Alternatives for Long-Term Immunomodulation

Long-term therapy with corticosteroids is not appropriate for all patients who require extended, aggressive anti-inflammatory treatment.

BY JOHN J. HUANG, MD

Noninfectious uveitis is a significant cause of morbidity and vision loss worldwide. Chronic and severe disease often requires long-term, aggressive anti-inflammatory therapy. Corticosteroids are currently the most widely used anti-inflammatory medication in ophthalmology and the primary therapy for patients with noninfectious uveitis. They are available as topical drops, regional injections, intravitreal injections, and oral and intravenous infusions. The number of ocular formulations has grown dramatically during the past decade, with additions such as a fluocinolone acetonide intravitreal implant (Retisert; Bausch + Lomb, Rochester, NY), difluprednate emulsion (Durezol; Sirion Therapeutics), intravitreal triamcinolone acetonide (Triesence [Alcon Laboratories, Inc.] and Trivaris [Allergan, Inc.]), and sustained-release biodegradable dexamethasone (Ozurdex; Allergan, Inc.).

Vision loss in chronic uveitis is commonly due to cystoid macular edema, glaucoma, band keratopathy, optic nerve pallor, and cataract formation. Uveitis-associated glaucoma results from a variety of mechanisms, including angle closure due to extensive anterior or posterior synechiae, trabeculitis, damage to the trabecular meshwork, and steroid response. Not all patients treated with corticosteroids will develop an increase in IOP. Steroid response most often occurs in children and patients with primary open-angle glaucoma, a family history of glaucoma, myopia, diabetes mellitus, and a history of connective tissue disease.

Aggressive immunomodulation therapy has become the standard of care for patients with chronic noninfectious uveitis that is recalcitrant and for affected individuals who are intolerant of ocular and systemic corticosteroid therapy, including significant steroid response. Currently, the majority of the immunomodulatory agents (ie, antimetabolites, calcineurin inhibitors, alkylating agents, and biologics) are used off label in the treatment of uveitis. With proper dosing and monitoring of patients, these medications have a long track record of safety and efficacy in the treatment of uveitis and systemic autoimmune disease.

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ANTIMETABOLITES

Methotrexate was discovered in 1963 and used to treat choriocarcinoma in women. This antimetabolite is an irreversible competitive inhibitor of dihydrofolate reductase, an enzyme responsible for the production of tetrahydrofolate. Over the past 2 decades, methotrexate has become one of the most commonly used immunosuppressive agents for systemic autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus. The drug is also popular for the first-line (off-label) treatment of disorders such as juvenile idiopathic arthritis and sarcoidosis-associated uveitis refractory to corticosteroid therapy. Patients taking methotrexate require folic acid replacement.

One of the newer immunosuppressive agents is mycophenolate mofetil, a drug in the antimetabolite class that was approved in 1995 by the FDA for use in solid organ transplant rejection. The drug has been used extensively off label to treat patients with noninfectious autoimmune inflammatory eye diseases (scleritis and uveitis). Due to its safety and efficacy and because it is extremely well tolerated, mycophenolate mofetil is rapidly gaining acceptance for the treatment of noninfectious uveitis.

ALKYLATING AGENTS

Alkylating agents such as cyclophosphamide and chlorambucil are used to treat severe autoimmune inflammatory diseases and systemic vasculitis. Both agents belong to the family of nitrogen mustard. First reported as a treatment for uveitis in the 1950s, cyclophosphamide now plays a major role in the management of several systemic vasculides with ocular involvement such as Wegener's granulomatosis, polyarteritis nodosa, necrotizing scleritis, and ocular cicatricial pemphigoid. Found to be effective in 1970 for the treatment of Adamantiades-Behçet's disease, chlorambucil remains one the most frequently used immunosuppressive agents for this indication. Patients taking alkylating agents require routine laboratory testing to prevent severe pancytopenia.

CALCINEURIN INHIBITORS

Cyclosporine is a calcineurin inhibitor in the pathway responsible for the activation of helper T cells. This fungal metabolite was shown to be useful in suppressing autoimmune uveitis[1] and has been used to treat a wide variety of ocular immune-mediated disorders, including idiopathic anterior uveitis, HLA-B27, sarcoidosis, Behçet's disease, and birdshot retinochoroidopathy.

Voclosporin represents a new generation of calcineurin inhibitor in the class of cyclosporine. Voclosporin has been shown to be highly potent in animal models of autoimmune disease and uveitis, and the agent has a stronger binding affinity for the calcineurin phosphatase and its target molecules than cyclosporine.[2] Voclosporin was recently evaluated in a clinical trial as a treatment of active anterior and posterior uveitis, as well as for the maintenance and control of quiescent uveitis. A twice-daily dose of 0.4 mg/kg proved superior to placebo for reducing active inflammation of the posterior segment at both 16 and 24 weeks. It also effected a 50% reduction in the rate of inflammation and exacerbation by 26 weeks in patients with medically controlled posterior segment disease.[3,4] Voclosporin is awaiting FDA approval for the treatment of noninfectious uveitis.

BIOLOGICS

Biologics may provide safer, more effective, and more rapid options for the treatment of ocular inflammation than traditional therapy. Biologics target specific mediators of the immune-inflammatory system. Their history dates back to the early 1970s with the introduction of intravenous immunoglobulin for the support of patients with hypogammaglobulinemia. The discovery that intravenous immunoglobulin effectively treated other autoimmune and inflammatory diseases came from the unexpected observation of an improvement of associated conditions such as immune thrombocytopenic purpura in patients with hypogammaglobulinemia.

In 1992, Maini presented the first clinical results for a new monoclonal antibody, later known as infliximab, that acted against tumor necrosis factor-alpha (TNFα). Maini treated 20 patients who had rheumatoid arthritis and achieved positive results. Pain symptoms decreased by 73%, the number of swollen joints fell by 72%, and the median duration of patients' morning stiffness dropped from 3 hours to 5 minutes.[5] The FDA approved the drug in August 1998 for the treatment of Crohn's disease, and the agent is also currently used for the treatment of rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, and ankylosing spondylitis. Infliximab has shown impressive efficacy as therapy for severe uveitis associated with disorders such as ankylosing spondylitis, sarcoidosis, Behçet's disease, Vogt-Koyanagi-Harada, and juvenile idiopathic arthritis.

Rituximab binds to the CD20 receptor on B cells. Upon receiving FDA approval in 1997 for the treatment of lymphoma that was refractory to other chemotherapy regimens, rituximab became the first anticancer monoclonal antibody. It is now standard therapy in the initial treatment of aggressive lymphomas (eg, diffuse large B-cell lymphoma) in combination with conventional chemotherapy. Rituximab has been used to treat Wegener's granulomatosis and associated uveitis, and it is being evaluated for the treatment of orbital inflammatory disease.

CONCLUSION

For decades, corticosteroids have been first-line agents for the treatment of inflammatory disease, both in ophthalmology and in other medical specialties. Chronic systemic corticosteroid therapy, however, can lead to a wide range of systemic and ocular complications, including diabetes mellitus, hypertension, Cushing's syndrome, aseptic hip necrosis, glaucoma, and cataract formation.

The goal of all uveitis treatment is to provide long-term control of inflammation while minimizing side effects.

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More than a third of all patients on long-term corticosteroid therapy will develop a steroid response in addition to systemic side effects. Overall, immunomodulatory agents have been safely used on an off-label basis for the treatment of severe, sight-threatening, corticosteroid-resistant noninfectious uveitis and of uveitic patients who cannot tolerate corticosteroid therapy. The efficacy of immunomodulatory agents for noninfectious uveitis has been demonstrated in numerous case series.[6-10] The dosing as well as the frequency and duration of treatment, however, have yet to be determined by large clinical studies. Despite these limitations, immunomodulatory agents play a crucial role in the treatment of ocular inflammatory diseases. ❑

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treatment may be necessary. Based on the limited data available, at least some SLT-treated eyes will avoid incisional surgery. Given that there are no significant downsides to SLT, the potential benefit more than justifies the small risk. ❑

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