OPHTHALMIC BIOLOGICS

An overview of how these bioengineered molecules are being used in eye care.

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Flu vaccines, insulin glargine injection 100 units/mL (Lantus, Sanofi-Aventis), adalimumab (Humira, AbbVie), bevacizumab (Avastin, Genentech), and onabotulinumtoxinA (Botox, Allergan)—these are just some of the familiar agents classified as biologics. These bioengineered molecules are isolated from a variety of natural sources such as humans, animals, and microorganisms.[1,2] Biologics are often used when conventional therapy fails to treat disease. They typically target the cellular receptors or cytokines responsible for inflammation.[2] The Biologics Control Act of 1902 gave the FDA the authority to regulate these products and ensure their safety.[3]

Most drugs are chemically synthesized into a known and repeatable structure.[2] As a result, they can be reproduced in mass amounts. Biologic agents differ from traditional pharmaceutical drugs because, as noted earlier, the former come from living organisms. Biologics are larger molecules, have a more complex structure, and are not easily reproduced.[4] These agents are also more sensitive to degradation via heat or microbial contamination. For this reason, most biologics are delivered as infusions or injectables or are frozen until ready for use.

Because biologics are derived from living organisms, they tend to have significant side effects, the most common of which are allergic hypersensitivity and injection site reactions. Other potential side effects include fever, rash, and headache. Because biologic agents frequently act to suppress the body's immune system, they tend to increase the risk of infection.[5]

Therapeutic advances using biologics have influenced eye care significantly, most notably for the management of inflammatory, corneal, and retinal disease (Table). This article will take a look at some of the biologics used in these areas, including two recently approved drugs.

INFLAMMATORY EYE DISEASE

Adalimumab

Uveitis is a potentially blinding inflammatory condition involving all or part of the eye's uveal coat. Corticosteroids remain first-line therapy for uveitis, but the ocular and systemic side effects of these drugs limit their long-term use.

Biologics have demonstrated efficacy for managing inflammation, and these agents can be used after a corticosteroid induction. The treatment of uveitis with biologic agents requires a multidisciplinary approach, with comanagement by rheumatologists and other medical specialists.[6] Careful patient screening for preexisting immunocompromising conditions such as hepatitis B and C, tuberculosis, human immunodeficiency virus, and a history of neoplasm must be ruled out before initiating therapy. Many biologics used for noninfectious uveitis, including adalimumab, target tumor necrosis factor alpha, a powerful cytokine that initiates inflammation and recruits other cytokines.

Adalimumab is administered via subcutaneous injection for the treatment of intermediate uveitis, posterior uveitis, and panuveitis in adults and children who are 2 years of age or older. The phase 3 multicenter VISUAL trials showed a 50% reduction in the risk of treatment failure in patients with active inflammation who were in the adalimumab group compared to those who received placebo. Additionally, there was a 43% reduction in uveitic flares in patients with inactive but steroid-dependent noninfectious uveitis.[7,8]

Repository Corticotropin Injection

Repository corticotropin injection 80 units/mL (Acthar Gel, Mallinckrodt Pharmaceuticals) is indicated for the treatment of severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa, such as keratitis, iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, and anterior segment inflammation. This biologic agent is a naturally sourced adrenocorticotropic hormone derived from porcine pituitary extract.[9] Because repository corticotropin injection stimulates the body's adrenal cortex to secrete cortisol, it has the ophthalmic side effects typical of corticosteroids, including cataract formation, glaucoma, and an increased risk of opportunistic infection. This biologic agent is administered via subcutaneous injection, and phase 4 clinical trials are ongoing.

AT A GLANCE

- Biologics differ from traditional pharmaceutical drugs because the former come from living organisms.
- Therapeutic advances using biologics have influenced eye care significantly, most notably for the management of inflammatory, corneal, and retinal diseases.
- The FDA recently approved: (1) a biologic that is the first drug for the treatment of thyroid eye disease, (2) the first biosimilar for the treatment of retinal diseases, and (3) a refillable ocular implant containing a biologic for the treatment of wet AMD.

Tocilizumab

Tocilizumab (Actemra, Genentech) targets interluken-6.[10] The FDA fast-tracked this biologic agent as a breakthrough therapy and approved it for the treatment of giant cell arteritis in May 2017.[11] In the Giant Cell Arteritis Actemra (GIACTA) trial, tocilizumab combined with a 26-week prednisone taper was superior to either a 26-week or 52-week prednisone taper plus placebo with regard to the sustained remission of giant cell arteritis.[10] Tocilizumab is administered by subcutaneous injection.

CORNEAL DISEASE

Autologous and Allogenic Eye Drops

Included in step 3 of the TFOS DEWS II dry eye management algorithm is a recommendation to prescribe autologous or allogenic serum eye drops.[12] Autologous serum eye drops (ASEDs) are derived from a patient's own plasma. A blood draw is used to harvest serum, which is then diluted with sterile saline to a concentration ranging from 20% to 50%.

ASEDs and natural tears contain similar components:

- Growth factors promote proliferation and differentiation of ocular surface cells.[13]
- Vitamins A, C, and E are antioxidants that protect the cornea against oxidative stress.[14]
- Albumin is a protein that inhibits caspase-3, a proteolytic enzyme that cleaves a variety of intracellular proteins resulting in apoptosis.[15,16]

ASEDs must be stored frozen and then refrigerated once opened. Dosage and concentration are at the doctor's discretion. The disadvantages of ASEDs, such as their cost, the requirement of a blood draw, storage, and a lack of FDA approval, prompted the development of allogenic biologics. StimulEyes (M2 Biologics) and Regener-Eyes (Regener-Eyes) are biologic eye drops derived from human amniotic fluid or placenta. Neither requires frozen storage or a patient blood draw.

Amniotic Membranes

Prokera Slim (Bio-Tissue) is a biologic corneal bandage made of a cryopreserved amniotic membrane graft fastened to an ophthalmic conforming ring.[17] The membrane is inserted into the eye and held in place by the upper and lower eyelids. The membrane typically dissolves in 5 to 7 days, after which the ring is removed.

TABLE. Biologics in Eye Care

AGENT	INDICATION(S)	MECHANISM OF ACTION	KEY POINTS
Adalimumab (Humira, AbbVie)	Noninfectious uveitis	Tumor necrosis factor alpha blocker	Risk of opportunistic infection
Repository corticotropin injection 80 units/mL (Acthar Gel, Mallinckrodt Pharmaceuticals)	Keratitis, uveitis, choroiditis, optic neuritis	Stimulates cortisol production	Risk of cataract formation, glaucoma, opportunistic infection
Tocilizumab (Actemra, Genentech)	Giant cell arteritis	IL-6 inhibitor	Risk of opportunistic infection
Rituximab (Rituxan, Genentech)	Pemphigus	Modulates CD20 B-cells	Risk of opportunistic infection
Autologous serum eye drops	Ocular surface disease	Promote cell growth, protect against oxidative stress and apoptosis	Blood draw needed, store frozen
StimulEyes (M2 Biologics)	Ocular surface disease	Antiinflammatory cytokines, growth factors	No refrigeration required, 1-year shelf life
Regener-Eyes (Regener-Eyes)	Ocular surface disease	Cytokines, chemokines, growth factors, hyaluronic acid	Refrigeration required, 3-year shelf life
Prokera (Bio-Tissue)	Superficial corneal disease	Suppresses inflammation, promotes epithelial healing	Cryopreserved amniotic membrane, ring may be uncomfortable
BioDOptix (Labtician Ophthalmics)	Superficial corneal disease	Suppresses inflammation, promotes epithelial healing	Contact lens required, dehydrated amniotic tissue
Cenegermin (Oxervate, Dompé Farmaceutici)	Neurotrophic keratitis	Recombinant nerve growth factor	Patient must prepare, dose six times per day for 8 weeks
Teprotumumab-trbw (Tepezza, Horizon Therapeutics)	Thyroid eye disease	Blocks IGF-1R	Reduces proptosis and diplopia
Ranibizumab-nuna (Byooviz, Samsung Bioepis)	Neovascular ARMD, Macular edema secondary to RVO, myopic choroidal neovascularization	VEGF-A inhibitor	First eye care biosimilar to reduce cost and improve patient access
Ranibizumab (Susvimo, Roche)	Wet ARMD	VEGF-A inhibitor	Refillable ocular implant

Abbreviations: ARMD, age-related macular degeneration; IGF-1R, insulin-like growth factor-1R; IL-6, interluken-6; RVO, retinal vein occlusion

Prokera Slim effectively treats superficial corneal diseases by suppressing inflammation and related pain, promoting epithelial healing, and preventing haze.[17] Related products are the thicker Prokera Plus and a version with a clear center, the Prokera Clear. All of these corneal bandage devices must be stored frozen until ready for use.

In contrast, BioDOptix amniotic extracellular matrix (Labtician Ophthalmics) is a dehydrated membrane allograft derived from human amniotic tissue that is intended for use in ocular tissue repair.[18] This product can be stored dry and has a shelf life of 5 years.

Cenergermin

Neurotrophic keratitis is a rare degenerative corneal disease caused by an impairment of trigeminal corneal innervation, leading to a decrease in or absence of corneal sensation. Management of this condition is challenging, and patients frequently develop corneal ulcers, melting, and perforation.[19] In 2018, the FDA approved cenegermin (Oxervate, Dompé Farmaceutici), a biologic recombinant nerve growth factor (NGF) that is structurally identical to endogenous NGF. Endogenous NGF stimulates tear secretion, epithelial cell proliferation, and the regeneration and survival of sensory nerves. In a clinical study, 72% of patients receiving cenegermin achieved complete corneal healing. In 80% of those individuals, healing remained complete at 1 year.[20] Cenegermin must be refrigerated. One drop is administered every 2 hours or six times per day for 8 weeks.

Rituximab

Ocular pemphigus is a debilitating ocular surface disease characterized by conjunctival scarring and corneal keratinization. The diagnosis and management of this condition are challenging.

In 2018, the FDA approved rituximab (Rituxan, Genentech) for the treatment of moderate to severe pemphigus vulgaris.[21] This biologic agent selectively targets B cells with the CD20 antigen and therefore spares stem cells and plasma cells needed for a healthy immune response.[22] Preexisting immunocompromising conditions must be ruled out before rituximab intravenous infusions are begun.

NEW KIDS ON THE BLOCK

First Drug for Thyroid Eye Disease

In January 2020, teprotumumab-trawl (Tepezza, Horizon Therapeutics) received breakthrough therapy designation and became the first drug approved by the FDA for the treatment of thyroid eye disease. Approval was based on the results of two studies involving a total of 170 patients with active disease who were randomly assigned to receive either teprotumumab or placebo. More than a 2-mm reduction in proptosis was observed in 71% and 83% of the patients who received teprotumumab in studies 1 and 2, respectively, compared with 20% and 10% of the patients who received placebo.[23]

Teprotumumab binds to insulin-like growth factor-1R and blocks its activation and signaling.[24] Insulin-like growth factor-1R is involved in the accumulation of glycosaminoglycans in the orbit, which expands the volume of fat and muscle tissue.[25] Teprotumumab was also shown to improve diplopia and reduce orbital pain, redness, and swelling. The drug is administered once every 3 weeks for a total of eight infusions.[26]

First US Biosimilar for Retinal Disease

In September 2021 the FDA approved the biosimilar ranibizumab-nuna (Byooviz, Samsung Bioepis). This is the first *biosimilar* that the agency has approved to treat an ocular condition.[27]

Biosimilars are not exact copies, but rather are highly similar to the active ingredient of the reference biologic.[4] Ranibizumab-nuna is the biosimilar to ranibizumab, and it is administered by intravitreal injection once a month. Ranibizumab-nuna is indicated for the treatment of neovascular age-related macular degeneration, macular edema following retinal vein occlusion, and myopic choroidal neovascularization.[28]

Anti-VEGF Refillable Ocular Implant

This October, the FDA approved ranibizumab in a refillable ocular implant (Susvimo, Roche; previously called the Port Delivery System) for the treatment of neovascular AMD.[29] The implant is about the size of a grain of rice and is surgically placed 4 mm posterior to the limbus.[30,31] Susvimo delivers ranibizumab 100 mg/mL continuously for at least 6 months so patients can manage wet AMD with just two treatments a year.

Results from the phase 3 Archway study showed Susvimo achieved and maintained vision gains equivalent to monthly ranibizumab injections. The implant was generally well tolerated with a favorable benefit-risk profile; however, 2.0% of patients experienced at least one episode of endophthalmitis. Nevertheless, this represents a first-of-its-kind therapeutic approach for patients who previously required monthly anti-VEGF injections.[30]

BIOLOGICS: A WELCOME ADDITION TO THE TREATMENT TOOLBOX

Biologics are naturally sourced molecules engineered to target specific pathways in many inflammatory and autoimmune disorders. Currently available agents represent a significant advance in the management of ocular diseases that are difficult to treat. ■

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> **BIOSIMILARS ARE NOT EXACT COPIES, BUT RATHER ARE HIGHLY SIMILAR TO THE ACTIVE INGREDIENT OF THE REFERENCE BIOLOGIC.**

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