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Uveitis in Children and Adolescents

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OVERVIEW

Epidemiology

Uveitis is an inflammatory ocular disease that can lead to sight-threatening complications. Early detection and timely treatment optimize visual outcomes. Childhood uveitis has an incidence of 4.3 per 100,000, and a prevalence of 27.9 per 100,000.[1] It occurs in isolation, as in idiopathic uveitis, but is also associated with infectious and noninfectious etiologies. Broadly, males and females are equally affected, and uveitis is most common in non-Hispanic White and Black children. Idiopathic anterior uveitis comprises approximately 29% of all pediatric diagnoses, followed by juvenile idiopathic arthritis-associated uveitis (JIA-U) (21%), pars planitis (17%), and infectious uveitis (6%).[2] Classification is by site of inflammation, with anterior location being most common. This review focuses on noninfectious causes of uveitis.

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Pathophysiology

In noninfectious uveitis, inflammation arises from an immune response triggered against antigens within the eye. This process is induced by T cells and mediated by B cells and other immune cells that propagate inflammation (Fig. 1).[3,4]

The eye is an immune-privileged site. There are several mechanisms in place that protect against intraocular inflammation, including blood-retinal barriers and immunosuppressive properties of the eye microenvironment, such as anterior chamber (AC)-associated immune deviation.[3-6] AC-associated immune deviation is an active regulatory process in which introduction of foreign antigen into the eye leads to specific, systemic immune tolerance. However, these systems are overcome when autoimmunity develops.

Autoimmune uveitis arises when an immune response is triggered against native intraocular antigens, either in the setting of trauma or through molecular mimicry of infectious pathogens.[7,8] It is largely regarded as a T cell-driven disease because T cells specific to ocular antigens are found in the peripheral blood of patients with uveitis,[9] and many therapies are T cell-directed. Furthermore, the most widely studied rodent model of uveitis is experimental autoimmune uveitis, a T cell-dependent model of chorioretinitis.[10] B cells and plasma cells are also found in the eye, and autoantibodies from the serum of patients with JIA-U bind to structures within the eye.[11-13] However, no animal model of uveitis to date has shown uveitis conferred from autoantibodies or induced by B-cell activity alone.[14-16]

Genetic and epigenetic factors also influence immune regulation and have been associated with uveitis in children. Polymorphisms in HLA molecules have been linked with uveitis risk and are thought to reflect recognition of particular antigens or epitopes (Table 1).[10] Several single-nucleotide polymorphisms and epigenetic factors, such as DNA methylation and microRNA expression, which influence gene expression patterns, have also been associated with uveitis risk.[17-20]

Uveitis biomarkers, such as s100 proteins, cytokines, and chemokines, are differentially expressed in the aqueous humor and serum of adults and children with uveitis.[21-26] They are also detected in tears from patients with uveitis and correlate with disease activity.[27-30] Further work is needed to discover sensitive biomarkers that diagnose and monitor uveitis, using noninvasive methods that are reproducible in the clinical setting.

COMMON UVEITIS SYNDROMES

Noninfectious Uveitis

Anterior uveitis—Anterior uveitis constitutes 45% of pediatric cases, where idiopathic chronic anterior uveitis is most common.[1] JIA-U occurs in up to 25% of children with oligoarthritis.[1,2,31-34] JIA-U is typically asymptomatic with a chronic and relapsing course. Acute anterior uveitis (AAU), which is typically symptomatic and unilateral, is most common in enthesitis-related arthritis and HLA-B27-positive patients with juvenile spondyloarthropathy. The American Academy of Pediatrics and other groups recommend regular ophthalmic screening of children with JIA for prompt detection of uveitis.[35-39] Children at highest uveitis risk are those with the oligoarthritis, polyarthritis rheumatoid

factor–negative, psoriatic, and undifferentiated JIA categories who are also less than 7 years old at JIA onset, antinuclear antibody positive, and have less than or equal to 4 years duration of JIA.[36,40] They need screening every 3 months. Other risk factors studied, but not included in the recommendations, are female sex and White race. At their initial ophthalmology visit, up to 45% of those with JIA-U already have ocular complications, such as cataracts and glaucoma.[34,36,41-43]

Nonanterior uveitis—Nonanterior uveitis occurs less frequently. Pars planitis, an idiopathic form of intermediate uveitis, is most common.[2,44] Mean age of onset is 7.8 years.[45,46] Patients with haplotypes HLA-DR2 or HLA-DR15, and pars planitis/periphlebitis on examination have an increased risk of developing multiple sclerosis.[47,48] Children diagnosed before age 7 have a worse visual prognosis.[49] Female sex and Hispanic ethnicity may predict greater rates of remission.[50] Prognosis varies, and treatment includes glucocorticoids (GC), systemic immunomodulatory therapy, and, in select patients, pars plana vitrectomy and panretinal photocoagulation.[45,51,52]

Behçet disease is a systemic vasculitis most common in individuals age 10 to 30, causing severe recurrent nongranulomatous uveitis and hypopyon, with recurrent aphthous and genital ulcers.[53-55] Onset age less than 25 years and male sex are risk factors for uveitis, and males have worse visual prognosis.[56-58] Posterior uveitis is associated with more sight-threatening complications, and can manifest as an occlusive retinal vasculitis of arteries and veins causing macular edema and retinal neovascularization.[59]

Blau syndrome and sarcoidosis are similar entities characterized by noncaseating granulomas affecting multiple organ systems. Inflammation occurs in any part of the uvea. Blau syndrome, caused by mutations in *NOD2*, classically presents with a triad of rash, arthritis, and uveitis before age 5.[46,60-63] Pediatric sarcoidosis has two distinct patterns. Early onset sarcoidosis is clinically indistinguishable from Blau syndrome except for the absence of a family history.[46,64] Later-onset sarcoidosis in children resembles adult sarcoidosis, with pulmonary involvement.[65] Elevated angiotensin-converting enzyme and lysozyme levels may support a diagnosis of sarcoidosis, although angiotensin-converting enzyme levels can normally be elevated in children.[66,67]

Vogt-Koyanagi-Harada disease is a bilateral granulomatous panuveitis most common in patients of Hispanic, Asian, Native American, Middle-Eastern, and Asian-Indian ancestry.[68-70] The pathogenesis is likely an autoimmune reaction to a melanin-associated antigen.[71,72] Approximately 8% to 16% of cases affect children younger than 16.[73,74] The initial prodromal phase presents with flulike symptoms, orbital pain, meningismus, sensorineural hearing loss, and tinnitus.[75] The acute uveitic stage follows with bilateral blurry vision, anterior uveitis, optic disk hyperemia, and subretinal fluid.[75] The convalescent stage includes vitiligo, poliosis, and choroid depigmentation. The chronic, recurrent phase, manifests as bouts of AAU.[76]

Tubulointerstitial nephritis and uveitis syndrome typically presents as a bilateral nongranulomatous anterior uveitis, although one-third of patients have vitreous cell and optic nerve hyperemia.[77] Nephritis precedes uveitis in 65% of cases, and antecedent flulike

symptoms occur in 50%. Median age of onset is 15 years, and 75% are female. Uveitis is typically mild and nephritis self-limited, only rarely progressing to require dialysis.[78] The diagnosis is strongly supported by elevated urine β_2-microglobulin.[46,77-79]

Infectious Uveitis

Infections are important but less common causes of childhood uveitis. In the United States, infections account for 3% to 8% of pediatric cases.[80,81] In other regions, infections account for approximately 30% of cases.[41,82-85] Toxoplasmosis and toxocariasis are most common, causing posterior uveitis or panuveitis, either unilateral or bilateral. Herpes simplex virus, cytomegalovirus, varicella zoster virus, tuberculosis, and Lyme disease are less common. *Bartonella henselae*, implicated in cat-scratch disease, may cause neuroretinitis. A thorough history and assessment for risk factors are important because laboratory investigations are useful. In select cases, polymerase chain reaction testing of intraocular fluid confirms the diagnosis.[86]

Masquerade Syndromes

Masquerade syndromes can mimic uveitis but do not represent true autoimmune or infectious processes. These include retinal detachments and intraocular tumors. Retinoblastoma is uncommon but is the most common intraocular childhood malignancy and should be considered based on presentation of leukocoria and family history of retinoblastoma.[87]

OCULAR COMPLICATIONS

Ocular complications are common, especially with uncontrolled inflammation or prolonged treatment with topical GC.[34,88,89] They can develop in any eye compartment, may be mild and transient, or lead to severe permanent vision loss. Temporary vision loss can affect the developing visual pathway especially in younger children and cause permanent amblyopia.[90] Up to 80% of patients with JIA-U develop cataracts (23%–83% of cases), glaucoma (17%–28%), synechiae (18%–44%), band keratopathy (14%–46%), cystoid macular edema (2%–30%), and hypotony (3%–10%).[2,91-93] Approximately 5% to 15% of patients experience blindness.[2,92] Table 2 and Fig. 2 describe various ocular complications.

Surgery is performed in 15% to 19% of children, including cataract extraction, glaucoma surgery, or vitrectomy.[2,92] Inflammation should be controlled for a minimum of 3 months before surgery to reduce postoperative complications. GC is used in the preoperative, intraoperative, and postoperative period, administered locally or systemically.[94-96] Dose and duration vary, and taper depends on the postoperative clinical course. Usual systemic treatment should be maintained.

OPHTHALMIC WORK-UP

Assessment of Disease Activity

In 2005, the Standardization of Uveitis Nomenclature (SUN) working group described a systematic way to classify uveitis based on anatomic involvement, disease course,

and disease activity.[44] Anterior uveitis is inflammation of the AC, intermediate uveitis involves the vitreous, and posterior uveitis involves the retina and/or choroid. Presence of complications, such as vascular sheathing and macular edema, does not affect anatomic classification. In severe anterior uveitis, there may be spillover of cells into the vitreous. Acute uveitis is described as sudden in onset, lasting less than or equal to 3 months. Chronic uveitis is persistent inflammation with recurrence within 3 months of discontinuing treatment. Recurrent uveitis is multiple episodes of uveitis separated by more than 3 months in the absence of treatment. Uveitis may be limited or persistent, with a cutoff of 3 months, and subjectively described as sudden or insidious. Disease activity in anterior uveitis is graded by AC cell and flare from 0 to 4. AC cell reflects the number of cells counted in a 1 mm × 1 mm slit lamp beam. AC flare reflects the degree to which the lens and iris are obscured by protein flare. In nonanterior uveitis, vitreous haze is graded from 0 to 5, reflecting the degree to which the posterior pole is obscured. There is no standardized nomenclature for grading vitreous cell.

Ophthalmic Examination Components

1. *Bedside examination* is an assessment of the ocular vitals and a dilated examination with an indirect ophthalmoscope to assess the posterior segment of the eye (Table 3).
2. *Slit lamp examination* assesses and grades inflammation. Precise intraocular pressure measurement with Goldmann applanation tonometry, assessment of corneal pathology, and the use of a gonioscope to evaluate the AC angle may be performed. Dilated examinations are performed at the slit lamp.
3. *Special tests* require specialized machinery to assess visual function and complications, as in visual field testing. Optical coherence tomography (OCT) assesses for macular edema and glaucomatous progression. Fluorescein angiography evaluates for retinal vasculitis or other signs of inflammation that are not detected by the ophthalmic examination.

Innovations in the Ophthalmic Work-up

Ophthalmic imaging and technology are rapidly changing, with advances in anterior and posterior segment imaging. Detection of anterior segment inflammation by anterior segment OCT and laser flare photometry enables standardized quantitative metrics for AC cell and flare, respectively.[97,98] Furthermore, OCT of the retina noninvasively measures blood flow through different levels of the retina. Quantitative metrics including measure of the foveal avascular zone area and vessel density can be acquired. A small retrospective cohort study reported a decrease in vessel density in childhood uveitic patients compared with control subjects.[99] As technologies improve and become available, there may be better end points for clinical disease measurement and clinical trials.

THERAPEUTIC OPTIONS

Timely local and/or systemic immunosuppression is critical. Recommendations for treatment have been country-specific until recently.[100,101] Guidelines developed by pediatric

rheumatologists and ophthalmologists in North America and Europe include the American College of Rheumatology/Arthritis Foundation (ACR/AF) and the Single Hub and Access point for pediatric Rheumatology in Europe (SHARE) recommendations.[38,102]

Glucocorticoids

Topical ophthalmic drops, periocular GC, and intraocular GC are used as sole treatment or in conjunction with systemic therapies.[103,104] Mode of administration is based on disease activity, ocular complications, and patient preference/cooperation. Prednisolone acetate 1% is the first-line topical GC for anterior uveitis. Difluprednate is more potent and reserved for severe inflammation, such as intermediate uveitis or treatment of cystoid macular edema. Limitations in difluprednate use are cost and side effects, such as ocular hypertension. Thorne and colleagues[105] report that prednisolone acetate 1% administered at less than or equal to two drops per day may not increase risk for cataract formation, although guidelines recommend discontinuing topical GC as a goal.[37,38]

Local GC injections are used when more aggressive therapy is necessary and/or systemic therapy is failing or not an option. Careful consideration is required because of the risk of ocular hypertension, glaucoma, and cataract. Young children can have difficulty cooperating. Periocular GC injections are given in the sub-Tenon space (virtual space between the capsule and sclera) with triamcinolone acetonide. Intravitreal GC injections (injection into the vitreous cavity), such as intravitreal triamcinolone acetonide and dexamethasone, are administered as GC implants or direct injection. The PeriOcular versus INTravitreal GC for uveitic macular edema (POINT) trial was a multicenter randomized controlled trial in adults, which showed that intravitreal therapies were superior to periocular triamcinolone acetonide injections in treating uveitic macular edema.[106]

Oral and intravenous GC are prescribed in nonanterior uveitis or severe ocular inflammation. Prolonged courses of GC as sole therapy are not recommended and systemic immunosuppression should be initiated in chronic uveitis. In general, GC are used as short-term bridging therapy while awaiting efficacy of GC-tapering therapy, for control of severe disease, or in children with macular edema.[38,102,107] The CARRA uveitis consensus treatment plan suggests that steroid taper begin no later than 2 weeks after initiation of a steroid-sparing agent.

Conventional Synthetic Disease-Modifying Antirheumatic Drugs and Tumor Necrosis Factor Monoclonal Antibodies as First-Line Agents

Methotrexate—Methotrexate (MTX) has been considered first-line GC-sparing medication, regardless of uveitis category or cause. In children with severe disease and sight-threatening complications at presentation, simultaneous use of tumor necrosis factor monoclonal antibodies (TNF mAb) is recommended.[102,107] Despite decades of experience with MTX, there is scant literature on its effectiveness in childhood uveitis. The earliest case series in 1998 reported six of seven children with JIA-U significantly reduced or discontinued topical GC.[108] A retrospective study of 38 patients with JIA-U describes 25 treated with MTX for uveitis.[109] The other 13 patients only required 3 months of GC

therapy. Most patients treated with MTX showed full or partial response; 6 of the 25 (24%) achieved remission over 12 months, whereas 4 of the 25 (16%) did not respond to MTX.

Meta-analysis of MTX studies in childhood uveitis, not limited to JIA-U, estimated that approximately 73% of children respond to MTX, defined as improvement in uveitis activity per SUN criteria. However, the durability of response varied across studies.[52] Most studies included only patients with JIA-U, thus likely representing anterior uveitis. A large multicenter cohort of adult and pediatric patients with uveitis found significantly higher rates of response with anterior and intermediate uveitis as compared with posterior or panuveitis.[110] Furthermore, children were less likely to respond to MTX compared with adults (adjusted hazard ratio for control of inflammation, 0.33; 95% confidence interval, 0.2–0.55).

The ACR/AF guideline recommends a threshold of 3 months for adding or changing systemic therapy. Earlier changes may be needed based on ophthalmic examination, duration of topical and systemic therapy, and ocular complications. The significant number of children who do not respond to MTX, and the proportion experiencing intolerable side effects, necessitate additional therapies.

Tumor necrosis factor inhibitors—Biologic disease-modifying antirheumatic drugs (DMARDs), such as TNF mAb, are commonly used for uveitis. Food and Drug Administration approval was granted for adalimumab for the treatment of noninfectious intermediate, posterior, and panuveitis in adult patients in 2016 and pediatric patients in 2018. A randomized controlled trial in 2017 describes patients with active uveitis on a stable dose of MTX randomized to either adalimumab or placebo.[111] Primary end point was time to treatment failure. The study, which enrolled 60 patients in the adalimumab arm, was stopped early because of the significantly different rates of treatment failure (27% in the adalimumab group vs 60% in the placebo group). The ADJUVITE trial was another randomized, placebo-controlled trial of adalimumab in patients with idiopathic or JIA-U and inadequate response to MTX.[112] Patients on adalimumab were more than twice as likely to have improvement in inflammation compared with the placebo group after 2 months.

Etanercept (which is a soluble TNF receptor and not an mAb) is not recommended for JIA-U, based on studies showing less benefit in treating or reducing risk of new uveitis as compared with TNF inhibitor (TNFi) mAb.[113-115] Infliximab is frequently used, but neither infliximab nor other commercially available TNFi mAb have Food and Drug Administration approval at present for the indication of uveitis. Although the intravenous administration of infliximab has benefits in certain situations (ie, when adherence is an issue), adalimumab may be superior. In one prospective study of adalimumab versus infliximab in 33 children with uveitis, nearly all achieved remission within a year, but there were fewer flares in the group who received adalimumab.[116] Another study used standard treatment protocols for JIA-U, beginning with GC, then MTX or cyclosporine, then adalimumab or infliximab. At 2 years of followup, 60% of patients on adalimumab were in remission, compared with 20% on infliximab.[117] Finally, in an open-label comparison in adults with Behçet-related uveitis, although remission rates after 1 year were similar between adalimumab and infliximab, Best corrected visual acuity and other parameters were better in the adalimumab group.[118]

Although these collective results seem compelling, the infliximab dose used in these European studies ranged from 5 mg/kg every 6 to 12 weeks in the two pediatric studies, and 3 to 5 mg/kg every 4 to 8 weeks in the Behçet disease study. These doses are lower than those used by North American practitioners, who may advance doses as high as 20 mg/kg every 4 weeks.[119] Thus, patients who fail either adalimumab or infliximab may still benefit from switching to another TNFi mAb or increasing dose.

Beyond Methotrexate and Traditional Tumor Necrosis Factor Inhibitors

Fewer studies have examined treatment after standard therapy. Guidelines recommend several options. Approximately 30% or more patients have severe uveitis refractory to TNFi mAb and conventional synthetic DMARDs.[120]

Tocilizumab—Tocilizumab, an anti-interleukin-6 receptor mAb, is promising for JIA-U and other types of uveitis in multiple case series.[121-123] The APTITUDE trial was a multicenter phase 2 trial evaluating subcutaneous tocilizumab in patients with JIA-U who failed standard therapy with TNF mAb and MTX.[124] The primary outcome was treatment response at Week 12; of 21 patients enrolled, seven (33%) met this outcome. Only six patients on tocilizumab continued past 12 weeks of treatment. Treatment nonresponse was the most common reason for discontinuing tocilizumab. Thus, the trial did not meet its primary end point.[124] As the authors noted, however, tocilizumab was effective for a subset of patients with refractory uveitis. Three of four patients with baseline macular edema improved. With few evidence-based options, tocilizumab may be a reasonable therapeutic option.

Abatacept—Abatacept, a CTLA-4-Ig fusion protein that blocks T-cell costimulation, showed promising results in small case series of TNFi-refractory patients.[125,126] However, another case series found that although 11 (52%) out of 21 patients with refractory JIA-U responded to abatacept, the response was not sustained for 8 out of the 11.[127] When used as first-line therapy, abatacept was effective for 57% of patients with JIA-U.[128]

Rituximab—Rituximab, an mAb against CD20, has been trialed with varying success for posterior uveitis, panuveitis, and uveitis associated with systemic conditions.[129-131] Miserocchi and colleagues[132] reported eight adults with long-standing, refractory JIA-U who achieved durable remission with a mean follow-up time of more than 44 months. All patients had oligoarticular persistent or extended JIA with ocular complications from uveitis damage or GC treatment. Although promising, little data support the use of rituximab in uveitis.

Janus kinase inhibitors—Janus kinase (JAK) inhibitors are targeted synthetic DMARDs that are small molecular inhibitors, which target multiple cytokine pathways and are being used in the treatment of multiple autoimmune and autoinflammatory conditions. Miserocchi and colleagues[133] reported four patients with JIA-U who were treated successfully with JAK inhibitors, either baricitinib or tofacitinib. Bauermann and colleagues[134] reported excellent response to tofacitinib in an adult with severe JIA-U. Currently, tofacitinib is the only JAK

inhibitor approved for use in children, and is indicated for polyarticular JIA. A phase 3 trial of baricitinib in childhood uveitis is in progress (NCT04088409).

TREATMENT WITHDRAWAL

Long-term systemic immunosuppressive therapy is critical, because uveitis recurrence is high. In Behçet-associated uveitis, 43% to 57% of patients flare, regardless of treatment duration.[135-137] In Vogt-Koyanagi-Harada disease, 39% to 72% of patients relapse, although this varies by ethnicity.[138-140] In JIA-U, 43% to 82% relapse off of medications, with a median time of 12 to 24 months.[49,141-146] Idiopathic uveitis may have a better prognosis than JIA-U, because one study reported 62% of 94 children with idiopathic uveitis remained in remission 4 years after discontinuing therapy compared with 17% of JIA-U.[144] Furthermore, those with JIA-U relapsed more quickly.[145] Some studies suggest that patients who initiated systemic immunomodulatory therapy within the first year of uveitis diagnosis and achieved remission within 6 months had a higher success of remaining in remission off of medications.[143,144] Longer duration of therapy may be important, because patients in remission on MTX for at least 2 years had improved success in weaning off medication than those in remission for a shorter duration.[147,148] Thus, guidelines recommend at least 2 years of remission on immunomodulatory therapy before attempting to wean medications.[38,102]

SUMMARY

Recommendations from SHARE and ACR/AF can guide treatment of children with JIA-U. SHARE recommends: (1) establishment of no cells in the AC as a goal for uveitis-directed therapy, (2) initiation of systemic therapy if uveitis cannot be controlled on topical GC within 3 months, (3) 2 years of uveitis inactivity off topical GC before tapering systemic therapy, and (4) recognition that patients on arthritis-directed systemic therapy may be at risk for uncovering uveitis when therapy is discontinued. MTX is recommended as the first-choice DMARD, followed by TNF mAb.[38] The ACR/AF issued similar recommendations regarding step-up therapy in JIA-U with MTX followed by TNF mAb, and further recommended (1) subcutaneous MTX over oral MTX, (2) starting MTX and TNF mAb simultaneously for severe uveitis, and (3) increasing TNF mAb dose to above-standard dosing for uncontrolled uveitis before switching to another agent.[102] The Childhood Arthritis and Rheumatology Research Alliance (CARRA) developed consensus treatment plans to suggest standardized treatment options for chronic anterior uveitis, either JIA-U or idiopathic. These include either subcutaneous or oral MTX, and adalimumab or infliximab. Standardizing patient care and data collection using the CARRA Registry may allow for better comparison of treatment approaches and uveitis outcomes.[107]

No standardized treatment approach of other types of childhood uveitis exists, such as in HLA-B27-associated AAU or pars planitis. Management of these conditions is often led by ophthalmologists. The presence of an underlying rheumatic condition may influence selection of systemic therapy, but MTX and TNFi mAb remain the agents of choice.

Close collaboration among rheumatologists, ophthalmologists, and other eye care specialists is critical.[39] Ophthalmology specialists perform ophthalmic examinations to assess uveitis

activity and ocular complications, which inform systemic treatment prescribed by pediatric rheumatologists. Continued and regular communication among all subspecialists optimizes vision outcomes of these children.

DISCLOSURE

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CLINICS CARE POINTS

- Vision loss profoundly impacts a child's quality of life and visual functioning, making an urgent need for improved strategies to diagnose uveitis early, before the development of irreversible ocular damage.
- In children at risk for uveitis (ie, JIA), regular ophthalmic screening is important for prompt detection and initiation of therapy.
- In children diagnosed with uveitis, ophthalmic monitoring should include standardized evaluations of uveitis activity, disease course, and development of new or recurring complications to direct therapy.
- Treatment initially consists of local or systemic GC for a short period. Prolonged GC should not be used, and systemic treatment should be initiated in children with refractory chronic disease.
- Methotrexate, infliximab, and adalimumab are the mainstays of therapy in noninfectious uveitis. Combination therapy or higher doses are often needed to control inflammation.
- Treatment of children with refractory uveitis includes golimumab, tocilizumab, abatacept, rituximab, and JAK inhibitors. Because there are few randomized controlled trials, we rely on CARRA consensus treatment plans and guidelines from expert opinion and retrospective studies.
- Duration of treatment is at least 2 years after uveitis is well controlled (no GC, no flares) because of high risk for remission and relapse.
- Goal of treatment is to control inflammation with minimal GC use, to prevent vision-threatening complications.
- Close collaboration and communication among rheumatologists, ophthalmologists, and other eye care specialists optimizes vision outcomes.

KEY POINTS

- Childhood uveitis can lead to sight-threatening complications.
- Ophthalmic screening of children with JIA at risk for uveitis needs to be performed per recommended schedules.
- Ophthalmic evaluation of children with uveitis is important to monitor disease activity, treatment response, and development of complications.
- Prolonged courses of glucocorticoids (GC) should not be used as sole therapy.
- Early and timely treatment with systemic immunosuppression improves vision outcomes.

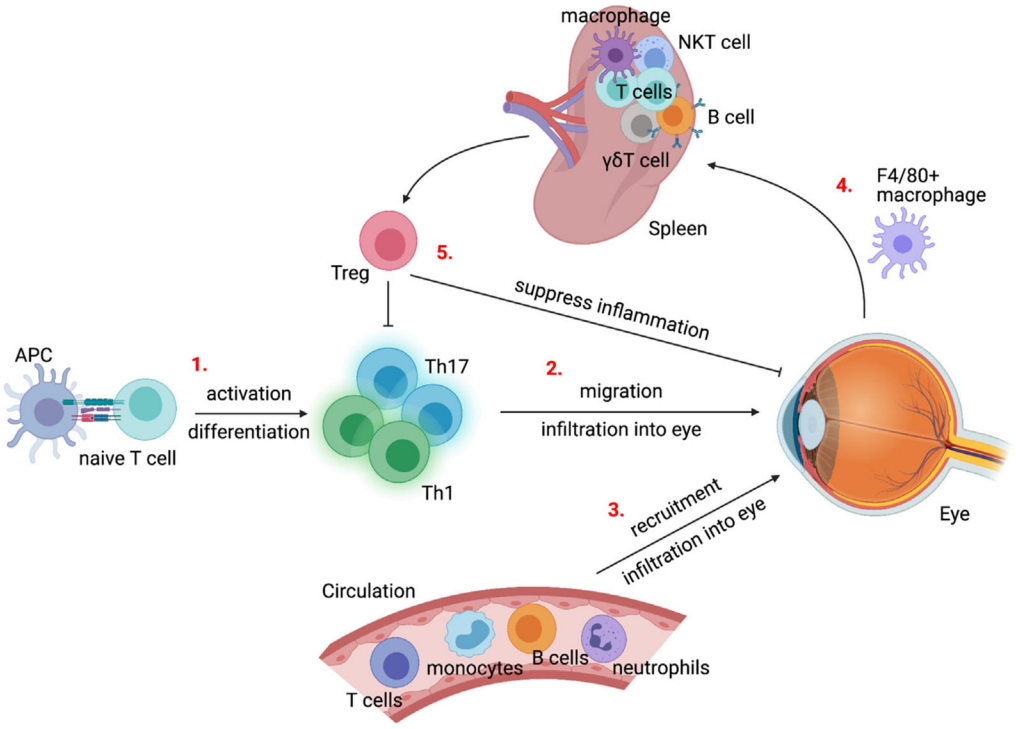

Fig. 1.

Pathogenesis of autoimmune uveitis. (1) Autoreactive T cells in the periphery are activated and polarized to Th1 and Th17 cells. (2) Activated T cells migrate to the eye, triggering local release of inflammatory cytokines and permeabilization of the retina-blood barrier. (3) Chemokines released from local inflammation recruits circulating leukocytes to the eye. (4) Macrophages carry ocular antigens to the spleen where they interact with T cells, B cells, natural killer T cells, and γδT cells to generate Tregs. (5) Antigen-specific Tregs suppress effector T-cell proliferation and local inflammation in the eye, promoting remission. Created withBioRender.com.

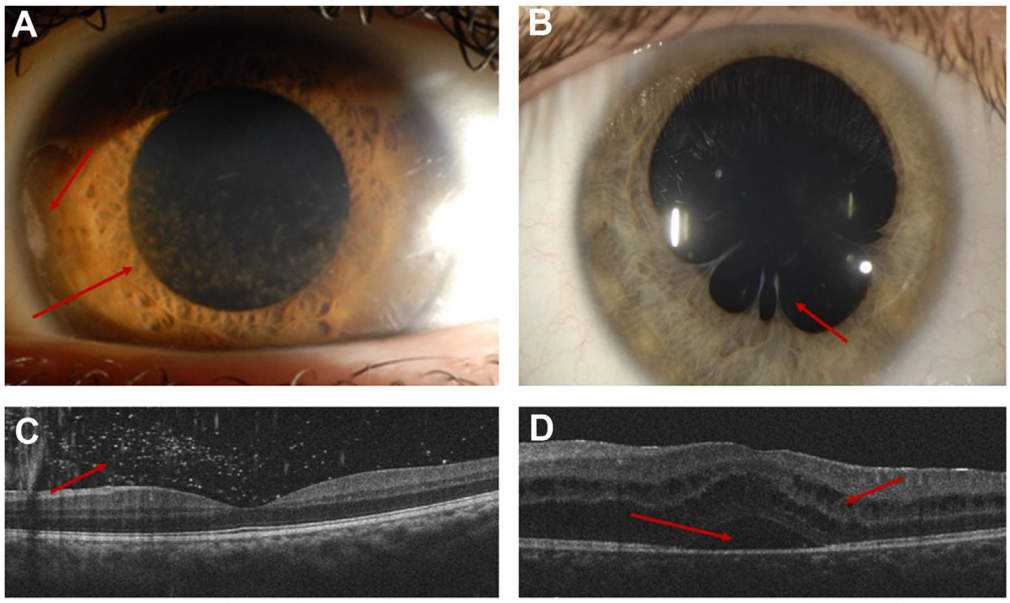

Fig. 2.

Anterior segment complications of uveitis include band keratopathy (*A, arrows*) and posterior synechiae (*B, arrow*). Optical coherence tomography displays posterior segment complications of images of the retina with vitreous opacities (*C, arrow*) and cystoid macular edema with subretinal fluid (*D, arrows*).

Table 1

HLA associations in uveitis

Disease	Genetic Associations	Location of Inflammation
Juvenile idiopathic arthritis–associated uveitis	DRB1*1104, DRB1*08, DRB1*09, DRB1*13, DPB1*0201, DR5	Anterior
Tubulointerstitial nephritis and uveitis	DQA1, DQB1, DRB1	Anterior
Spondyloarthritis-associated uveitis	B27, DR8	Anterior
Pars planitis	DR2, DR3, DR15, DR51, DR17, B8, B51	Intermediate
Behçet disease	B51	Panuveitis
Birdshot chorioretinopathy	A29	Panuveitis
Sarcoidosis	B8, DRB1*1101, DRB3*0101	Panuveitis
Vogt-Koyanagi-Harada disease	DRB1*04, DQB1*04, DQA1*03, DPB1*05	Panuveitis

Table 2

Complications of childhood uveitis

Complication	Description	Location/ Findings	Treatment
Band keratopathy	Calcium deposits in the cornea, if within the visual axis, can cause vision loss Often a sign of chronic inflammation	Cornea/anterior segment	Local chelation Photorefractive keratotomy
Hypotony	Ciliary body shutdown in certain types of uveitis may cause intraocular pressure to become low Can be transient or chronic	Corneal folds Optic nerve edema Choroidal folds Macular edema	*Depends on etiology* Corticosteroids may be beneficial in certain types of uveitis
Peripheral anterior synechiae	Iris adhesions onto the trabecular meshwork, which can block aqueous outflow and lead to angle closure and ocular hypertension	Anterior segment	Treat underlying cause Cycloplegic drops If ocular hypertension, treat accordingly (topical drops and/or glaucoma surgery)
Posterior synechiae	Iris adhesions to anterior surface of lens, these adhesions can limit view of posterior segment structures If severe may cause angle closure and iris bombe	Anterior segment	Cycloplegic drops Surgical release of adhesions
Cataract	Clouding of the lens	Anterior segment	Surgical removal ± intraocular lens placement
Vitreous cell/ opacities	Infiltration of inflammatory cells into the vitreous cavity	Vitreous cavity	Treatment of inflammation by oral corticosteroids or systemic immunosuppression Local steroid injection Topical drops are less efficacious in penetrating the vitreous cavity
Epiretinal membrane	Thickening of the inner retina, which is associated with vitreous traction, macular hole formation, or macular edema	Retina/posterior segment	Pars plana vitrectomy with membrane peel if symptomatic
Cystoid macular edema	Retinal thickening, edema, and/or subretinal fluid	Retina/posterior segment	Treatment of inflammation with topical drops, oral corticosteroids, and/or systemic immunosuppression Local corticosteroid injections
Glaucoma	Permanent damage to the optic nerve associated with high intraocular pressures and visual field loss	Optic nerve/retinal nerve fiber layer	Eyedrops Surgery Treat underlying cause

Uncontrolled uveitis may lead to reversible and irreversible complications. Not all complications listed are seen in all types of uveitis.

Table 3

Components of the ophthalmic examination

Category	Examination	Notes
Bedside examination	History	Assess history of photophobia
		Ask parents if the child ever has their eyes misaligned
		For children 1–2 y of age, does the child grip objects well?
		For children older than 5 y of age, does the child watch television from an appropriate distance?
	Visual acuity testing	Patients should be positioned 20 feet (6 m) from the chart
		Testing should be performed using glasses of the correct prescription
		Consider picture card for ages 2–3; tumbling “E” or HOTV for preliterate children older than 3 y of age
		The unused eye should be occluded or patched to prevent peeking
	Pupillary examination	Advanced cases of posterior synechiae may be grossly visible
		A relative afferent pupillary defect may suggest optic nerve pathology (eg, severe glaucoma, optic neuritis)
		Patients with active anterior uveitis may demonstrate consensual photophobia
	Extraocular motility and alignment	The presence of strabismus may raise concern for amblyopia
	Confrontational visual fields	May detect large visual field defects suggestive of glaucoma
		Formal machine-based visual field testing remains the gold standard
	Corneal and external examination	Redness and ciliary flush may support a diagnosis of anterior uveitis
		In some cases, band keratopathy may be visible
		Fluorescein staining may be used to evaluate for corneal pathology
	Intraocular pressure	The eye pressure can be taken by various types of commercial hand-held tools
	Direct ophthalmoscopy	May be used to assess the optic nerve
		Assessment of the red reflex can evaluate for cataract or retinoblastoma
	Indirect ophthalmoscopy	May be used to evaluate for vitreous haze, optic nerve edema, retinal vascular pathology
		Assessment of the red reflex can evaluate for cataract or retinoblastoma
Slit lamp examination	Anterior chamber cell and flare	Quantify the degree of inflammation in the anterior chamber
	Goldmann applanation tonometry	Increased intraocular pressure is associated with increased risk for permanent glaucomatous vision loss
		Goldmann applanation tonometry performed at the slit lamp is the gold standard, but is difficult to perform in children
	Corneal and external examination	Redness and ciliary flush may support a diagnosis of anterior uveitis
		Allows for detailed diagnosis of corneal pathology
	Gonioscopy	Used to visualize the anterior chamber angle to assess for angle closure and glaucoma risk
		May visualize peripheral anterior synechiae that may otherwise be difficult to see
	Dilated fundoscopic examination	Allows for the most detailed direct visualization of the posterior segment
		Evaluate for vitreous cell and haze, retinal or choroidal inflammation, vasculitis, optic nerve pathology, macular edema
Special tests	Visual field testing	Formal machine-based visual field testing is necessary to diagnose visual field loss
		Visual field deficits are often related to glaucoma

Category	Examination	Notes
		Testing requires maintained concentration and is difficult in young patients
	Optical coherence tomography	High-resolution image, which delineates the layers of the retina
		Retinal nerve fiber layer thickness and optic nerve morphology correlate with glaucomatous progression
		May reliably detect and monitor macular edema
	Fluorescein angiography	Use of intravenous fluorescein to visualize and diagnose retinal vasculature pathology
		Assess posterior segment inflammation, including optic disk hyperfluorescence, macular edema, and retinal vascular leakage
	Retinoscopy	Most commonly used to assess refractive error in preverbal children younger than 2 y of age
		Requires cycloplegic eyedrops to suppress accommodation for accurate results