Promising Pipeline for Treatment of Noninfectious Posterior Uveitis

Agents and delivery mechanisms in development may offer physicians assistance in treating this heterogeneous disorder.

BY STEVEN YEH, MD

Uveitis is a heterogeneous group of conditions that is broadly characterized by intraocular inflammation that can result in visual impairment. Typically classified by anatomic location (anterior, intermediate, posterior, or panuveitis), the inflammation can occur as the result of an infectious process, or it may be related to systemic autoimmune disease. Laboratory testing and appropriate workup may reveal that some cases have no known systemic disease association, either infectious or autoimmune. Other conditions, such as primary intraocular lymphoma, are considered uveitis masquerade syndromes and should be ruled out to ensure that appropriate therapy is initiated.

NONINFECTIOUS POSTERIOR UVEITIS

Noninfectious uveitis of the posterior segment involves inflammation of the retina and choroid and represents the majority of cases seen in a tertiary referral center for uveitis. Cystoid macular edema (CME) is a leading cause of vision loss in noninfectious posterior uveitis. Both inflammation and alterations in vascular permeability that lead to CME may have to be considered in the treatment of this disease process.

Although treatment algorithms for uveitis are complex (especially if all types and etiologies of uveitis are considered), a concrete, anatomy-based approach can assist in initiation of appropriate therapy. For noninfectious uveitis of the posterior segment, there are many factors to weigh in determining an effective management plan. For example, laterality (whether both eyes are affected), the presence or absence of CME, and the possible side effects of any potential treatments or their interactions with other health conditions should be considered in choosing a therapeutic strategy.

CURRENT THERAPIES

Oral Corticosteroids

Long the mainstay of treatment for posterior noninfectious uveitis, oral corticosteroids are preferred for rapid control of active uveitis. However, significant side effects, both ocular (glaucoma and cataract development) and systemic (weight gain, insomnia, anxiety, gastrointestinal problems, hypertension, and diabetes),

At a Glance

- Disease severity, laterality, the presence of CME, and potential side effects should be considered when selecting a therapeutic strategy for the treatment of noninfectious posterior uveitis.
- Although oral corticosteroids are the preferred therapy for rapid control of uveitis, they carry the potential for significant side effects.
- There is an ongoing need for uveitis treatments with better efficacy and improved side effect profiles.
- Multiple promising drug candidates and new routes of administration are being investigated.

TABLE. EMERGING THERAPIES FOR UVEITIS

Therapeutic Agent (Manufacturer)	Drug Class and Delivery Mechanism	US Approval Status
Local Therapy		
triamcinolone acetonide (CLS-1001, Clearside Biomedical)	Suprachoroidal injection; corticosteroid	Phase 3 clinical trial set to begin for macular edema associated with noninfectious uveitis
sirolimus (DE-109, Santen)	Intravitreal; mTOR inhibitor	Phase 3 SAKURA 1 complete; SAKURA 2 under way
dexamethasone phosphate (EGP-437, Eyegate Pharma/Valeant)	Iontophoresis of reformulated corticosteroid to ocular surface	Phase 3 anterior uveitis study planned; may test in posterior noninfectious uveitis in future; also in trials for dry eye
fluocinolone acetonide implant (Medidur, Alimera Sciences/pSivida)	Sustained-release corticosteroid implant	Phase 3 for posterior uveitis; approved for DME (as Iluvien)
Systemic Therapy		
tocilizumab (Actemra, Roche)	Subcutaneous or intravenous injection; IL-6 inhibitor	Phase 1/2 STOP-UVEITIS study; approved for rheumatoid arthritis and other systemic indications
adalimumab (Humira, AbbVie)	Subcutaneous injection; TNF-α inhibitor	Phase 3 VISUAL studies in uveitis; FDA-approved for several systemic inflammatory conditions
abatacept (Orencia, Bristol-Meyers Squibb)	Intravenous infusion; T-cell antigen	Phase 2 study ongoing
rituximab (Rituxan, Genentech)	Intravenous infusion of a chimeric monoclonal antibody targeting pan-B-cell marker CD20	Phase 2 study completed for Behçet disease-associated posterior uveitis and retinal vasculitis
sarilumab (SAR153191, Sanofi/Regeneron)	Subcutaneous injection; IL-6 inhibitor	Phase 2 SATURN study; also in trials for rheumatoid arthritis
gevokizumab (Xoma 052, Xoma)	IL-1 inhibitor, recombinant humanized antibody	Phase 3 EYEGUARD studies ongoing

Abbreviations: DME, diabetic macular edema; FDA, US Food and Drug Administration; IL, interleukin; mTOR, mammalian target of rapamycin; TNF-α, tumor necrosis factor-alpha

are associated with prolonged use of systemic corticosteroids. Because of these side effects, it is ideal to be able to reduce the steroids to minimal levels (less than 10 mg per day) over a 3-month period. If the active inflammation cannot be controlled in that time frame, other alternatives should be considered.

Local Corticosteroids

Local corticosteroid options include intravitreal triamcinolone acetonide injectable suspensions (Triesence, Alcon; Trivaris, Allergan), the 0.59-mg sustained-release fluocinolone acetonide intravitreal implant (Retisert, Bausch + Lomb), and the dexamethasone intravitreal implant (Ozurdex, Allergan). These options constitute the only local treatments for noninfectious uveitis of the posterior segment approved by the US Food and Drug Administration.

In prospective clinical trials, the dexamethasone intravitreal implant was significantly better than sham in achieving visual acuity improvement and improvement in disease activity.[1] The side effect profile was favorable in terms of cataract development or glaucoma and was not significantly greater at 26-week follow-up in patients receiving the dexamethasone intravitreal implant than in those receiving sham treatment.

The fluocinolone acetonide intravitreal implant offers a longer-term sustained-release therapy. It was compared to systemic immunosuppression over 24 months in the

MUST trial.[2] Both approaches had similar visual acuity outcomes, but there was a greater decrease in inflammation and vitreous haze in the implant group.[2] Eyes that received the fluocinolone acetonide implant had a greater risk for cataract development and glaucoma requiring therapy, which was consistent with prior literature. The authors concluded that individual patient circumstances may dictate whether systemic immunosuppression or local intravitreal sustained-release corticosteroid should be used. For example, pseudophakic patients without glaucoma, with no known history of steroid-associated ocular hypertension, could be considered for the fluocinolone acetonide implant.

Long-Term Therapy

Many patients with chronic uveitis will need long-term therapy to avoid vision loss over time. Examples of such long-term therapy include antimetabolites (methotrexate, azathioprine, mycophenolate), T-cell inhibitors (tacrolimus, cyclosporine), and alkylating agents (chlorambucil, cyclophosphamide), as well as the biologic response modifiers that have recently become commonly used as immunosuppressive agents for uveitis. Although these are all considered off-label uses of drugs that are approved for use in rheumatology, transplant care, and other fields of medicine, retrospective data support their use in patients with uveitis.[3,4]

EMERGING THERAPIES

Biologics

Established biologic therapies include the tumor necrosis factor-alpha (TNF-α) inhibitors infliximab (Remicade, Janssen) and adalimumab (Humira, AbbVie). Newer agents, including certolizumab (Cimzia, UCB) and golimumab (Simponi, Janssen) have not been studied completely. These medications are manufactured in biologic systems to target specific inflammatory pathways. A panel of uveitis experts recently recommended infliximab and adalimumab as first-line immunomodulatory agents for the treatment of ocular manifestations of Behçet disease and as second-line immunomodulatory agents for the treatment of posterior uveitis.[4]

Ophthalmologists tend to shy away from systemic therapy, but evidence suggests that these agents should be used for uveitis patients. Long-term immunomodulating agents, although not free of side effects, are generally well-tolerated and effective as corticosteroid-sparing therapy about 60% to 70% of the time.[5-7]

However, that still leaves a significant gap in treatment. There is an ongoing need for treatments with better (or more targeted) efficacy and improved side effect profiles. Several new and potentially more targeted treatments have been reported in the research pipeline (Table).

mTOR Inhibition

Sirolimus is a mammalian target of rapamycin (mTOR) inhibitor with antiinflammatory and antiangiogenic effects, making it potentially useful in inflammatory and neovascular uveitis. mTOR plays a critical role in stimulating T-cell proliferation, leading to the release of proinflammatory cytokines. By inhibiting mTOR, sirolimus interrupts a critical pathway that perpetuates the inflammatory process, controlling the disease's progression.

Systemic sirolimus (Rapamune, Pfizer) has been used in organ transplantation and cardiology, so there is good information on safety at much larger doses than would be needed for ocular delivery. The phase 1 and 2 SAVE trials demonstrated that local administration of sirolimus, either intravitreally or subconjunctivally, was safe, tolerable, and effective in reducing vitreous haze and cells, improving visual acuity, and decreasing the need for systemic corticosteroids.[8]

A formulation of sirolimus for intravitreal delivery (DE-109, Santen) is under investigation in the phase 3 SAKURA 1 and SAKURA 2 trials. These trials are evaluating intravitreal injection of three active doses of sirolimus as monotherapy treatment of active noninfectious posterior uveitis. Santen recently reported that SAKURA 1 met its primary endpoint, with vitreous haze reduced to a score of 0 at 5 months, along with other promising outcomes.[9] SAKURA 2 is ongoing.

Alternative Drug Delivery Mechanisms

Clearside Biomedical is developing a method for suprachoroidal delivery of an established therapeutic agent—preservative-free triamcinolone—which could offer potentially less toxicity and less risk of inducing cataract or glaucoma. Early studies in animal models suggest that triamcinolone delivery in the suprachoroidal space supplies high levels of medication to posterior segment tissues (retina, choroid) with lower levels in anterior segment structures.[10,11]

Other drug delivery mechanisms may also limit the number of injections. EyeGate Pharma, for example, is developing an iontophoresis delivery mechanism for anterior uveitis. These and other novel drug delivery mechanisms warrant exploration over the short and medium term.

Interleukin Blockers and Other New Biologics

A number of new and potentially better targeted systemic medications are in various stages of development as well.

Increasing attention has been focused on blocking cytokine mediators of inflammation, specifically interleukins IL-1 and IL-6. Studies have shown efficacy in immune-mediated systemic disorders such as rheumatoid arthritis.[12] Additional studies are needed to determine the level of toxicity in

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ocular treatment, frequency of dosing, and the potential to reach the relevant posterior segment structures.

Rituximab (Rituxan, Genentech) is a monoclonal antibody that targets the CD20 surface marker on B cells. It is used to treat lymphoma but has shown some benefit in scleritis and orbital inflammatory conditions.[13,14] More research in noninfectious uveitis is warranted, but this appears to be a promising agent.

Prospective clinical trials are also under way for treatment of posterior noninfectious uveitis with TNF-α inhibitors already in use for other indications, but these inhibitors have not been compared prospectively against available therapies.

CONCLUSION

An array of new drug delivery mechanisms, as well as new local and systemic agents, may play important roles in the treatment of posterior noninfectious uveitis in the future. Because uveitis is such a heterogeneous disorder, it is unlikely that any single therapy will be a magic bullet that can be used in all cases. Rather, in the coming decade, it will be paramount to learn which agent works best for different types of uveitis, how best to combine therapies, and how to minimize toxicity and side effects for our patients. ■

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