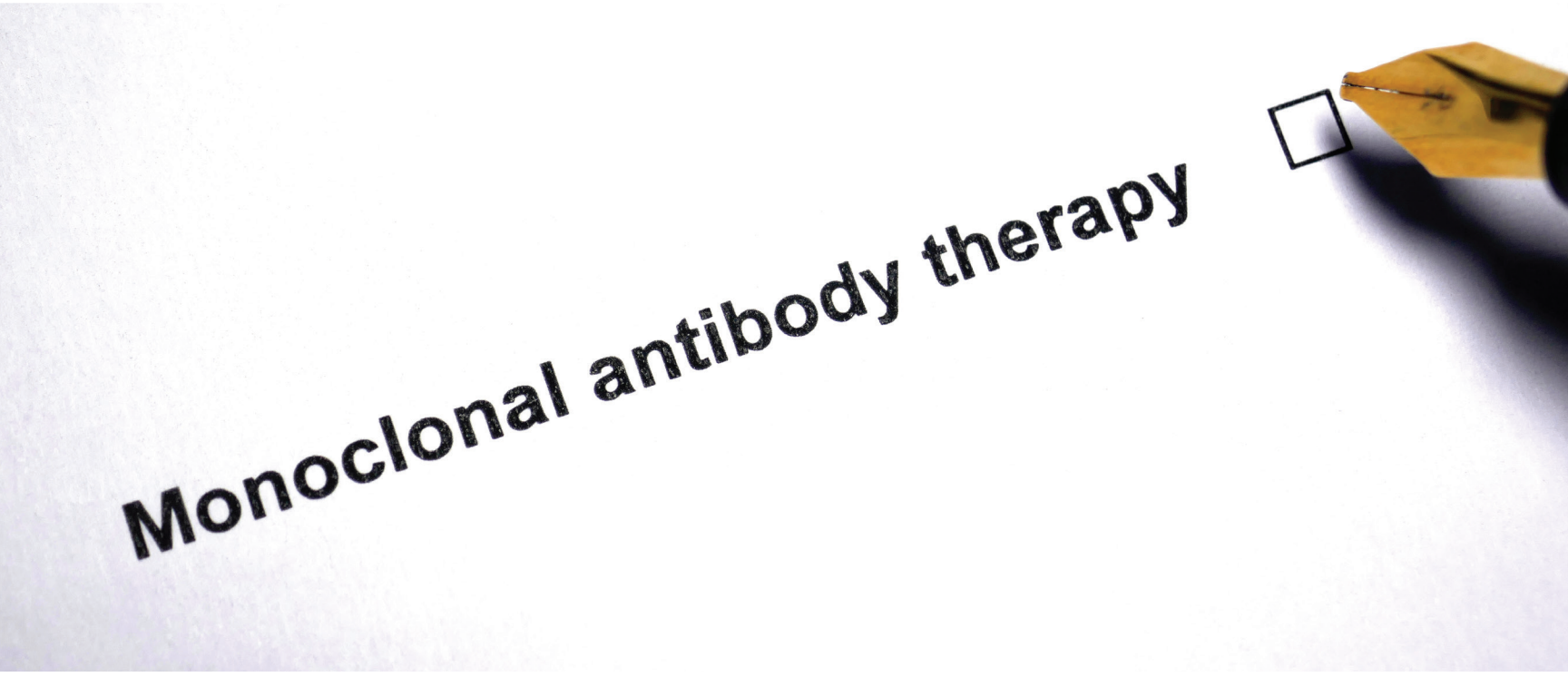

KNOW YOUR MONOCLONAL ANTIBODIES


These pharmaceutical agents are used to treat a variety of ocular diseases. Knowing how they're dosed and their potential side effects will serve you and your patients well.

BY ALISSA COYNE, OD, MS, FAAO, FASOS, AND TRACY OFFERDAHL, PHARMD, FAAO

Whether you've noticed or not, pharmaceutical companies have been advertising high-tech, genetically engineered medications in the biologic category. *Biologics* are not a new discovery and include examples such as insulin, blood products, gene therapy, and vaccines. The newer generation of biologics offer an ever-increasing list of mechanisms of action (MOA) and indications, including agents that treat cancer, autoimmune disease, type 2 diabetes, obesity, and wet age-related macular degeneration (AMD). What makes these agents unique compared with other traditional small molecule drugs is their large structures; human, animal, or microbial sourcing; their targeted MOA; and high price tag (see *Biologics: the Basics*).

Ocular biologics, including monoclonal antibodies (mAbs), are part of this newer grouping of biologics, and it is important for optometrists to have a working knowledge of these agents. This article provides an overview of the mAbs commonly encountered by optometrists, broken down by the disease state that they treat.

THYROID EYE DISEASE

In patients with thyroid eye disease (TED) secondary to Graves disease, we typically see progressive enlargement of orbital fat and extraocular muscles (EOMs). Other signs and symptoms include eyelid retraction, exophthalmos, EOM restriction or dysfunction, diplopia, compressive

optic neuropathy, and corneal exposure.[1,2] Pathogenic autoantibodies, or thyroid-stimulating immunoglobulins (TSIs), target the thyrotropin receptor (TSHR) and serve as the presumed underlying cause of TED. However, newer research suggests that insulin-like growth factor type 1 (IGF-1) also plays a role in TED.[1,2]

Orbital fibroblasts express both TSHR and IGF-1 receptor, with overexpression of the latter in patients with TED.[1] Orbital fibroblast differentiation can result in increased volumes of fat, muscle, and water content in the orbit of patients with TED, and these changes are associated with the clinical manifestations observed in TED.[2]

Treatment

Teprotumumab-trbw (Tepezza, Horizon Therapeutics) is a human mAb used in the treatment of TED.[1-6] The drug is prescribed as an intravenous infusion every 3 weeks for 8 weeks. The most common side effects include muscle spasms, alopecia, transient hearing loss, and hyperglycemia. Teprotumumab's unique MOA targets IGF-1R and blocks IGF-1 and insulin-like growth factor type 2 (IGF-2) from binding to IGF-1R. This results in several key improvements, including blocked autoantibodies, leading to a decreased effect on orbital fibroblasts; inhibition of the inflammatory cytokine cascade; and prevention of muscle and fat remodeling. Treatment outcomes include improvement in proptosis, diplopia, clinical activity scores, and Graves orbitopathy quality of life score.

UVEITIS

Uveitis is classified based on the location of intraocular inflammation and/or its underlying etiology. Noninfectious uveitis (NIU) may be primary or secondary to an underlying systemic condition, such as HLA-B27–associated conditions, sarcoidosis, Vogt-Koyanagi-Harada syndrome, and Behçet disease. Most importantly, NIU is formally diagnosed after infectious etiologies and malignant causes are ruled out. Topical ophthalmic corticosteroids and topical ophthalmic cycloplegic agents serve as baseline management of intraocular inflammation; however, prolonged corticosteroid therapy utilized in NIU can result in ocular and systemic side effects. Refractory cases of NIU typically require advanced immunotherapy management to control ocular inflammation.[7-9]

Immunotherapy, including mAbs, is initiated when conventional therapy is ineffective in controlling NIU. Additionally, it is imperative to remember that NIU is oftentimes a manifestation of an underlying systemic condition that lacks specific or unidentified therapeutic targets.[10]

Treatment Options

Infliximab (Remicade, Janssen Biotech) and adalimumab (Humira, AbbVie) are the most commonly prescribed biologics used in the treatment of NIU. Both biologics are anti-tumor necrosis factor-α (TNF-α) mAbs. TNF-α is a major inflammatory cytokine released by immune and nonimmune cells throughout the body and is known to be overexpressed in patients with certain types of autoimmune disease. Infliximab and adalimumab inhibit the inflammatory cascade, signaling activation by TNF-α.[9,11-13]

Infliximab is given as an intravenous infusion, beginning with a loading dose, at weeks 0, 2, and 6, followed by maintenance doses typically given every 4 to 6 weeks, based on clinical response.

Adalimumab is initially given as an 80-mg subcutaneous single injection, followed by 40-mg subcutaneous doses every other week, beginning 1 week after the initial injection. Side effects include injection site reactions, increased susceptibility to infections (eg, viral and bacterial), reactivation of latent tuberculosis, and secondary malignancies.

Tocilizumab (Actemra, Hoffmann-La Roche) is another mAb that has shown efficacy in the treatment of NIU. It binds interleukin-6 receptors (IL-6R), resulting in the blocking of proinflammatory actions of IL-6, which may be overexpressed in some patients with autoimmune diseases.[9-11,14] Tocilizumab is prescribed as either an IV infusion at 4 mg/kg to 8 mg/kg every 4 weeks, or as a 162-mg subcutaneous injection every 1 to 2 weeks. Side effects associated with this drug include injection site reactions, increased susceptibility to infections (eg, viral and bacterial), reactivation of

AT A GLANCE

- Ocular biologics, including monoclonal antibodies (mAbs), are part of a newer grouping of biologics that feature targeted mechanisms of action; high cost; large structure; and human, animal, or microbial sourcing.
- Immunotherapy, including mAbs, is initiated when conventional therapy is ineffective in controlling noninfectious uveitis.
- Keeping up to date on mAb biologic agents is a good start towards knowing what is available and how to dose and monitor patients within an interprofessional treatment realm.

BIOLOGICS: THE BASICS

- Compared with traditional small molecule drugs (eg, nonsteroidal antiinflammatory drugs, antibiotics, glaucoma medications, glucocorticosteroids), biologics are large structures.
- Biologics have the ability to treat diseases and conditions better than some traditional choices.
- Biologics may offer cures for some diseases and conditions where no other treatment options exist.
- Biologics come from naturally occurring sources, such as human, animal, or microbial, whereas traditional "small molecule" drugs can come from synthetic sources or from plant/animal sources.
- Extensive clinical workups are needed before initiating some biologics include:
    - Bloodwork to evaluate general, overall health status, including kidney and liver function
    - Assessment for latent infections including TB, Hep B and Hep C also may also be indicated, as some biologics can "activate" latent microbial infections
    - Review of immunization records to determine if any immunizations should be updated before initiating therapy

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latent tuberculosis, increased serum cholesterol, gastrointestinal effects, and secondary malignancies.

DME AND NEOVASCULAR AMD

Advanced glycated end products are associated with chronic elevation of blood glucose levels that may disrupt the blood-retina barrier, leading to retinal edema. The inflammatory cascade also contributes to accumulation of interstitial fluid within the macula, with inflammatory factors such as vascular endothelial growth factor (VEGF), interleukins, and TNF present. AMD is a multifactorial disorder with complex pathophysiology as a result of dysregulation of many pathways, including the complement, lipid, and antiinflammatory pathways. The presence of choroidal neovascularization characterizes wet AMD. Intravitreal anti-VEGF is the mainstay of treatment in diabetic macular edema (DME) and neovascular AMD.[15-18]

Treatment Options

There are several mAb biologics available for the treatment of DME and wet AMD. Bevacizumab (Avastin, Genentech) binds all isoforms of circulating VEGF-A, inhibiting the protein from binding the receptors on endothelial cells. Systemically, bevacizumab is an anti-neoplastic agent used in the treatment of certain types of cancer. When prescribed for patients with wet AMD, bevacizumab is given as a monthly 1.25-mg intravitreal injection for 3 months, then monthly or as needed based on ophthalmologic status and examination. Dosing in patients with DME consists of an initial 1.25-mg intravitreal injection, which is repeated every 4 weeks, based on ophthalmologic status and examination.

Ranibizumab (Lucentis, Genentech) also binds all VEGF-A isoforms, but with an affinity of about six times that of bevacizumab. When prescribed for patients with neovascular AMD, ranibizumab is dosed as a 0.5-mg intravitreal injection once per month, although the frequency may be reduced after the first three or four injections to once every 3 months in some patients. Dosing in patients with DME or retinopathy consists of a monthly 0.3-mg intravitreal injection.

The newest intravitreal treatment to enter the market is faricimab (Vabysmo, Genentech), which dually targets VEGF-A and angiopoietin-2 (Ang-2) and is designed to treat both DME and AMD. Ang-2 acts as a vascular-destabilizing molecule. Inhibition of Ang-2 decreases vascular permeability with dual inhibition of VEGF-A and Ang-2.[18,19-22] In patients with neovascular AMD, faricimab is given as a 6-mg intravitreal injection once every 4 weeks for four doses. Subsequent doses of 6 mg are given as an 8-, 12-, or 16-week regimen and are based on individual visual assessments.

In patients with DME, faricimab is typically given as an intravitreal injection of 6 mg once every 4 weeks for six doses. Then subsequent doses of 6 mg are administered based on

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individual visual assessments every 4 to 16 weeks. Side effects include infectious endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, IOP elevation, anterior ischemic optic neuropathy, retinal venous occlusions, retinal venous occlusions, and sixth nerve palsy.

IT PAYS TO BE IN THE KNOW

The treatment options for the management of ocular diseases and conditions have significantly expanded in the past couple of decades. With the expanded scope of practice in many states, the contemporary optometric physician is well suited to be part of the team treating patients with significant ocular issues. Keeping up to date on mAb biologic agents is a good start towards knowing what is available and how to dose and monitor patients within this interprofessional treatment realm. ■

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