

SYSTEMIC OPTIONS FOR TREATING UVEITIS



Biologics is the name of the game. Here's a peek at what's been approved and what may be soon to come.

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The term noninfectious uveitis encompasses a large, heterogeneous group of diseases characterized by immune-mediated inflammation of intraocular structures.¹ These conditions often present not only a diagnostic dilemma for clinicians, but a therapeutic dilemma as well. According to a large population-based study in Northern California, the rate of uveitis is increasing and is estimated to be three times higher now than in previously published reports.²

Untreated or refractory uveitis can lead to ocular sequelae that can cause permanent vision loss without appropriate or effective treatment. Initial treatment typically takes the form of topical, periocular, or systemic corticosteroids; however, these medications carry ocular and systemic adverse effects, which limits their long-term usefulness.³ This article reviews nonsteroidal alternatives that are approved for use in patients with uveitis or are being studied for this indication.

STEROID-SPARING THERAPIES

Standard immunosuppressive drugs hold an important place in the therapeutic armamentarium and play a key role in avoiding the overuse of corticosteroids.⁴ Common and well-tested steroid-sparing immunosuppressive therapies include antimetabolites

such as methotrexate, azathioprine, and mycophenolate mofetil.⁴ Another class of immunosuppressive agents, T-cell inhibitors, includes cyclosporine, tacrolimus, voclosporin, and sirolimus.⁴ More powerful agents, reserved for selected cases unresponsive to the aforementioned therapies, include alkylating agents such as cyclophosphamide and chlorambucil.⁴

A BOOM IN BIOLOGICS

Recently, biologics that directly target specific inflammatory pathways have become popular therapeutic options for patients with uveitis. The biologics most commonly used to treat uveitis and systemic inflammatory diseases are those that target the

inflammatory effects of tumor necrosis factor alpha (TNF-alpha), an integral cytokine in the uveitic pathway. Several such drugs, as well as some other promising agents, are profiled below.

Adalimumab

Multiple trials, most recently the VISUAL clinical trials,^{1,5,6} have documented success with adalimumab (Humira, AbbVie), a recombinant human monoclonal antibody anti-TNF-alpha agent, in the treatment of uveitis. These trials enrolled patients with noninfectious intermediate, posterior, and panuveitis. VISUAL I, a double-masked, multicenter, randomized, placebo-controlled clinical trial, compared adalimumab in 110 patients and

AT A GLANCE

- ▶ Standard immunosuppressive drugs hold an important place in the therapeutic armamentarium for patients with uveitis; they play a key role in avoiding overuse of corticosteroids.
- ▶ Biologic agents that directly target specific inflammatory pathways have become popular therapeutic options for patients with uveitis.
- ▶ Recently approved therapies and others in development represent promising options for controlling uveitic flares and reducing patients' long-term dependence on corticosteroids.

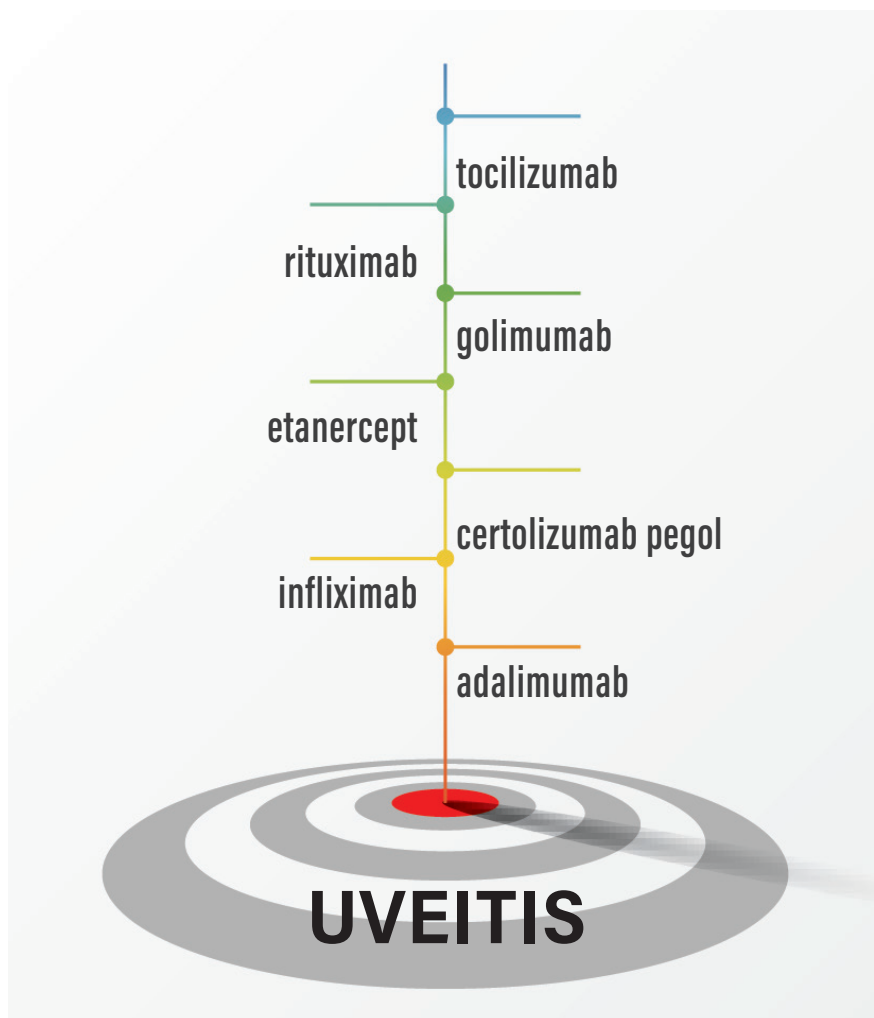
placebo in 107 patients for the control of active uveitis previously uncontrolled on 10 mg to 60 mg of daily prednisone therapy. Enrolled patients received 60 mg prednisone daily and were tapered off the steroid over the next 15 weeks, with a primary endpoint of time to treatment failure. The adalimumab group had significantly lower rates of treatment failure (HR, 0.5; 95% CI, 0.36 to 0.70, $P < .001$), and median time to failure was 24 weeks in the adalimumab group compared with 13 weeks in the placebo group.¹

VISUAL II was designed similarly, and it assessed adalimumab in patients with quiescent disease who were corticosteroid-dependent at doses of 10 mg to 35 mg daily, with prednisone tapering commencing after week 2 and completed by week 19. Rates of treatment failure were higher in the placebo group (55%), and time to treatment failure was significantly better in the adalimumab group (39%).⁵

VISUAL III was an open-label extension study including patients who completed VISUAL I and II. All patients received adalimumab, and providers were allowed to adjust prednisone and other medications more freely. Of the 242 patients who had active uveitis at study enrollment, 60% were quiescent at 78 weeks, and, of them, 66% were corticosteroid free.⁶

Another randomized clinical trial, SYCAMORE, evaluated adalimumab plus methotrexate versus placebo plus methotrexate in patients with juvenile idiopathic arthritis–associated uveitis.^{7,8} There was a 75% reduction in treatment failures in the adalimumab group compared with the group receiving placebo. Additionally, a significantly higher proportion of patients in the adalimumab group were able to reduce or eliminate topical glucocorticoids.⁸

To date, adalimumab is the only biologic agent to receive US FDA approval for treatment of uveitis. It is indicated for treatment of noninfectious intermediate, posterior, and panuveitis.



Infliximab

Infliximab (Remicade, Janssen Biotech), a chimeric antibody directed against TNF-alpha, has also shown positive results in the control of recalcitrant noninfectious uveitis. In a cohort of 88 patients, 72 (81.8%) achieved clinical remission while taking intravenous infliximab; however, only five patients could be tapered off the drug after an extended treatment course.⁹

Etanercept

Etanercept (Enbrel, Amgen), a soluble fusion protein binding all isoforms of the TNF receptor, has not shown as much success in controlling uveitis

flares, especially when compared with adalimumab and infliximab.¹⁰

Certolizumab

Certolizumab pegol (Cimzia, Union Chimique Belge) is a less well studied anti-TNF-alpha agent. Certolizumab is a pegylated recombinant fragment of a monoclonal antibody that selectively binds to TNF-alpha. In a case series of 14 eyes, most achieved quiescence after failure of other anti-TNF-alpha agents.¹¹ Another case series of 24 eyes showed similar control rates in patients with uveitis related to spondyloarthritis who had previously not responded to anti-TNF-alpha medications.¹²

Golimumab

Another agent with limited published efficacy data is golimumab (Simponi, Janssen Biotech), a human monoclonal antibody that also impedes the effects of TNF- α . In a cohort of 17 patients with Beçhet disease, 16 patients had control of Beçhet manifestations while receiving golimumab. The best control, however, was seen in patients receiving disease-modifying agents in addition to golimumab therapy, as opposed to golimumab monotherapy.¹³

Rituximab

Rituximab (Rituxan, Genentech) is a monoclonal antibody that targets CD20, a protein expressed on the surface of B-lymphocytes. It has shown impressive safety and efficacy in refractory noninfectious scleritis or orbital inflammation.^{14,15} In a group of 12 patients with scleritis unresponsive to corticosteroids and immunosuppressive therapy, 75% responded to rituximab.¹⁴ Similar rates of control were achieved in patients with orbital inflammation.¹⁵

Tocilizumab

Interleukin (IL) blockers are a relatively recently introduced class of drug used to treat uveitis. Tocilizumab (Actemra, Genentech), a humanized monoclonal antibody, is an IL-6 receptor blocker. Limited studies have shown improvement in patients with unmanageable noninfectious uveitis.¹⁶ This drug has also shown an ability to reduce or eliminate refractory macular edema.¹⁷ After withdrawal of the agent, however, edema may recur.¹⁷

Other Systemic Options

Abatacept (Orencia, Bristol-Myers Squibb) is a soluble protein that downregulates T-cell responses to antigens by binding to CD80 and CD86, both of which are integral to T-cell activation.¹⁸ Results with this agent have been mixed, but, in one study analyzing 21 patients with uveitis refractory to corticosteroids, immunosuppressives, and at least one TNF- α inhibitor, inactivity occurred in 11 patients. Uveitis recurred in eight of these patients.¹⁸

Secukinumab (Cosentyx, Novartis), an anti-interleukin-17A monoclonal antibody, has failed to demonstrate the ability to control uveitis in multiple published studies when compared with placebo.¹⁹ Similarly, gevokizumab (Xoma), a recombinant humanized monoclonal antibody that binds IL-1 β , showed initial promise but was withdrawn from further study after it failed to control ocular inflammatory episodes in a trial in patients with Beçhet disease.²⁰

IN THE WORKS

Studies currently under way include a phase 2, randomized, placebo-controlled trial to evaluate the JAK-1 inhibitor filgotinib (Gilead Sciences) in active

noninfectious intermediate, posterior, or panuveitis. Ustekinumab, a human IL-12 and IL-23 antagonist, is being investigated in a trial for noninfectious uveitis at the National Institutes of Health.

Taken together, the therapies described above constitute a robust present and promising future armamentarium of options to control uveitic flares and reduce patients' long-term dependence on corticosteroids. ■

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