

A Review of Biologics for Uveitis

Treatment of uveitis with these agents is increasingly promising.

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Biologics are bioengineered molecules produced in living systems. They are used therapeutically to target cellular receptors or cytokines responsible for inflammation in many pathologic conditions. Biologics are increasingly being used to treat uveitis that is unresponsive to more conventional forms of immunosuppression. There is limited evidence for the use of some biologics in ophthalmology, but familiarity with commonly used biologics, especially the anti-tumor necrosis factor (TNF) agents,¹ can be of great utility to retina specialists managing chronic noninfectious uveitis refractory to steroids and first-line steroid-sparing agents.² Retina specialists can greatly improve patient outcomes by working with rheumatologists or uveitis specialists when using these agents.

This article reviews some frequently used biologics (and some of those in the pipeline), including approved and potential uses, contraindications, and side effects.

AVAILABLE BIOLOGICS

Infliximab

Infliximab (Remicade, Janssen) is a monoclonal mouse/human chimeric immunoglobulin G (IgG) antibody directed against TNF- α that is approved by the US Food and Drug Administration (FDA) for treatment of a variety of conditions, including rheumatoid arthritis, juvenile idiopathic arthritis (JIA), Crohn disease, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and ulcerative colitis. It is given intravenously. Infliximab is approved for the treatment of many rheumatic illnesses in a wide range of doses, which may allow flexibility in its dosing. This could be beneficial because treatment with infliximab for uveitis alone can be challenging. Administration typically begins at 3 mg/kg/day to 5 mg/kg/day at weeks 0, 2, and 6, and then every 8 weeks. If necessary, the dose and frequency can be increased to 10 mg/kg every 4 weeks.

An expert panel has recommended FDA approval of infliximab as first-line treatment for ocular Behçet

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disease,¹ and in Japan the medication is approved for this purpose.³ Investigators have documented success using infliximab in the management of JIA-related uveitis,⁴⁻⁹ especially at high doses (10-20 mg/kg/dose).¹⁰ A large retrospective series¹¹ suggested that clinical remission can be achieved in 81.8% of patients with recalcitrant uveitis, with a discontinuation rate of 19.3% due to adverse events including skin rash, fatigue, chronic infections, and drug-induced lupus.

Because infliximab is a chimeric antibody, prolonged treatment with this biologic can lead to new autoantibody formation,¹² especially antinuclear antibody and anti-DNA antibody. To reduce the risk of autoantibody formation,

At a Glance

- Biologics are often used to treat uveitis that does not respond to conventional forms of immunosuppression.
- Side effects associated with interferon treatment include flu-like illness, leukocytopenia, anemia, and increased liver enzymes.
- The use of different uveitis grading systems, inclusion criteria, and outcome measures in studies of biologic agents limits cross-study comparisons.

patients receiving infliximab may be given combination therapy with methotrexate or a similar agent.

Patients beginning therapy with anti-TNF agents should be screened for tuberculosis infection, hepatitis B, hepatitis C, and HIV. Underlying malignancy and immune compromise are contraindications, and patients should be up to date on vaccines before beginning therapy. There may also be an increased risk of demyelinating disease, including multiple sclerosis. Infliximab, adalimumab (Humira, AbbVie), and etanercept (Enbrel, Amgen) are considered category B in the FDA's categorization of risk for drug use in pregnancy, so they may be preferred to agents such as methotrexate (which is category X, the highest risk) in women of childbearing age.

Adalimumab

Adalimumab was the first human monoclonal antibody approved by the FDA. It reduces inflammation by binding and neutralizing TNF- α . Relative to infliximab, adalimumab is less immunogenic, and it can be administered subcutaneously via preloaded syringes rather than intravenously. It is generally given 40 mg/0.8 mL every 2 weeks, but this can be increased to 40 mg/0.8 mL weekly, if needed.

Adalimumab has been used to treat refractory uveitis in patients with various conditions, including JIA, sympathetic ophthalmia, and Vogt-Koyanagi-Harada syndrome. In a series of 77 patients with ankylosing spondylitis, adalimumab was shown to decrease the frequency of uveitis attacks by 72%.¹³ Several series suggest that adalimumab may be of greater benefit to uveitis patients than infliximab,^{9,10} and prospective studies are under way to compare adalimumab with methotrexate in patients with JIA-associated uveitis.¹⁴

Etanercept

Etanercept is a humanized recombinant fusion protein that is part TNF- α receptor and part Fc tail domain of human immunoglobulin G that prevents TNF from binding to cell surface receptors. Evidence suggests that etanercept has lower efficacy in the treatment of some forms of uveitis than either infliximab or adalimumab.^{15,16} Moreover, etanercept showed no significant efficacy compared with placebo in preventing uveitis relapse in patients being tapered from methotrexate. Expert panels have concluded that, although etanercept may be beneficial in the treatment of some forms of ocular inflammatory disease, it has been associated with development of uveitis in JIA patients and of sarcoid-like disease in others. Patients taking etanercept for other indications with existing incompletely

“Patients beginning therapy with anti-TNF agents should be screened for tuberculosis infection, hepatitis B, hepatitis C, and HIV.”

controlled uveitis or new ocular inflammatory disease should be counseled to consider switching to infliximab or adalimumab if possible.

Rituximab

Rituximab (Rituxan, Genentech/Biogen; Mabthera, Roche) is a chimeric monoclonal antibody specific for protein CD20, which is present only on mature B cells. When rituximab binds to B lymphocytes, it leads to apoptosis and a reduction in B cells lasting up to 9 months. Rituximab has been used to treat JIA-associated uveitis,¹⁷⁻¹⁹ granulomatosis with polyangiitis with ocular and orbital involvement,^{20,21} anterior scleritis,²² and primary intraocular lymphoma.²³ Notably, in one series of patients with intraocular lymphoma, regular intravitreal treatment with methotrexate and rituximab was associated with reduction in interleukin (IL)-10 levels over time. Rituximab is associated with infusion reactions and infectious complications, such as pneumonia and opportunistic infections, as well as progressive multifocal leukoencephalopathy.

Interferon

The interferons (IFNs) are a group of signaling proteins that activate immune cells and increase expression of major histocompatibility complex antigens to eradicate pathogens and regulate immune function. They are most frequently prescribed for central nervous system autoimmune diseases, such as multiple sclerosis. Most of what we know about the use of IFNs for uveitis comes from case series of patients with refractory Behçet disease. In one such series, all patients given IFN- α 2a showed a positive response²⁴; 50% showed a complete response without additional major ocular inflammation during the follow-up period, with improvements in Behçet symptoms, relapse rate, and steroid-sparing effect. Other studies have reported similar success.²⁵

IFN treatment carries the risks of flu-like illness, leukocytopenia, thrombocytopenia, anemia, increased liver enzymes, increase in triglycerides, and allergic reactions. Interestingly, IFN- α 2a has also been associated with the development of anti-IFN- α -binding antibodies, the clinical relevance of which is unclear.

BIOLOGICS IN THE PIPELINE

Improvements in the understanding of patterns of cytokine expression and disease-specific pathogenesis have led to the development of new biologic targets, including ILs. For example, anakinra (Kineret, Swedish Orphan Biovitrum AB) is an antagonist of the IL-1 receptor for which efficacy has been reported in selected cases.²⁶ Tocilizumab (Actemra, Genentech), an antagonist of the IL-6 receptor, showed some promise in a series of eight patients with noninfectious posterior uveitis²⁷ and is being investigated in the prospective STOP-UVEITIS multicenter clinical trial. Daclizumab (Zenapax, Roche) is a monoclonal antibody directed against the IL-2 receptor that has been given for uveitis without statistically significant benefit in measures including anterior chamber cell, vitreous cell, and vitreous haze.²⁸ Gevokizumab (Xoma Corp.) is a monoclonal antibody with allosteric modulating properties that binds strongly to IL-1 β . It has been granted orphan drug designation by the FDA for the treatment of resistant forms of uveitis^{4,29} and is under investigation in three phase 3 EYEGUARD studies.³⁰

CONCLUSION

Although many studies have documented the utility of biologics in the management of noninfectious uveitis, especially in patients with Behçet disease, there are few studies to guide the recommendation of one biologic over another in this setting. This is because the use of different uveitis grading systems, inclusion criteria, and outcome measures limits cross-study comparisons. Adalimumab and infliximab are the best-studied anti-TNF agents and are first-line treatment options for ocular Behçet disease and second-line treatment for other forms of uveitis.¹ Other biotherapies for uveitis are in development and are being explored in clinical trials. ■

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