

Biologic Therapy for Posterior Uveitis and Panuveitis

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B iologic response modifiers (often referred to as *biologics*) are proteins produced by recombinant DNA or monoclonal antibody technology designed to block specific mediators of the cell-mediated immune response. They are mostly either recombinant antibodies or antibody-derived proteins. Monoclonal antibodies (mAb), when used as medications, are given a generic name ending in “-mab.” An antecedent “u” (-umab) indicates a human antibody (eg, adalimumab), whereas “xi” (-ximab) indicates a mixed human-murine (chimeric) antibody (eg, infliximab). Fusion proteins containing receptor domains are given a generic name ending in “-cept” (eg, etanercept). In general, fully humanized antibodies are less likely than chimeric antibodies to cause hypersensitivity reactions or to elicit neutralizing antibody formation.

Systemically administered biologics are approved by the US Food and Drug Administration for several immune-mediated diseases, including rheumatoid arthritis, inflammatory bowel disease, and juvenile idiopathic arthritis (JIA). Biologics have also been used off-label for ocular inflammatory diseases, including uveitis. The most commonly used systemic biologics for ocular conditions to date are tumor necrosis factor-alpha (TNF- α) inhibitors, including infliximab (Remicade; Centocor Ortho Biotech, Inc.) and adalimumab (Humira; Abbott Laboratories), and the interleukin-2 (IL-2) antagonist daclizumab (Zenapax; Roche). In a randomized controlled trial, the anti-TNF fusion protein etanercept (Enbrel; Amgen, Inc., and Pfizer, Inc.) was no more effective than placebo at controlling anterior uveitis in patients with JIA.¹ Infliximab and adalimumab are generally believed to be more effective than etanercept for treating ocular inflammatory disorders.^{2,3} However, no head-to-head studies comparing the various TNF- α inhibitors have been performed.

WHEN TO USE BIOLOGICS IN UVEITIS

Corticosteroids are still the mainstay of treatment for most patients with uveitis.⁴ In a minority of cases, corticosteroid-sparing immunosuppressive drugs (eg, methotrexate, mycophenolate mofetil, azathioprine, cyclosporine, tacrolimus, and cyclophosphamide) and biologics (Table 1) may be required to control inflammation in recalcitrant or chronic diseases. Due to their costs and long-term safety profiles, biologics are not routinely recommended as first-line therapy in most patients. We generally follow a stepladder approach of treatment, beginning with corticosteroid therapy (topical, local and/or systemic), and followed by immunosuppressive agents and then biologics.⁵ Biologics are generally reserved for cases where more conventional immunosuppression has either failed or been poorly tolerated due to adverse effects. Situational exceptions for the early use of biologics may be made for Behçet disease (BD)-related uveitis, in which a number of clinical studies have shown that infliximab may be rapidly effective for controlling vision-threatening disease.

WHEN NOT TO USE BIOLOGICS IN UVEITIS

Systemic biologics, including TNF- α inhibitors and daclizumab, are potent immunosuppressives, and, like other immunosuppressives, they are not recommended for the treatment of infectious uveitis. Class effects of TNF- α blockers prominently include risk of serious infection, most significantly including reactivation of tuberculosis and fungal infections, and increased risk of malignancy. Both of these side effects appeared to be dose-related. Other uncommon but potentially severe side effects include initiation or worsening of demyelinating disease, congestive heart failure, thromboembolic events, and lupus-like reactions. Less serious side effects include hypersensitivity reac-

tions, headache, flu-like symptoms, and gastrointestinal adverse effects.^{6,7}

BIOLOGICS FOR UVEITIS ASSOCIATED WITH POSTERIOR SEGMENT DISEASE

This review focuses on biologic therapy for uveitis associated with posterior segment pathology. The most commonly reported clinical studies of the use of systemic biologics to date are for BD, and these include randomized clinical trials, retrospective case series, and reports. Results regarding the use of biologics for other forms of uveitis have come primarily from retrospective case reports and series.

BEHÇET DISEASE

BD may cause chronic, relapsing occlusive vasculitis and uveitis as well as dermatologic, rheumatologic, gastrointestinal, and neurologic manifestations. Infliximab has been reported to be a rapid and very effective therapy for the treatment of BD-related panuveitis,⁸⁻¹¹ posterior uveitis, and retinal vasculitis.^{12,13} Associated neovascularization of the optic disc may regress after infliximab therapy.¹⁴

Sfikakis and colleagues reported that in a prospective study of 25 patients with BD-related uveitis, the majority of patients (> 90%) experienced resolution of vitritis, retinitis, retinal vasculitis, and cystoid macular edema (CME) within 28 days after initiation of infliximab therapy and often as early as within 1 week of initial treatment.¹² However, in some patients with initial response, infliximab may become less effective in controlling uveitis attacks after 1 year of therapy.¹⁵

A recent retrospective study of 11 patients with BD-related uveitis showed that adalimumab led to complete resolution of inflammation in 10 (91%) of 11 patients and an improvement in visual acuity of more than 3 lines in 17 (81%) of 21 eyes with an average follow-up of 10.8 months.¹⁶ Adalimumab may also be effective in patients who are intolerant of or refractory to previous infliximab therapy.^{16,17} Patients with quiescent uveitis after infliximab infusions may successfully switch to adalimumab injections to maintain disease remission and prevent relapses.¹⁸

Although the TNF- α inhibitors infliximab and adalimumab may provide excellent therapeutic outcomes in BD-related uveitis, an interleukin-2 (IL-2) antagonist, daclizumab, failed to improve visual outcomes in BD-related uveitis compared with standard immunosuppressive therapy.¹⁹ In a prospective, randomized study, 9 patients received daclizumab and 8 patients received intravenous placebo, with a median follow-up of 15 months. The patients treated with daclizumab

had a greater median ocular attack rate (1.27 attacks/year) than those receiving placebo (0.27 attacks/year). Furthermore, the placebo group experienced a greater reduction in immunosuppressive agents.¹⁹

SARCOIDOSIS

Sarcoidosis is a multisystem granulomatous disorder with systemic and ocular manifestations. Uveitis is the most common ocular involvement, ranging from mild iridocyclitis to severe panuveitis. Corticosteroids are the mainstay of therapy. Immunomodulators are useful in refractory cases. The TNF- α inhibitors may also be effective in treating sarcoidosis-related systemic diseases and uveitis.^{20,21} However, in patients receiving TNF- α inhibitors for treatment of other immune-mediated diseases, multiple case reports and series suggest that TNF- α inhibitors (infliximab,²²⁻²⁶ etanercept,^{22,25} and adalimumab²⁵⁻²⁷) may cause sarcoidosis-like disease with pulmonary,^{23,24,28} renal,²³ ocular,²² and cutaneous²⁶ involvement. Etiology remains unclear, but drug-induced sarcoidosis is likely a class effect of TNF- α inhibitors.²⁹ Therefore, we recommend caution when considering use of a TNF- α inhibitor in patients with sarcoidosis-related ocular diseases.

SYMPATHETIC OPHTHALMIA

Sympathetic ophthalmia (SO) is a chronic, bilateral, granulomatous panuveitis with frequent exacerbations. Initial treatment with systemic corticosteroids as well as prompt and aggressive immunomodulation is strongly recommended to control inflammation and prevent ocular morbidity. Due to chronicity of the disease, long-term immunosuppression is almost always indicated, often with multiple immunosuppressive agents, including alkylating agents in severe cases.⁵

Despite aggressive corticosteroid-sparing therapy, adequate control of inflammation may not be achieved. Gupta et al recently reported a case of a 7-year-old patient with SO following severe ocular trauma complicated by retained intraocular foreign body and endophthalmitis in one eye.³⁰ SO developed at 6 weeks after the injury. All attempts to taper prednisone to 7.5 mg/day or less failed despite concurrent use of cyclosporine, mycophenolate mofetil, and intravenous daclizumab (2 mg/kg every 2 weeks). Daclizumab was replaced by infliximab (10 mg/kg every 4 weeks), and the uveitis was well-controlled with subsequent discontinuation of cyclosporine, prednisone, and mycophenolate at 13, 17, and 24 months after initiation of infliximab, respectively. No published data on the use of other biologics for SO are currently available.

TABLE 1. CHARACTERISTICS, DOSAGE, ROUTES OF ADMINISTRATION, AND SIDE EFFECTS FOR SELECTED BIOLOGIC AGENTS.

Generic Names (Trade Names)	Specific Targets	Dosages	Routes	Approved Systemic Indications	Selected Side Effects
1. Tumor necrosis factor (TNF)-α inhibitors					
Infliximab (Remicade)	TNF- α	3 to 5 mg/kg loading at week 0, 2, and 6, then maintenance 3 to 10 mg/kg every 4 to 8 weeks; maximal dose: 20 mg/kg in children	IV	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease (adult and pediatric), ulcerative colitis, plaque psoriasis	Susceptibility to infections, including reactivation of tuberculosis, histoplasmosis and hepatitis B; demyelinating disease; lupus-like syndrome; malignancy; thromboembolic events; hypersensitivity reactions; heart failure; sarcoidosis
Adalimumab (Humira)	TNF- α	40 mg every 1 to 2 weeks (if body weight <30 kg, 20 mg every 2 weeks); loading doses of 80 to 160 mg recommended for Crohn's disease and plaque psoriasis	SQ	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, JIA	
Etanercept (Enbrel)	TNF- α , β	Adults: 25 mg twice a week or 50 mg once a week; children: 0.8 mg/kg per week (max 50 mg per week)	SQ	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis, and JIA	
Certolizumab (Cimzia)	TNF- α	400 mg at week 0, 2, and 4, then every 4 weeks	SQ	Rheumatoid arthritis, Crohn's disease	
Golimumab (Simponi)	TNF- α	50 mg monthly	SQ	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis	
2. Lymphocyte inhibitors					
Daclizumab (Zenapax)	T cells (IL-2)	1 to 2 mg/kg every 2 or 4 weeks	IV, SQ	Organ transplant	Hypersensitivity reactions; headache; gastrointestinal upset
Rituximab (Rituxan)	B cells (CD20)	500 or 1000 mg at week 0 and 2	IV	Rheumatoid arthritis, Wegener's granulomatosis, microscopic polyangiitis, chronic lymphocytic leukemia, non-Hodgkin's lymphoma	Infusion reactions; severe mucocutaneous reactions; hypertension; nausea; progressive multifocal leukoencephalopathy
Basiliximab (Simulect)	T cells (IL-2R α ; CD25)	40 mg at week 0, 2, 4, 8 and 12	IV	Organ transplant	Gastrointestinal side effects; urinary tract infection; headache
Abatacept (Orencia)	T cells (CTLA-4)	500 or 1000 mg at week 0, 2, 4 then every 4 weeks (children: 10 mg/kg, max 1000 mg)	IV	Rheumatoid arthritis, JIA	Serious infections; allergic reactions; malignancy; respiratory problems in patients with chronic obstructive pulmonary disease
3. Cytokine receptor antagonists					
Anakinra (Kineret)	IL-1 receptor	100 mg daily	SQ	Rheumatoid arthritis	Injection-site reaction; infections, especially if concurrently used with TNF-inhibitors
Alefacept (Amevive)	CD2-receptor	15 mg IM weekly or 7.5 mg IV weekly for 12 weeks	IM, IV	Plaque psoriasis	Hypersensitivity reactions; malignancy; infections

VOGT-KOYANAGI-HARADA DISEASE

Vogt-Koyanagi-Harada (VKH) disease is a chronic, bilateral granulomatous panuveitis with accompanying neurologic, integumentary, and auditory involvement. Many patients with VKH disease require immunosuppressive therapy due to the chronic, recurrent nature of the condition. In two case series, infliximab was successfully used to control ocular inflammation in adults with VKH disease who either did not respond to or were intolerant of azathioprine and cyclosporine therapy.^{31,32} With limited follow-up data in the other patients, uveitis remained quiescent at 24 months after discontinuation of all medications in one patient who previously received 14 infliximab infusions.³¹ In 2 children with VKH disease who were treated with prednisone, methotrexate and infliximab, complete resolution of the exudative retinal detachments was observed at 3 weeks following treatment in 1 patient, while subretinal fluid remained at 2 months in another patient.³³ Subcutaneous injections of adalimumab (40 mg every 2 weeks) were also successfully used to treat one patient who inadequately responded to prednisone and cyclosporine. Adalimumab led to discontinuation of both prednisone and cyclosporine while maintaining quiescence of uveitis over 8 months of follow-up.³⁴

BIRDSHOT CHORIORETINOPATHY

Birdshot chorioretinopathy (BSCR) is a chronic, bilateral posterior uveitis strongly related to HLA-type A29. Typical presentations include nyctalopia, floaters, and CME. Corticosteroid-sparing immunomodulators including mycophenolate mofetil, azathioprine, methotrexate, and cyclosporine may be used. Sobrin et al retrospectively reported the use of intravenous daclizumab (1 mg/kg every 2 weeks) in 8 patients who had refractory BSCR or who were intolerant to previous immunosuppressive therapy. Daclizumab was shown to stabilize or improve vision with complete resolution of vitreous inflammation in 7 patients (88%), including complete resolution of vasculitis confirmed by fluorescein angiography in 6 patients (75%). Four patients (50%) remained quiescent with daclizumab monotherapy.³⁵ A prospective trial reported improvement of visual acuity with control of inflammation following infliximab therapy for BSCR in 2 (50%) of 4 patients.¹¹

SERPIGINOUS CHOROIDOPATHY

Serpiginous choroidopathy (SC) is a chronic, progressive choroidopathy presenting with helicoid choroidal lesions, which may cause vision loss either by direct retinal involvement or due to secondary choroidal neovascularization (CNV). Corticosteroid therapy alone is

We reserve biologics for patients for whom the potential benefits justify the risk and cost of these potent agents.

usually ineffective. Triple therapy (prednisone, cyclosporine, and azathioprine) has been reported to induce remission, as has the use of alkylating agents. In 2 refractory cases, successful control of ocular inflammation with infliximab has been reported;^{36,37} however, 1 patient died due to disseminated tuberculosis despite previously negative purified protein-derivative (PPD) skin test.³⁷ Mackensen et al reported a high likelihood (52%) of obtaining a positive QuantiFERon test in 21 serpiginous-like choroiditis patients, suggesting that tuberculosis may play an important etiologic role in some patients with SC.³⁸ Therefore, TNF- α inhibitors should be used with caution in these patients.

SUBRETINAL FIBROSIS AND UVEITIS

Subretinal fibrosis and uveitis (SFU) is an uncommon, asymmetric panuveitis that generally affects healthy, myopic women aged 14 to 34 years. Despite aggressive immunosuppressive therapy, long-term visual prognosis is usually poor. One case report showed that infliximab effectively improved vision and controlled inflammation in a patient with diffuse subretinal fibrosis refractory to prednisone, cyclosporine, and azathioprine therapy.³⁹

REFRACTORY UVEITIC CME

CME is the most common cause of vision loss in patients with uveitis. In a prospective interventional case series of 10 patients (14 eyes) with refractory uveitic CME and otherwise quiescent inflammation, Markomichelakis et al reported that a single dose of intravenous infliximab (5 mg/kg) significantly reduced macular thickness, as measured by optical coherence tomography (OCT), over 2 months and significantly improved vision over 6 months.⁴⁰ Subcutaneous injections of interferon alfa-2a were reported to improve uveitic CME in 21 (88%) of 24 refractory cases.⁴¹ One case report showed that 37 weekly injections of the anti-CD11a antibody efalizumab effectively treated refractory uveitic CME, and the effect was sustained for 6 months after discontinuation of therapy.⁴² Efalizumab, however, was withdrawn from the market due to potential risk of developing progres-

sive multifocal leukoencephalopathy.⁴³

Intravitreal ranibizumab (0.5 mg)⁴⁴ and intravitreal bevacizumab (1.25 mg⁴⁵ and 2.5 mg⁴⁶) have been reported as possible effective treatment options for refractory uveitic CME without active ocular inflammation. However, the effect has been limited to 6 to 8 weeks, and reinjections are often required.^{47,48} Small series utilizing intravitreal TNF- α blockers have been published, with mixed results.^{49,50} Due to lack of a strong efficacy signal and questions of toxicity encountered in studies with noninflammatory diseases, a call for a moratorium on the use of intravitreal TNF- α blockers outside well-designed clinical trials has been suggested.⁵¹

UVEITIS-RELATED CNV

CNV can occur as a complication of various ocular inflammatory diseases, such as multifocal choroiditis and panuveitis (MCP), punctate inner choroidopathy (PIC), presumed ocular histoplasmosis, VKH disease, and SC. Intravitreal bevacizumab is currently the most promising treatment option for patients with or without active inflammation. Mansour et al demonstrated that intravitreal bevacizumab injections (1.25 mg or 2.5 mg) may lead to long-term (at 24 months) visual improvement of 2.2 lines or more and reduction in macular thickness measurements in patients with inflammatory ocular neovascularization.⁵² Smaller case series reported similar promising results but with shorter follow-up.⁵³⁻⁵⁶ Ranibizumab may also be effective in some patients.⁵⁷ It is important to keep in mind, however, that anti-VEGF agents are not effective for the treatment of active inflammation. The addition of a systemic immunosuppressive agent, such as methotrexate or azathioprine, can help prevent recurrences in some patients.

SUMMARY

Biologics are potent new medications that may benefit some, but not all, patients with refractory noninfectious posterior uveitis. Increasing evidence suggests that infliximab and adalimumab may be particularly effective in BD-related uveitis and retinal vasculitis. Among the TNF- α blockers, etanercept may not be as effective for eye diseases as infliximab and adalimumab. Several lines of evidence suggest that TNF- α inhibitors may cause sarcoidosis. Daclizumab may be effective in some forms of posterior uveitis, excluding BD-related uveitis. Side effects of biologics are common and can be serious, and cost is also a limiting issue. We therefore reserve biologics for patients for whom the potential benefits justify both the risk and cost of these potent agents—typically those who are either intolerant of or not responsive to more conventional immunosuppressive therapies. ■

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Dr. Suhler reports research grant support from Abbott, Celgene, Genentech, LuxBio, and Novartis in the past year and prior research support from Centocor. He can be reached at suhlere@ohsu.edu.

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