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Immunosuppression for the Uveitides

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The uveitides are a collection of more than 30 diseases characterized by intraocular inflammation. Many cases of juvenile idiopathic arthritis–associated uveitis, many cases of intermediate uveitis, and most cases of posterior and panuveitides requiring treatment are treated with corticosteroids and immunosuppression. Disease-specific, time-updated modeling of clinical data for several uveitides suggests superior prevention of ocular complications and visual outcomes with immunosuppression. These studies also suggest that oral corticosteroids at doses low enough for safe long-term therapy (i.e., <7.5 mg/day) are ineffective, implying that immunosuppression should be part of the initial regimen. The Multicenter Uveitis Steroid Treatment (MUST) Trial and Follow-up Study was a randomized comparative effectiveness trial comparing systemic therapy with oral corticosteroids and immunosuppression with regional corticosteroid treatment. It demonstrated that, when used properly, oral corticosteroids and immunosuppression can be given safely for up to 7 years with no evident increased risk of systemic side effects compared with regional corticosteroid therapy, except for greater antibiotic use for infections. The Systemic Treatment for Eye Diseases (SITE) Cohort Study suggested long-term safety for this approach, when the immunosuppressive agents were antimetabolites or calcineurin inhibitors. Thus, oral corticosteroids and immunosuppression may be a preferred initial therapy for many noninfectious, intermediate, posterior, and panuveitides. Nonalkylating-agent immunosuppression has a low rate of sustained, drug-free remissions, <10%/year. Nonalkylating-agent immunosuppression for >3 years with control of the inflammation for >2 years is associated with a decreased risk of relapse after discontinuing immunosuppression. Alkylating agents can induce sustained drug-free remissions but likely increase the lifetime risk of cancer. Biologics, which target specific cytokines and pathways, hold promise for the future. Monoclonal antibodies directed against tumor necrosis factor (TNF)-α have been studied most often, and one, adalimumab, is U.S. Food and Drug Administration approved for the treatment of noninfectious, intermediate, posterior, and panuveitides. *Ophthalmology 2017;■:1–10 © 2017 by the American Academy of Ophthalmology*

The uveitides are a collection of more than 30 diseases characterized by intraocular inflammation.[1] The prevalence of the uveitides in the United States is estimated to be as high as 115 to 133 per 100 000.[2–5] Collectively, they are the fifth or sixth leading cause of blindness.[6–8] Because the uveitides affect persons of all ages, including children, they potentially have substantially greater years of vision loss than age-related diseases. The cost of treating the uveitides is estimated to be similar to that of treating diabetic retinopathy.[9] Patients with uveitis have greater medical resource use and need for prescription drugs, more work loss days, and more disability days than patients without uveitis.[10] Thus, proper management of the uveitides is critical to maximizing vision and minimizing the impact of the disease on patients' lives.

The uveitides are categorized as a matrix of diseases characterized by the anatomic class and whether they are infectious, associated with a systemic disease, or eye-limited and presumably immune-mediated (Table 1).[1,11] Uveitides not classifiable as a specific disease are characterized as undifferentiated with the course and anatomic class (e.g., undifferentiated chronic anterior uveitis).[1,11] Treatment of noninfectious uveitides is guided by the anatomic class, course, and natural history. Some diseases are self-limited and spontaneously remitting with a good visual prognosis (e.g., acute posterior multifocal placoid pigment epitheliopathy and multiple evanescent white dot syndrome); these diseases typically do not need treatment. Acute monophasic and recurrent acute uveitides (e.g., spondylitis/human leukocyte antigen-B27–associated uveitis) typically need treatment only of the acute attacks. Conversely, most chronic, noninfectious uveitides need chronic treatment to suppress the inflammation.[1,12,13] For noninfectious uveitides, which comprise more than 90% of the cases of uveitis in the United States,[3,4] the anatomic class guides the initial treatment approach. Anterior uveitides are treated with topical corticosteroids; intermediate uveitides with regional corticosteroid injections (periocular or intravitreal) or oral corticosteroids and, when needed, immunosuppression; and posterior and panuveitides typically with oral corticosteroids and immunosuppression.[12,13]

Treatment Target

The decision to treat an individual patient and the choice of therapy always represent risk–benefit decisions. Not every case of uveitis needs treatment. In Fuchs' uveitis syndrome

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Table 1. Major Uveitic Diseases

Anatomic Class	Infectious	Systemic Disease	No Systemic Disease
Anterior	Cytomegalovirus anterior uveitis Herpes simplex anterior uveitis Herpes zoster anterior uveitis Syphilis	Spondylitis/HLA-B27–associated anterior uveitis JIA-associated anterior uveitis Behçet disease Sarcoidosis Tubulointerstitial nephritis with uveitis	Fuchs' uveitis syndrome
Intermediate	Syphilis Lyme disease	Multiple sclerosis–associated uveitis Sarcoidosis	Pars planitis
Posterior	Acute retinal necrosis Cytomegalovirus retinitis Lyme disease Syphilis Toxoplasmic retinitis Tuberculosis	Sarcoidosis	Acute posterior multifocal placoid pigment epitheliopathy Birdshot chorioretinitis Multiple evanescent white dot syndrome Multifocal choroiditis with panuveitis Punctate inner choroiditis Relentless placoid choroiditis Serpiginous choroiditis
Panuveitis	Syphilis Lyme disease	Behçet disease Vögt-Koyanagi-Harada disease	Sympathetic ophthalmia

HLA = human leukocyte antigen; JIA = juvenile idiopathic arthritis.
Adapted from Jabs and Busingye.[1]

(also known as "Fuchs' heterochromic iridocyclitis"), treatment appears not to have beneficial effects and typically is not given. Some 25% to 35% of patients with pars planitis have mild disease, no macular edema or other complications, and good vision, and do not need treatment; these patients maintain good vision with up to 10 years of follow-up.[14,15] However, when treatment is needed, the goal is complete suppression of the inflammation (i.e., to "grade 0" inflammation).[11] For anterior and intermediate uveitides, semiquantitative grading scales of cells and haze are used; studies have shown good interobserver agreement for the Standardization of Uveitis Nomenclature scales.[11,16] For chorioretinal disease, multimodal imaging may be required, and for many (but not all) posterior uveitides, fundus autofluorescence appears to correlate with active disease.[17–19]

Sophisticated, time-updated modeling in juvenile idiopathic arthritis (JIA)-associated chronic anterior uveitis demonstrates that any inflammation doubles the risk of visual impairment (worse than 20/40) and triples the risk of blindness (20/200 or worse)[20]; increasing grades of inflammation are associated with greater risks of visual loss.[21] The Systemic Immunosuppressive Treatment for Eye Diseases (SITE) Cohort Study found similar results for Behçet disease, in which active uveitis increased the risk of visual impairment 2.5-fold and blindness 2.7-fold.[22] Although approximately 25% to 33% of patients with intermediate uveitis can be managed successfully with intermittent regional therapy,[14,15] the remainder of the chronic uveitides benefit from sustained suppression of the inflammation. In birdshot chorioretinitis, intermittent treatment can control the macular edema but does not prevent progressive retinal damage measured by loss of visual field and electroretinogram.[23] Immunosuppression reverses visual field loss and normalizes the retinal damage seen on optical coherence tomography.[24,25] In the SITE Cohort Study, complete suppression of inflammation halved the risk of choroidal neovascularization versus active uveitis, whereas minimally active uveitis was no different from active active.[26] In the Multicenter Uveitis Steroid Treatment (MUST) Trial and Follow-up Study, at 7 years of follow-up, regional therapy with the fluocinolone acetonide implant was associated with an 81% excess risk in the odds of blindness versus systemic therapy with oral corticosteroids and immunosuppression.[27] This difference appeared to be due to retinal damage from relapse of the uveitis before reimplantation.[27] A problem with regional therapies, particularly short-acting regional therapies, is the variable duration of effect; reinjection or reimplantation is performed after relapse. Each relapse before reinjection or reimplantation results in cumulative damage; although typically there is some recovery after reinjection or reimplantation, the long-term result is poorer visual outcomes, a phenomenon sometimes termed the "saw-tooth decline." Scheduled replacement or reinjection before relapse might improve the results with regional therapies, but given the variable duration of action, the timing of scheduled replacement is difficult and, in practice, not typically done.

Oral Corticosteroids

Oral corticosteroids are critical for the initial control of ocular inflammation, even when immunosuppression is used. Studies of patients with sarcoid uveitis have shown that oral corticosteroid therapy is associated with a 93% reduction in the odds of visual impairment.[28] The initial dose of prednisone should be 1 mg/kg/day up to a maximum of 60 mg/day.[12,13] Doses >60 mg/day are associated with an increased risk of ischemic necrosis of bone and should be avoided.[29] After 2 to 4 weeks, prednisone should be tapered; for chronic diseases, the target dose is <7.5 mg/day. A systematic review of randomized trials of prednisone 7.5 mg/day in rheumatoid arthritis showed no