteroid-sparing immunomodulatory therapy is advised. These medications broadly include antimetabolites, T-cell inhibitors, alkylating agents, and biologics.¹³

NSAIDs

Although it is worth noting NSAIDs as treatment options in uveitis, they are not typically the drug of choice for the majority of pediatric uveitis due to severity and chronicity. Of the NSAIDs, naproxen and tolmetin are the medications most frequently used in pediatric uveitis.

Antimetabolites

Methotrexate is the most frequently used immunomodulating medication in pediatric uveitis and is generally the first line of therapy in chronic autoimmune uveitis.¹³ Methotrexate can be administered subcutaneously or orally; however, the bioavailability of methotrexate is reduced in the oral form. Side effects include renal, liver, and gastrointestinal toxicity, and the medication should be taken with folic acid supplements.

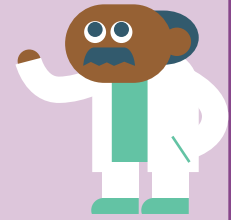
Azathioprine is another antimetabolite but has been used less frequently due to a combination of factors, including its unfavorable side effect profile, lower efficacy, and limited data on pediatric dosage.¹³

Biologic Response Modifiers

Biologic medications include anti-tumor necrosis factor alpha (TNF- α), anti-IL-1, anti-B-cell, and anti-T-cell inhibitors.

Adalimumab, an anti-TNF- α drug, is the only biologic

CURRENT STRATEGIES



These recommendations by the American College of Rheumatology and the Arthritis Foundation for immunomodulatory therapy in juvenile idiopathic arthritis may be leveraged for other forms of chronic uveitis in children:¹

- Subcutaneous methotrexate is superior to oral methotrexate for starting treatment.
- For severe disease, a combination of methotrexate and a biologic is recommended for initial treatment.
- Other tumor necrosis factor alpha (TNF- α) inhibitors are superior to etanercept in chronic anterior uveitis.
- TNF- α inhibitor dose intervals should be shortened in cases of inadequate response to standard dosing.
- A second TNF- α inhibitor should be employed if a patient fails on the first one.
- Abatacept and tocilizumab can be employed in patients who fail methotrexate and two TNF- α inhibitors.
- All effective medications should be continued for 2 years before tapering therapy.

In addition, a review by Maleki et al found that, in the acute uveitis setting, topical and systemic corticosteroids should be used first with the addition of methotrexate or another antimetabolite if chronic uveitis or a systemic condition is present. If this fails, TNF- α inhibitors should be added. Should this fail, medications such as rituximab, tocilizumab, abatacept, or other emerging therapies may be tried.²

1. Onel KB, Horton DB, Lovell DJ, et al. 2021 American College of Rheumatology guideline for the treatment of juvenile idiopathic arthritis: recommendations for nonpharmacologic therapies, medication monitoring, immunizations, and imaging. *Arthritis Rheumatol.* 2022;74(4):570-585.

2. Maleki A, Anesi SD, Look-Why S, Manhapra A, Foster CS. Pediatric uveitis: A comprehensive review. *Surv Ophthalmol.* 2022;67(2):510-529.

agent FDA-approved for noninfectious uveitis in children. It is a fully humanized monoclonal antibody that is administered subcutaneously every 2 weeks and, arguably, could be given more frequently in refractory cases.¹² In the SYCAMORE trial, researchers found that adalimumab was associated with a lower rate of treatment failure than placebo in patients with active JIA-associated uveitis on a stable dose of methotrexate.¹⁷ Adalimumab is also effective in cases of early onset, chronic, anterior uveitis refractory to topical therapy and methotrexate.

Infliximab is another commonly used TNF- α inhibitor drug administered as an intravenous infusion. When used to treat pediatric uveitis, it demonstrates efficacy in both retrospective and prospective studies. A meta-analysis demonstrated the efficacy of adalimumab and infliximab in the treatment of chronic pediatric uveitis with adalimumab showing some superiority to infliximab. However, the dose of infliximab can be escalated to elicit a response.^{11,12,16} These

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two medications have similar side effect profiles and are generally well tolerated.

Abatacept binds to CD80/CD86 on antigen presenting cells and prevents T-cell activation.¹³ It is approved for children 2 years of age and older with polyarticular JIA, but the efficacy in pediatric uveitis is limited.¹² Tocilizumab is a humanized recombinant anti-IL-6 receptor antibody that inhibits T-cell activation and immunoglobulin secretion. Tocilizumab was studied in JIA-associated uveitis patients refractory to both methotrexate and anti-TNF- α medications in the APTITUDE trial.¹⁸ Unfortunately, this trial did not meet the phase 2 primary endpoint. Tocilizumab's efficacy in autoimmune uveitis is currently being evaluated in the STOP-Uveitis and JIA-associated uveitis (JIA-U) trials.^{19,20}

Rituximab targets the CD20 B-cell marker and causes B-cell apoptosis. Promising results have been shown in JIA-associated uveitis, but it is used less frequently due to the unfavorable efficacy profile and lack of robust data compared with other medications.²¹

Emerging Treatments

Janus kinase inhibitors have been recently evaluated in adults for the treatment of uveitis, and a study evaluating baricitinib in pediatric JIA-associated uveitis or chronic anterior ANA-positive uveitis is currently underway.²²

FOLLOW-UP

Pediatric patients with uveitis should be seen frequently until remission is achieved, and frequent follow-up is necessary due to the increased risk for flares in these patients. Once in remission, the interval between follow-up visits can be extended, between 8 and 12 weeks, depending on the medications used and clinical stability.¹³ If activity cannot be assessed in a clinical setting, an EUA must be pursued. High-risk blood monitoring tests should be performed at regular intervals and will depend upon the medication regime.

Ocular complications and sequelae to monitor for include cataracts, band keratopathy, glaucoma, synechiae, hypotony, cystoid macular edema, epiretinal membrane formation, retinal detachment, and neovascularization.

In addition to a thorough ophthalmic examination, a physical examination by a pediatrician and pediatric rheumatologist should be pursued to evaluate and monitor for associated systemic disease findings. ■

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