

Biologics: Spotting and Managing Ocular Adverse Effects

The global biologics market, growing by leaps and bounds, is expected to reach around \$540 billion by 2026.¹ Derived from cells, blood components, and tissues, among other substances, these drugs treat everything from cancer and autoimmune diseases to ophthalmic conditions and rare genetic disorders.²

“Despite the possibility of great efficacy, biologics also have the potential to cause ocular adverse effects,” said Asim V. Farooq, MD, at the University of Chicago. “As more and more biologics are approved and utilized by our colleagues in other specialties, we will be seeing more of these patients.”

The Ophthalmologist's Role

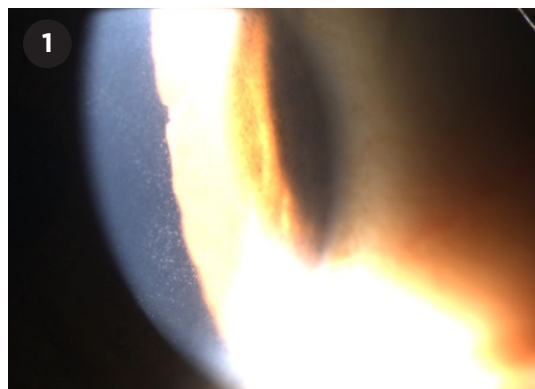
Although there is a growing recognition of the importance of a multidisciplinary approach for patients taking biologics, sometimes eyes are seen as separate by other specialists, said Joann J. Kang, MD, at Montefiore Medical Center in the Bronx, N.Y. “For example, if a rheumatoid arthritis patient experiences a corneal melt but shows no systemic signs of inflammation, the rheumatologist may insist it's only an eye problem,” she said. “But nothing is isolated, as evidenced by the impact of systemic therapies on the eyes.”

Beware a growing source of toxicity. Ocular surface disease is being seen with a number of new biologics, particularly with antibody-drug

conjugates (ADCs), a class of targeted therapy designed to treat cancer, said Dr. Farooq. “Common adverse events range from dry eye to keratopathy. Rare conditions such as corneal melt or perforation have been reported with some drugs in this category.”

Currently, about eight ADCs either have been approved by the FDA or are being investigated in clinical trials, said Winston D. Chamberlain, MD, PhD, at the Casey Eye Institute in Portland, Oregon. These include belantamab mafodotin (Blenrep, next page) and others that treat ovarian, cervical, or breast cancer, he said. “Because the mechanism of action on the cornea is nonspecific—probably pinocytosis—we'll likely see more drugs in this class leading to keratopathy.”

Immunotherapy drugs constitute another class of biologics that can cause ocular surface disease, as well as corneal and intraocular adverse events, such as uveitis, said Dr. Farooq. One example is dupilumab (Dupixent, next page), with adverse reactions including conjunctivitis, blepharitis, keratitis, eye pruritis, and dry eye. Secondary conjunctivitis has been reported in two similar FDA-approved drugs, and more drugs are likely on the way, he said.



MECS. A slit-lamp photograph demonstrating microcyst-like epithelial changes, which are visualized as small dots just adjacent to the light beam reflecting off the iris.

Investigate thoroughly. Both an exam and thorough history are essential, including getting a complete list of the patient's medications, said Dr. Kang. “Have a high index of suspicion, especially if you see something unusual. If you're not sure what you're looking at, you may miss toxicity because early findings may be subtle or appear more consistent with other epithelial disease.”

Collaborate with specialists. Ophthalmologists need to stay vigilant, report findings, and communicate well with their colleagues, said Dr. Farooq. “That may be easier to do at a hospital system with a collaborative, multidisciplinary team of specialists. Regardless, it's really important to communicate with the prescribing physician, and say something like, ‘I'm not familiar with this drug, but this is what I'm seeing, and this is how I'm treating it. What do you think?’”

When communicating with phy-

BY ANNIE STUART, INTERVIEWING WINSTON D. CHAMBERLAIN, MD, PHD, ASIM V. FAROOQ, MD, AND JOANN J. KANG, MD.

sicians outside his system, Dr. Farooq sometimes prefers an analog approach: “I fill out a form or write a letter, hand it to the patient, and ask them to take it to their hematologist, for example.”

Belantamab Mafodotin

Developed by GlaxoSmithKline, belantamab mafodotin (Blenrep) is an ADC used for the treatment of relapsed and refractory multiple myeloma in patients who’ve previously tried multiple other drugs, said Dr. Farooq. “Approved in 2020, belantamab is not commonly known by ophthalmologists.” It binds to plasma cells, giving it a site-specific action in bone marrow-derived cells, said Dr. Chamberlain, and likely a non-specific action in the cornea since these receptors are not found here.

Risk factors. “In the DREAMM-2 study [which looked at belantamab in multiple myeloma patients], there was an association between grade 2 or greater keratopathy and patients who had a history of dry eye,”³ said Dr. Farooq. Also, patients with comorbidity on the ocular surface, such as those with Sjögren syndrome or those threatened by chronic conjunctivitis from allergies or atopic disease, are potentially susceptible to a more severe form of toxicity, added Dr. Chamberlain.

Ocular side effects. “In an ancillary DREAMM-2 clinical trial,⁴ a majority of patients developed corneal adverse events—microcyst-like epithelial changes [MECs],” said Dr. Farooq. Occurring in 72% of patients, this keratopathy may cause epithelial breakdown and corneal ulceration, said Dr. Chamberlain.

Blenrep toxicity may also cause vision changes and light sensitivity, he said. Those with central corneal lesions may have blurry vision, which may not be correctable with glasses, said Dr. Farooq. And lesions that are less central may still affect the contour or shape of the cornea, causing a shift in a patient’s prescription following each infusion. “Although this might be correctable, it’s not practical to get a new pair of glasses every three to four weeks,” he said.

Evaluation. “Blenrep is prescribed under a Risk Evaluation and Mitigation Strategy [REMS] protocol,” said Dr. Kang, “which means that patients

need a baseline eye exam before they can be dosed with this drug and before each subsequent dose.” The oncologist initiates this process by requesting that the eye care professional use the Keratopathy and Visual Acuity (KVA) scale. Crucially, how you grade the keratopathy will influence the dosing, which ultimately affects not only the eyes but the entire body, she said.

Eye exams prior to each infusion involve a standard visual acuity exam as well as a refraction to detect vision changes, and a slit-lamp evaluation to visualize lesions in the epithelium, said Dr. Farooq. “It’s necessary to use high magnification and either retroillumination or indirect illumination to see them. Fluorescein stain also helps identify any changes on the ocular surface, such as worsening dry eye.”

Management and prognosis.

Although multiple myeloma is a life-threatening disease, said Dr. Chamberlain, the ophthalmologist will greatly influence the course of treatment and is responsible for communicating with the hematologist when a reduction in vision is dramatically reducing a patient’s quality of life.

Changes in vision are tied to the dosage of Blenrep, said Dr. Farooq. If a patient has a certain level of ocular adverse event, a dose modification protocol is followed. “The data have shown that the most potent way to mitigate or resolve lesions is by stopping the drug for a period of time,” he said.

“For the most part, lesions resolve, and the patient can then be started back on a lower dose, so the cornea will fare better.”

Preservative-free lubricant eyedrops are also recommended while the patient is on the drug, said Dr. Farooq, adding that topical corticosteroids were not found to be beneficial in the DREAMM-2 study. They may be less helpful than in other situations because toxicity, not inflammation, is likely the primary driver of damage, said Dr. Chamberlain.

Although contact lenses may play a role for patients with severe ocular surface toxicity, he said, it’s generally recommended that patients on Blenrep avoid them.

Dupilumab

Jointly developed by Sanofi and Regeneron, dupilumab (Dupixent) treats moderate-to-severe atopic dermatitis (eczema) that isn’t well managed with topical medications. A fully human monoclonal antibody, the biologic is FDA approved for this indication in patients 6 months and older.

Dupilumab inhibits the signaling of the interleukin-4 (IL-4) and interleukin-13 (IL-13) pathways. But its mechanism of action on the eye is not well understood, said Dr. Farooq. “Although data are lacking, targeted therapies like this may theoretically cause ocular surface inflammation via a number of pathways, including by affecting the

MORE RESOURCES

For a deeper dive into the relationship between biologics and ocular adverse effects or to report drug-induced ocular side effects, try these resources:

Eye drug registry. The National Registry of Drug-Induced Ocular Side Effects (eyedrugregistry.com) maintains an international clearinghouse of information on adverse ocular effects linked with drugs, chemicals, and herbals. The Academy and the Casey Eye Institute at Oregon Health and Science University support the Registry.

Book. Data from the Registry are also available to clinicians and researchers in the book, *Drug-Induced Ocular Side Effects*, updated in 2020.

EyeWiki. For more information about biologics’ impact on the eye, read these EyeWiki articles: “Dupilumab-Induced Conjunctivitis” and “Microcyst-Like Epithelial Changes (MECs) Associated With Antibody-Drug Conjugates (ADCs)” at aao.org/eyewiki.

ocular surface microbiome.”

Risk factors. “Although Dupixent is quite effective at treating atopic dermatitis,” said Dr. Farooq, patients who have a history of conjunctivitis related to atopic dermatitis may be at greater risk for Dupixent-associated ocular surface disease. Dr. Chamberlain added, “Atopic dermatitis patients frequently have baseline ocular disease, which may be a risk factor for side effects. In contrast, patients in Dupixent trials for treatment of asthma and sinusitis have not experienced ocular side effects.”

Ocular side effects. With Dupixent, the most common side effect is conjunctivitis. Keratitis and blepharitis have also been observed.⁵ Other common findings, said Dr. Chamberlain, are limbitis, papillary reactions, erythema, increased mucus production, superficial punctate keratopathy, and blepharitis. Corneal ulceration and perforation are rare.⁶

The most common ocular symptoms reported by patients, said Dr. Chamberlain, are light sensitivity, redness, watery eyes or discharge, and itching. “If patients haven’t reported these prior to starting Dupixent,” he said, “it’s reasonable to assume that the drug is what is driving the symptoms. These symptoms most often show up four to six months after starting the drug, but it’s important to remember that many patients with atopic dermatitis already have baseline ocular surface disease. The drug may cause a new form of disease that synergizes with baseline disease, causing intermittent or chronic symptoms.”

Pediatric patients. Although the pediatric population has been getting this drug for a shorter period of time (since its approval), clinicians are seeing a handful of children with findings similar to those seen in adults, said Dr. Chamberlain. “Many younger patients [age 6 months to 18 years old] may be more prone toward baseline atopic ocular surface disease, which is not related to the drug.”

Evaluation. For all dupilumab patients, take a thorough medical history, asking about systemic conditions the patient has and medications they are taking, said Dr. Farooq. Conduct a

complete exam, assessing signs and symptoms, looking for ocular surface disease. “Carefully examine the lid margin, eyelid skin, and conjunctiva, assessing for redness, discharge, blepharitis, and keratitis. Fluorescein dye is helpful and lissamine green may be considered to detect noncorneal staining.”

If Dr. Farooq sees a patient on Dupixent with severe conjunctivitis, he recommends considering a culture and checking for an overgrowth of bacteria. “If present, treat it either before or in addition to prescribing topical corticosteroids.”

Management and prognosis. “My Dupixent patients love the medication because it often does wonders for their dermatitis,” said Dr. Kang. “That’s why many of them want to do everything they can to stay on the medication, but that can make it difficult to mitigate symptoms.”

With milder forms of Dupixent-associated ocular surface disease problems, preservative-free tears and compresses may be sufficient, said Dr. Farooq. They have the added benefit, said Dr. Chamberlain, of washing away inflammatory mediators. Systemic, oral, and topical antihistamines may also play a role in decreasing the inflammatory response.

“In our experience, patients often have a better response to topical steroids than anything else,” said Dr. Chamberlain, who works at an academic center that’s engaged in many early trials on biologics. “But with the potential for ocular side effects, these need to be prescribed by an ophthalmologist.”

Scoring system. Ophthalmologists developed a special symptom scoring system, which provides useful guidance for dermatologists, said Dr. Chamberlain. “We suggest that they try over-the-counter [OTC] artificial tears or allergy medication if the patient has no more than two Dupixent-related [scoring-system] symptoms. And they should follow up with an ophthalmologist if symptoms are worsening, or if the patient has more than two symptoms or was treated with OTC medications but did not improve.”

1 [Businesswire.com](https://www.businesswire.com): “Global Biologics Market

Report 2022.” Published online May 18, 2022.

2 Neves da Silva H et al. *Ther Adv Ophthalmol*. 2022;14:25158414211070878.

3 Lonial S et al. *Lancet*. 2020;21:207-221.

4 Farooq AV et al. *Ophthalmol Ther*. 2020;9(4):889-911.

5 Bohnner A et al. *Cornea*. 2021;40(5):584-589.

6 Phylactou M et al. *Cornea*. 2022;41(8):981-985.

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Dr. Farooq is a cornea specialist and associate professor of ophthalmology at the University of Chicago. *Relevant financial disclosures:* Ambrx: C; Amgen: C; Daiichi-Sankyo: C; Eisai: C; Glaxo-SmithKline: C; Sanofi: C; Seagen: C; AstraZeneca: Data Monitoring Committee (DMC).

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CORNEA SUBSPECIALTY DAY

Be sure to stop by Cornea Subspecialty Day for sections on keratoplasty, corneal ectasia, keratitis, ocular surface disease, and new discoveries. **When:** Saturday, Oct. 1, 8:00 a.m.-5:00 p.m. **Where:** Room E354.

