EyeNet Selections

Retina 2021
Recent Articles From EyeNet® Magazine

• There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA.

• Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA.

• Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments.

WARNINGS AND PRECAUTIONS

• Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.

• Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular inflammation has been reported with the use of EYLEA.

• There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

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777 Old Saw Mill River Road, Tarrytown, NY 10591
PROVEN VISUAL OUTCOMES AT YEAR 1 IN THE VIEW STUDIES

Fewer injections with EYLEA Q8 vs ranibizumab Q4

Demonstrated in the largest phase 3 anti-VEGF trials completed to date in Wet AMD (N=2412)\(^1\)\(^3\)

Proportion of patients who maintained vision (<15 ETDRS letters lost of BCVA) at Year 1 from baseline\(^1\)^\(^3\)^\(^*\)

<table>
<thead>
<tr>
<th>Primary Endpoint (Year 1)</th>
<th>VIEW 1</th>
<th>VIEW 2</th>
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<tr>
<td>EYLEA Q4</td>
<td>95% (12.5 injections(^†))</td>
<td>95% (12.6 injections(^†))</td>
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<tr>
<td>EYLEA Q8(^‡)</td>
<td>94% (7.5 injections(^†))</td>
<td>95% (7.7 injections(^†))</td>
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<td>ranibizumab Q4</td>
<td>94% (12.1 injections(^†))</td>
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EYLEA was clinically equivalent to ranibizumab.

VIEW 1 and VIEW 2 study designs: Two multicenter, double-masked clinical studies in which patients with Wet AMD (N=2412; age range: 49-99 years, with a mean of 76 years) were randomized to receive: 1) EYLEA 2 mg Q8 following 3 initial monthly doses; 2) EYLEA 2 mg Q4; 3) EYLEA 0.5 mg Q4; or 4) ranibizumab 0.5 mg Q4. Protocol-specified visits occurred every 28 (±3) days.\(^1\) In both studies, the primary efficacy endpoint was the proportion of patients with Wet AMD who maintained vision, defined as losing <15 letters of visual acuity at Week 52, compared with baseline.\(^1\)

SEE WHAT EYLEA COULD DO FOR YOUR PATIENTS WITH WET AMD AT HCP.EYLEA.US

anti-VEGF, anti-vascular endothelial growth factor; BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; Q4, every 4 weeks; Q8, every 8 weeks.

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.
- Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

INDICATIONS

EYLEA\(^*\) (aflibercept) Injection 2 mg (0.05 mL) is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).


Please see Brief Summary of Prescribing Information on the following page.
Table 1: Most Common Adverse Reactions (≥5%) in Wet AMD Studies

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Baseline to Week 52</th>
<th>Baseline to Week 96</th>
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<tr>
<td><strong>EYLEA (N=595)</strong></td>
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<td>Baseline control</td>
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<td>Active control (n=588)</td>
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EyeNet Selections

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COVER PHOTOGRAPH
© The American Society of Retina Specialists.
As vitreoretinal surgeons know all too well, a surprise can arise anytime during or after surgery—and it may be a substantial one.

“A case that really hit home for me was a diabetic gentleman who’d had a retinal detachment repaired elsewhere,” said Lisa S. Schocket, MD, at the University of Maryland in Baltimore. “As far as I could tell, the prior surgeon had done a good job fixing the retina, but the cornea had completely failed and the patient’s vision in one eye was light perception only.” When Dr. Schocket attempted to fix a retinal detachment in the other eye, the entire epithelium sloughed off, even though she hadn’t touched the cornea—let alone scraped it for better visualization of the retina.

What went wrong? Although the retina was free of retinopathy, diabetes had devastated this patient’s cornea and his vision. It’s a cautionary tale for vitreoretinal surgeons: You must also pay attention to the condition of the cornea to ensure an overall positive outcome.

**Remembering Risks to the Cornea**

Rahul S. Tonk, MD, MBA, is at the Bascom Palmer Eye Institute in Miami. He repeatedly sees corneal problems following vitreoretinal surgery—from infections to neurotrophic keratitis and epithelial defects. An important step for surgeons, he said, is to simply be aware of patients who are at increased risk.

**Diabetes.** Vitreoretinal surgery is safer for diabetic patients than it used to be, leading to fewer corneal and anterior segment complications than 20 years ago, said Jay Stewart, MD, at UCSF Health in San Francisco. “Small-gauge instrumentation with less dissection of the ocular surface makes surgery safer, creating less post-op vascularization and irritation at the ocular surface.”

However, he said, patients with diabetes have compromised nerves and blood flow, which can underlie some of the complications that may arise, such as abnormal vascularization or non-healing corneal epithelial defects. Dr. Schocket added, “Before going into the OR, be sure to take a thorough history.”

**Aphakia.** In aphakic patients, vitreoretinal surgery causes more turbulence of irrigation fluid flow at the corneal endothelium, said Dr. Stewart, who suggested application of a viscoelastic agent in the anterior chamber for protection.

**Recent incisions.** Dr. Stewart also suggests being mindful of corneal incisions from prior cataract or other anterior segment surgeries. “If the surgery was recently performed, incisions could be unstable,” he said. “To avoid leakage through those incisions, it may be advisable to place sutures through the incisions prior to placement of the vitrectomy trocars.”

**Prior refractive surgery.** A LASIK flap wound never heals completely, said Dr. Schocket, who’s experienced a dislocation twice. In fact, studies have shown that the strength of the healed wound margin is on average only 28% of the normal cornea.1 This can lead to flap dislocation during retina surgery. “I’ve learned to specifically ask patients multiple times whether they’ve had LASIK, not just eye surgery,” she said, “because many don’t think of it as a surgical procedure.” (See sidebar, “Dislocation of a LASIK Flap.”)

**Complication.** Use care when repositioning a dislocated LASIK flap in order to avoid epithelial ingrowth, pictured above.

Originally published in January 2021

BY ANNIE STUART, CONTRIBUTING WRITER, INTERVIEWING LISA S. SCHOCKET, MD, JAY STEWART, MD, AND RAHUL S. TONK, MD, MBA.
When Neurotrophic Keratitis Occurs
A degenerative disease characterized by decreased corneal sensitivity and poor corneal healing, neurotrophic keratitis (NK) makes the cornea susceptible to injury.

Because surgery can trigger or exacerbate NK, it’s important for vitreo-retinal surgeons to discern which of their patients already have it or to anticipate which patients may be predisposed to NK, said Dr. Tonk. Patients at greatest risk may include those with diabetes, as well as those—with or without diabetes—who will undergo heavy endolaser photoablation for complex retinal detachments. In the latter scenario, “the heavier or more confluent the laser, the greater the risk of damage to the sensory long ciliary nerves,” he said.

As you look for NK, it’s important to note that it has several stages.

Stage 1 NK may simply look like severe dry eye, said Dr. Tonk, except that it doesn’t often respond to lubricant drops alone. “Clues that you are dealing with NK include a diffuse pattern of punctate keratopathy and a swollen, irregular epithelium, all of which can be responsible for several lines of decreased vision.”

Stage 2 NK is associated with recurrent or persistent epithelial defects or delayed healing following epithelial scraping, said Dr. Tonk. These defects are often bordered by rolled, loose edges of swollen epithelium.

Stage 3 NK is characterized by a corneal ulcer wherein the stroma may melt or even perforate. Surgeons should investigate for melt when looking at any epithelial defect, said Dr. Tonk. This can be done easily with a thin, high-powered slit beam or by obtaining an anterior segment optical coherence tomography scan. Even in the best case, melts are associated with corneal haze and irregular astigmatism and can limit final visual outcome.

Managing Corneal Challenges During and After Surgery
Although some corneas may not heal as quickly as others, retina surgeons can take steps to lower the risks of corneal complications.

Dislocation of a LASIK Flap
If you’re not aware that a patient has a LASIK flap, you may inadvertently do things during retina surgery to destabilize it, said Dr. Schocket. “For example, if you’re placing viscoelastic jelly on the surface of the cornea and the wound is not perfectly sealed, the material can slowly ooze under the flap and loosen it.” The view to the retina then becomes unclear, she said. Not realizing that this is due to a flap dislocation, the lead surgeon may scrape the cornea, which completes the displacement of the flap.

Here’s how to avoid a LASIK flap dislocation.

Avoid a buckle. “I’ve only seen a dislocation happen with a buckle,” said Dr. Schocket. “It’s not always possible, but it’s best to try to avoid a buckle in patients with prior LASIK. During a buckle, viscoelastic material can potentially seep under the flap and lift it off.”

If you must scrape. “If you need to scrape, do it carefully, starting from the corneal apex and scraping toward the limbus,” said Dr. Tonk. “If you scrape from the limbus uphill toward the corneal apex, your blade may get under the LASIK flap, and you may inadvertently lift it.”

If dislocation occurs. Proper repositioning of the LASIK flap is critical to avoid striae, irregular astigmatism, and epithelial ingrowth within the flap interface. In addition, these eyes must be watched carefully for diffuse lamellar keratitis postoperatively.

Rinse the surface and interface thoroughly with BSS to wash away any released epithelial cells and prevent epithelial ingrowth, said Dr. Schocket. Then carefully reposition the flap, before completing the vitrectomy, which may be more challenging now due to multiple interfaces.

If the flap does not reposition smoothly into the stromal bed, Dr. Tonk advises the following:
1. Remove the epithelium from over the top of the flap to reduce “bunching.”
2. Use hypotonic saline or sterile water to swell and stretch out the flap.
3. If all else fails, secure the flap with four to six sutures, but remove them within a few months to avoid inducing irregular astigmatism.

Protect nerves. Try to avoid laser photocoagulation at the 3 o’clock and 9 o’clock meridians along the course of the long ciliary nerves.

Keep the cornea moist. A buckle can prolong the surgical time, which increases the risk of the cornea drying out, said Dr. Schocket. Viscoelastic applied to the surface of the cornea can help. “But if I’m concerned about a cornea in a person who had LASIK or has diabetes, I may let the resident do less, so I can speed things along.”

Avoid scraping, if possible. Don’t scrape the corneal epithelium for visualization if you don’t have to, especially high-risk patients such as those with diabetes or a LASIK flap, said Dr. Schocket.

To reduce epithelial edema and corneal clouding, Dr. Tonk noted that, to the extent possible, it’s important to limit surgical case time, infusion pressure, and excess fluid volume passed through the eye (such as from leaky wounds). He added that surgeons can also use 50% glyc erine to clear the cornea via osmotic action, obviating the need to scrape.

If you must scrape to achieve adequate visualization, said Dr. Stewart, try to remove relatively small areas of central epithelium. “A smaller epithelial defect has a better chance of healing in
a shorter time. It’s not usually necessary to scrape the corneal epithelium out to the far peripheral portion of the cornea where the limbal stem cells are located."

**Alter post-op regimen.** “A standard post-op regimen might include only a visit on post-op day 1 and post-op week 1,” said Dr. Stewart. “But patients who required scraping should potentially be seen more frequently to ensure the epithelium is healing and an infection is not developing.”

**Don’t delay.** “Surgeons must take decisive action to promote rapid corneal re-epithelialization,” said Dr. Tonk. Persistent epithelial defects that haven’t healed within four weeks of surgery, he said, are frequently associated with corneal haze and melt, or worse, infection or perforation.

**Speed closure.** “If you have scraped the epithelium,” said Dr. Tonk, “give yourself a strict timeline for partial and complete re-epithelialization—within a week or two, at the most.”

To speed closure, Dr. Tonk advises surgeons to do the following:

1. Place a bandage soft contact lens at the time of surgery or the morning after.
2. Use preservative-free artificial tears.
3. Limit toxicity to the eye by modifying the use of eyedrops. For example, consider replacing glaucoma drops with an oral medication, reducing antibiotics to prophylactic dosing—typically two to four times a day—and reducing steroids to the minimum amount needed to reduce inflammation.
4. Consider punctal occlusion. **Take aggressive steps—or refer.** "If the epithelium has not closed within two weeks, treat aggressively as a persistent epithelial defect," said Dr. Tonk. Surgeons might try autologous serum eyedrops (available through a local compounding pharmacy), temporary tarsorrhaphy, amniotic membrane (placed in the office or operating room), or the use of Oxervate (Dompé), a nerve growth factor, to treat NK.2

“But if you’re concerned about a post-op problem with the cornea,” said Dr. Schocket, “get it managed by a cornea specialist as quickly as possible so you know you have the best chance of healing the cornea.”


Dr. Schocket is a vitrectinal surgeon and associate professor, vice chair for clinical affairs, and chief of the retina division at the University of Maryland, Department of Ophthalmology, in Baltimore. **Relevant financial disclosures:** None.

Dr. Stewart is a vitreoretinal surgeon and professor of ophthalmology at the University of California, San Francisco. **Relevant financial disclosures:** None.

Dr. Tonk is a cornea specialist at Bascom Palmer Eye Institute and assistant professor of ophthalmology at the University of Miami Health System in Miami. **Relevant financial disclosures:** None.

For full disclosures, see this article at aao.org/eyenet.

**MORE ONLINE.** Learn about removal of corneal tissue from the vitreous cavity. See this article at aao.org/eyenet.
Dry age-related macular degeneration (AMD) is traditionally thought to progress to two forms: geographic atrophy (GA) and neovascular AMD. But researchers are uncovering more nuanced approaches to dry AMD.

Both types of dry AMD—with and without GA—are being studied, said Baruch D. Kuppermann, MD, PhD, at the University of California, Irvine. “While there is a continuum of disease, for clinical trial purposes it may be useful to consider them as separate patient pools with distinct types of treatment.”

And clinicians are keenly awaiting the outcomes of this research. “We don’t have a lot to offer patients with GA,” said David S. Liao, MD, PhD, in practice in Los Angeles. If treatments currently in development “prove safe and effective, then we’re going to have a fantastic opportunity to help a large number of people.”

Promising approaches include hacking the complement cascade, repurposing a glaucoma drug, and coaxing induced pluripotent stem cells to become retinal pigment epithelium (RPE) cells.

**Complement Cascade**
The complement system augments the innate immune system through a central cascade of multiple factors, notably complement factor 3 (C3), the downstream complement factor 5 (C5), and further downstream factors C5α and C5b.

**Pegcetacoplan.** “Complement has been clearly identified in drusen, and there’s a lot of excitement around the science of complement inhibition in retinal disease,” said Dr. Kuppermann. Pegcetacoplan (APL-2; Apellis) inhibits C3. In a phase 2 study, 246 patients were randomized 2:2:1:1 to receive intravitreal injections of the drug either monthly or every other month (EOM)—or sham injections on a monthly or EOM basis. At 12 months, GA growth rate was reduced by 20% with EOM injections and a more robust 29% with monthly injections of the active drug.1 APL-2 is now in global phase 3 trials with 1,200 patients.2 Results showed a significant decrease in the growth of GA lesions with a clear dose/response effect,” said Dr. Liao. “Inhibition of the C3 molecule leads to a blockade of all complement pathways, slowing the progression of GA with ongoing treatment.”

A key concern is the process of conversion from dry to wet AMD. “An increased incidence of [new-onset] exudative AMD was seen in this study,” Dr. Liao said. Exudative AMD was identified more frequently in those who received monthly pegcetacoplan and in those who had a history of choroidal neovascularization (CNV) in the fellow eye.1 For instance, new-onset investigator-determined exudative AMD was detected in 20.9% (18/86) patients who received monthly pegcetacoplan, in 8.9% (7/79) who received the drug every other month, and in 1.2% (1/81) who received sham injections. Of note, patients who converted to wet AMD showed no change in best-corrected visual acuity at the time of diagnosis. In addition, Dr. Liao said, “visual outcomes with anti-VEGF treatment were good in those patients who did convert.”

**Zimura.** This drug “works in the
complement pathway at C5a and C5b, where it directly inhibits formation of inflammasome and membrane attack complex (MAC), which cause cell death,” said Dr. Kuppermann.

In a phase 2/3 trial known as GATH-ER1, Zimura (avacincaptad pegol; Iveric bio) was administered to 286 patients.1 In part 1 of this study, patients were randomized in a 1:1:1 ratio to 1 mg Zimura (n = 26), 2 mg Zimura (n = 25), and sham (n = 26). In part 2, they were randomized in a 1:2:2 ratio to 2 mg Zimura (n = 42), 4 mg Zimura (n = 83), and sham (n = 84).

Both the 2- and 4-mg doses of the active drug met their primary efficacy endpoints. At 12 months, those who received 2- and 4-mg doses of Zimura, respectively, experienced 27% and 28% less growth in GA than did those who received sham treatments.2 At 18 months, that differential had increased to 28% and 30%, respectively, for the 2- and 4-mg doses of Zimura (vs. sham).3

No adverse events or cases of inflammation were reported through 18 months. However, choroidal neovascularization was observed in the study eyes of two patients who received 1 mg of Zimura (7.7%), eight who received 2 mg (11.9%), and 13 who received 4 mg (15.7%), as well as in three patients (2.7%) in the sham group.4

A confirmatory clinical trial, GATH-ER2, is currently enrolling patients; participants in this trial will be randomized to receive either Zimura 2 mg or sham.

**Repurposing a Glaucoma Drug**

In another approach, when brimonidine was delivered via a biodegradable intravitreal implant (Brimo DDS; Allergan) in a randomized phase 2 trial, it showed ability to reduce GA.5

“We injected the brimonidine implant every six months into eyes with geographic atrophy, and at 12 months it showed a robust effect, with a 29% decrease in the growth rate of lesions in the 132 µm-dose group [n = 49],” said Dr. Kuppermann. Those who received the higher-dose implant (264 µm, n = 41) had an even better result: reduction by 31%.5 A larger phase 2b study of 310 patients compared a 400-µm implant and sham injections every three months on patients with smaller GA lesions.6

The upshot? Larger lesions had the bigger benefit. “When the lesion size was 6 mm2 or greater, the growth rate was slowed down by 38%, which was found in a later analysis,” said Dr. Kupffermann. “The brimonidine implant seems safe, with a low rate of infection and/or inflammation, and it didn’t lower IOP at any of those doses.” A phase 3 study has been designed but is not yet initiated, he said.

“Brimo DDS seems to be both neuroprotective and cytoprotective,” Dr. Kuppermann said; thus, it appears to protect photoreceptors and retinal neurons as well as RPE cells.

**Developing an RPE Patch**

Central to GA pathogenesis is the RPE. “Between the GA lesion and the healthier part of the retina is the ‘transition zone,’ where the RPE cells are gone but the photoreceptors are still alive,” said Kapil Bharti, PhD, at the NEI. Past attempts to graft a patient’s older RPE genetic changes and eat the Mediterranean diet, you get even more of a beneficial treatment effect,” Dr. Chew said.

**If you make just one change.** What one dietary change should ophthalmologists encourage their patients to adopt? “What really drove the results of the Mediterranean diet was eating fish,” she said. “Patients should consider eating fish twice a week.”

**If you go full Mediterranean.** The nine “eating points” from the Mediterranean diet are as follows: Decrease your intake of 1) red meat and 2) alcohol even as you increase your intake of 3) fish, 4) vegetables, 5) whole fruit, 6) whole grains, 7) nuts, 8) legumes, and 9) “good” fats. The latter, notably olive, walnut, and safflower oils, have a beneficial ratio of MUFA:SFA (monounsaturated fatty acid to saturated fatty acid).

**And remember AREDS2 supplements.** Dr. Chew’s work has also confirmed the benefits of the AREDS2 supplements.7 “They reduce the risk of developing vision-threatening late disease by about 25%,” Dr. Chew said. “We hope ophthalmologists are recommending this to their patients with intermediate AMD.”

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tissue from a healthier part of the eye have had mixed results, he said. But “with the theory that RPE cell death precedes photoreceptor cell death, we wondered: If we transplanted RPE cells into that zone, would it stop photoreceptors from dying further?”

Enter the RPE patch. This novel approach creates autologous tissue from induced pluripotent stem cells (iPSCs). Like embryonic stem cells, these cells have the capacity to make any tissue. “They’re called ‘induced’ because you can make them from any adult tissue,” said Dr. Bharti. “This is the first time in the United States that anyone has isolated a few cells from a skin biopsy or blood and made patient tissue in a dish for clinical use, so you can imagine: The phase 1 FDA application was 12,500 pages long.”

Dr. Bharti’s lab converts iPSCs into RPE tissue that sits on a biodegradable scaffold and becomes the 2 mm × 4 mm RPE patch. “We start with 200 mL of a patient’s blood and reprogram the blood cells into iPSCs, which takes about three months to make including the quality control,” he said, “then we convert those iPSCs into RPE progenitor cells and put the progenitor cells on the scaffold.” As the scaffold degrades, the progenitor cells mature. “At the end of this process, they’re fully polarized, fully functioning RPE cells that have made their own membrane, by secreting the right proteins to replace the scaffold,” Dr. Bharti said.

The RPE is one cell-layer thick with a unique architecture. “On the basal side, the cells have a membrane separating the eye from the choroid blood supply, and the apical side has hair-like projections that ‘talk to’ the photoreceptors,” Dr. Bharti said. “We recreated all those apical and basal structures in a dish and did all kinds of assays to study how closely they resembled native RPE cells, and they had every physiological feature of native cells.”

A deep understanding of cell physiology and developmental cues is required to make these cells. “For the iPSCs to become RPE cells, a sequence of growth factors follows an intricate process, with the right growth factors going up and down in the right time, place, and concentration, to give rise to the given tissue,” Dr. Bharti said. “We can now recreate those processes in a dish using human stem cells.”

The implant procedure uses a three-port vitrectomy surgery developed by vitreoretinal surgeon Steve Charles, MD. “He helped us develop a tool that takes this tissue in the correct orientation, goes through the vitreous, and delivers it under the retina—and then, the retina is flattened on top of the transplant,” Dr. Bharti said.

**References:**


Dr. Bharti is senior investigator, Ocular and Stem Cell Translational Research, at the NEI in Bethesda, Md. Financial disclosures: None. Dr. Chew is director of the Division of Epidemiology and Clinical Applications and chief of the Clinical Trials Branch at the NEI in Bethesda, Md. She is also editor-in-chief of *Ophthalmology Science.* Financial disclosures: None. Dr. Kuppermann is chair of ophthalmology, director of the Gavin Herbert Eye Institute, and codirector of the Center for Translational Vision Research at the University of California, Irvine. Financial disclosures: Alcon: C,S; Allegro: C,S; Allergan: C,S; Apellis: S; Aprea: C; Cell Care: C; Clearside: S; Dose: C; Eyedaptic: C; Galmedix: C; Genentech: C,S; GSK: S; Interface Biologics: C; Ionics: C; Iveric bio/Ophthotech: C,S; jCyte: C,S; Novartis: C,S; Oculis: C; Ocuence: C; Regeneron: C,S; ReVana: C; Ripple Therapeutics: C; Tervance Biopharma: C.

Dr. Liao is a vitreoretinal specialist in private practice in Los Angeles. Financial disclosures: Apellis: S; Clearside: S; Genentech: S; Iveric bio: S; jCyte: S; Regeneron: S. For disclosure key, see page 5.
Anti-VEGF therapy has become the gold standard for managing sight-threatening retinal diseases such as age-related macular degeneration, foveal edema secondary to retinal vein occlusion, and center-involved diabetic macular edema. As a result, intravitreal injection (IVI) is now the most common ophthalmic procedure in the United States—and among the most common in all of medicine. These trends seem likely to continue, given the aging of the population.

The procedure is seemingly simple but requires many small maneuvers that can introduce inefficiency and compromise sterility along the way. Although the safety profile of IVI is well established, complications can lead to devastating visual outcomes, said Kenneth Taubenslag, MD, at the Vanderbilt University Medical Center in Nashville, Tennessee. “You really need to strive for perfect technique and stay up to date on best practice guidelines because, in the end, IVIs are not as trivial as meets the eye,” he said.

**Taking It Step by Step**

In many academic institutions and resident-run clinics, trainees perform a majority of IVIs—learning from faculty everything from proper consent and tray organization to body position and injection location. “For practicing ophthalmologists, reviewing these steps is also important,” said Lisa S. Schocket, MD, at the University of Maryland Medical System in Baltimore. “We perform so many of these injections that we often forget about where the mistakes can be made.”

**Knowing the indication.** It might seem obvious, but first the physician should determine whether the patient needs to undergo the procedure, said Sharon D. Solomon, MD, at the Wilmer Eye Institute in Baltimore. “Does the patient indeed have active choroidal neovascularization, for example, or center-involved diabetic macular edema that’s causing significant vision loss? Depending on the clinical indication, the patient may do well without IVI treatment,” she said.

**Patient consent.** Communicating risk is another important step prior to performing the IVI, said Dr. Solomon. The ophthalmologist needs to explain to the patient why therapy is recommended in the first place and to make sure that the patient has a good understanding of the potential complications of the procedure, including the risk of endophthalmitis, retinal tear, vitreous hemorrhage, and puncture of the lens, which can cause premature cataract progression, she said. (For more about informed consent, see [omic.com/anti-vegf-drugs-in-adults.](https://omic.com/anti-vegf-drugs-in-adults.)

**A tidy workspace.** Keeping your Mayo stand clean and positioned correctly is also critical, said Dr. Schocket. “I make it very clear to our residents from day one that they must keep an organized workspace for two important reasons. One, you’re more likely to make a mistake if you’re trying to navigate chaos, and two, you want to convey to the patient that they are in a clean and organized environment and that you are serious about preventing infection.” If a patient develops a postoperative complication, it’s important to know that you did everything possible to prevent infection and that you gave the patient a sense of confidence in your care, she said.

**Separating the syringes.** If your anesthetic preference is a subconjunctival lidocaine injection rather than topical jelly, be sure that you draw (and apply) the agent before drawing the anti-VEGF medication in a second
syringe, said Dr. Schocket. “Don’t leave two drawn syringes on your tray. This is something that seems obvious but, remember, we’re trying to eliminate any variable that can introduce risk.” Drawing up the two syringes at once can lead to accidentally swapping the order of the injections.

**Body positioning.** Placing yourself in proper relation to the patient is another often overlooked aspect of performing an IVI. “Avoid having the patient sit upright,” said Dr. Solomon. A recumbent position is more comfortable for the patient, and it allows the ophthalmologist to have more control over the patient’s body. “It also leads to better adherence of the povidone-iodine [Betadine] antiseptic to the eye’s surface since nothing will be running down the patient’s face,” she said.

For reasons of body positioning, Dr. Schocket prefers injecting inferotemporally in case the patient lifts an arm or leg toward the eye. Standing next to the patient’s body rather than at the head of the bed allows the physician to prevent the patient from moving or reaching forward.

**Precise injection site.** To prevent lens touch, the ophthalmologist should aim for injection 4.0 mm behind the limbus in phakic patients and 3.5 mm for pseudophakic and aphakic eyes, said Dr. Schocket. “Injecting the drug too close to the lens will cause an instant cataract, while an injection that is too posterior can cause a retinal tear,” she said. And for maximum safety, she instructs her residents to place the needle fully into the vitreous cavity before injecting—not halfway or a quarter of the way.

**Preventing Endophthalmitis**
The most feared complication of IVI is infectious endophthalmitis. Incidence rates are low, ranging from 0.019% to 0.09%, but visual prognosis is poor despite current treatments. That’s why it’s especially important to be aware of the most up-to-date clinical protocols for IVIs—as they’re in a constant state of refinement, said Dr. Taubenslag.

**Lid retraction.** Eyelids and eyelashes are significant sources of infection, and the lid speculum is the most common tool for avoiding any contamination of the procedural needle. But is it the only way? Not necessarily, said Dr. Taubenslag. To prevent the eyelids and eyelashes from coming in contact with the injection site, he often performs intravitreal injections with manual eyelid retraction. He noted that many patients prefer this, as clumsy insertion or removal of the speculum can be uncomfortable and even cause corneal abrasions in rare cases. Nevertheless, he said, “I would always encourage use of the lid speculum for procedures requiring anterior chamber paracentesis, for tap and inject, and for those patients who have difficulty keeping their eyes open or following instructions.”

**Betadine.** Drs. Schocket and Solomon are strong proponents of lid speculums, especially in combination with Betadine. “In my experience, these are the two most important ways to prevent infection,” said Dr. Solomon. For the IVI clinical trials in which she has participated, she noted that patients with Betadine allergies are excluded. “It’s mandatory,” she said. For injection prep, she places the sterile lid speculum inside the eyelid and applies 5% Betadine to the conjunctiva and 10% to the eyelids and eyelashes (Fig. 1). Because the antiseptic can be caustic, she thoroughly rinses the eye with sterile saline solution following the procedure.

**Lidocaine use.** To gel or not to gel is a controversial topic when considering the delivery of lidocaine. Recent studies have shown that the use of lidocaine jelly or tetracaine gel may increase the risk of endophthalmitis following IVI. The reasoning is that the gel can act as a barrier to antisepsis, preventing the Betadine from coming in contact with the conjunctiva and therefore promoting bacterial survival prior to the injection, said Dr. Schocket.

Other studies have shown that subconjunctival 2% lidocaine/0.1% methylparaben may actually reduce the incidence of endophthalmitis after IVI due to the methylparaben’s intrinsic antibacterial properties. It’s also believed that the subconjunctival lidocaine dilutes any pathogens adhering to the injection needle, retarding the entry of bacteria from the ocular surface through the injection track.3

“I’ve certainly witnessed cases of endophthalmitis following the use of lidocaine gel,” said Dr. Taubenslag. However, he pointed out that it has advantages. For example, it can be applied by staff and therefore may help with patient flow in a busy clinical environment. “What is critical is to ensure that the Betadine is applied prior to the application of the gel anesthetic and once again prior to injection,” he said.

**Masking and draping.** The COVID-19 pandemic has created a need for personal protective equipment for both physicians and patients. Early advocates assumed that universal mask protocols would also be beneficial for reducing risk of infection during IVIs. However, now that all patients are masked due to COVID-19, it is crucial to either tape the upper edges of the mask to create a seal or use an adhesive surgical drape around the eye that is being injected.

—Dr. Schocket
patient’s breath toward the eye,” she said. Now that all patients are masked due to COVID-19, she said that it is crucial to either tape the upper edges of the mask to create a seal or use an adhesive surgical drape around the eye that is being injected.

**Patient Takeaways**

Because IVIs are used to treat so many retinal diseases, there’s a tremendous burden on ophthalmologists to perform the safest in-office procedure possible. And the risk of complications doesn’t end when the patient walks out the door. That’s why Dr. Solomon recommends handing out documentation of warning signs and symptoms. “Especially if this is their first injection, it’s good practice to provide your patient with a checklist of troublesome symptoms—decreased vision, flashes of lights, floaters, shadows, infection, anything new that seems unusual from baseline. This will ensure that in the rare event a complication does arise, you and your patient can quickly address the situation.”


Dr. Schocket is an associate professor and chief of the retina division at the University of Maryland Medical System in Baltimore. Relevant financial disclosures: None.

Dr. Solomon is a professor of ophthalmology at the Wilmer Eye Institute in Baltimore. Relevant financial disclosures: None.

Dr. Taubenslag is a second-year fellow and instructor in ophthalmology and visual sciences at the Vanderbilt University Medical Center in Nashville, Tenn. Relevant financial disclosures: None. For full disclosures, view this article at [aao.org/eyenet](http://aao.org/eyenet).

**MORE ONLINE.** View this article at [aao.org/eyenet](http://aao.org/eyenet) to see an example of proper tray setup and for advice about pre- and intra-operative care of cataract surgery patients who have undergone even a single IVI.
Diabetic Macular Edema: Diagnosis and Management

Diabetic retinopathy (DR) is the leading cause of new cases of blindness among adults aged 18 to 64 years in the United States. Diabetic macular edema (DME), a severe complication of DR that occurs specifically as a result of inadequately treated diabetes mellitus (DM), has overtaken proliferative diabetic retinopathy as the most common cause of vision impairment in individuals with DM. In recent epidemiologic studies, approximately 30% of patients worldwide with DM were found to have vision-threatening DR; and in the United States, 3.8% of patients were found to have DME.

DME, which is characterized by hard exudates and edema within the macula secondary to damage to retinal microvasculature, is detected by clinical examination or with OCT. Before the advent of pharmacotherapy for DME, first-line treatment was focal laser photocoagulation of the macula. More recently, clinical evidence from the DRCR.net has established intravitreal anti-VEGF injections as the first-line therapy, followed by the use of intravitreal corticosteroids if treatment response is unsatisfactory.

Etiology and Pathogenesis

DR. DR develops from the loss of both endothelial tight junctions and pericytes in retinal capillaries, eventually leading to leakage of protein, lipids, inflammatory molecules, and other plasma components into the interstitial space. Further production of proinflammatory cytokines and VEGF by retinal pigment epithelium, glial cells, and macrophages leads to breakdown of the blood-retina barrier, causing further leakage of fluid into the retina.

DME. DME arises from the accumulation of fluid, protein, and lipids throughout the layers of the retina in the form of intraretinal cystic spaces, best seen by OCT. It is now believed that the etiology of DME, though complex, is largely twofold.

First, retinal microvascular obstruction and capillary dropout throughout the retina in patients with poorly controlled DM lead to retinal ischemia. The subsequent hypoxia-induced upregulation of VEGF then causes neovascularization both in the retinal periphery and in existing macular vessels, increasing vascular permeability.

Second, in many patients with long-standing DM, production of free radicals and accumulation of advanced glycosylation end products cause upregulation of proinflammatory cytokines such as interleukin (IL)-1β and IL-6. This process leads to further vision-threatening consequences of DME as inflammation develops and vascular pericytes are lost. Compromised junctional proteins in macular microcapillaries cause them to become more liable to leakage, contributing to the extravascular fluid and hard lipid exudates that are a hallmark of DME.

Diagnosis and Screening

Because of the insidious nature of both DR and DME, all diabetic patients should have an ophthalmic evaluation to screen for eye disease, consisting of a comprehensive eye examination, with ancillary testing and imaging as appropriate. According to the Academy’s Preferred Practice Patterns guidelines for DR, patients with type 1 DM should be screened for DR starting five years after diagnosis of DM, while patients with type 2 DM should be screened for DR upon diagnosis and then annually or more often, depending on the severity of their systemic disease.
Imaging. OCT has become a mainstay in screening and diagnosis. This modality allows clinicians to detect thickening, structural changes, and edema that are difficult to capture in a clinical funduscopic exam.

Nonmydriatic or mydriatic digital retinal photography is often used in comprehensive ophthalmology settings for noninvasive screening. It has the potential to be employed in combination with advanced artificial intelligence algorithms that automate the diagnostic process.8,9

Classification. After DME has been detected, a detailed clinical examination is needed to determine its severity. DME is typically classified in the following three categories:

• Mild: Retinal thickening and hard exudates are present in the posterior pole but fall more than 1,000 µm outside the central macular subfield.

• Moderate: Retinal thickening or hard exudates are present within the central subfield of the macula but do not involve the center.

• Severe: Retinal thickening or hard exudates involve the center of the macula.10

Treatment and Prevention
Treatment of DME begins with management of the systemic disease. Stringent regulation and treatment of hyperglycemia, hypertension, and hyperlipidemia can delay the onset and progression of various microvascularopathies, including DR and DME.

Treatment options for DME vary depending on the severity of disease and the patient’s baseline visual acuity (VA). However, on the basis of recent studies by the DRCR.net, discussed below, ophthalmologists have generally adopted anti-VEGF intravitreal therapy as the first-line treatment. (See Table 1 for an overview of treatment studies.)

Laser. Laser photocoagulation became the primary therapy for DME in the mid-1980s, when the Early Treatment Diabetic Retinopathy Study demonstrated its ability to decrease the risk of vision loss. However, the introduction of anti-VEGF drugs in the 2000s changed the treatment paradigms because these drugs can reverse vision loss, an outcome that is uncommon with laser therapy.11 The DRCR.net Protocol I study showed a significant improvement in participants treated with ranibizumab and laser therapy (whether on a fixed or flexible schedule) compared with those treated with sham injections and laser therapy.

Anti-VEGF agents. The RISE and RIDE studies, performed in 2010, looked at three groups of patients with a baseline VA of 20/30 or worse: The

<table>
<thead>
<tr>
<th>Study</th>
<th>Groups</th>
<th>Conclusions</th>
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| Protocol I | • Sham + laser  
• Ranibizumab + laser  
• Ranibizumab + deferred laser  
• Corticosteroid + laser | Both groups that received ranibizumab showed greater improvement (independent of when laser photocoagulation was performed) than other groups. |
| RISE/RIDE | • Sham injections  
• 0.3-mg ranibizumab  
• 0.5-mg ranibizumab | Both dosages of ranibizumab improved VA compared with sham injections. |
| VISTA/VIVID | • Intravitreal aflibercept injection (IAI)  
2 mg every 4 weeks (2q4)  
• IAI 2 mg every 8 weeks after 5 initial monthly doses (2q8)  
• Macular laser photocoagulation | Both IAI groups had similarly effective improvement in BCVA, significantly superior to those in the laser photocoagulation group. |
| Protocol T | • Ranibizumab  
• Bevacizumab  
• Aflibercept | All three anti-VEGF agents are effective when VA loss is mild. In more severe cases, aflibercept is significantly more effective than the other two in improving VA and reducing central retinal thickness on OCT. |
| Protocol V | • Observation  
• Laser photocoagulation  
• Aflibercept | No significant difference was seen between patients who were initially managed with aflibercept and those who were given aflibercept only when VA worsened from baseline by 10 letters. |
| Protocol U | • Ranibizumab + sham  
• Ranibizumab + dexamethasone implant | Simultaneous administration of corticosteroids with ranibizumab decreased retinal thickness on OCT at six months, but the addition of steroid did not yield better VA results than ranibizumab alone. |
| MEAD | • Dexamethasone 0.35 mg  
• Dexamethasone 0.7 mg  
• Sham procedure | Improved BCVA in the dexamethasone groups was significantly greater than sham. |
treatment groups received either 0.3-mg or 0.5-mg doses of ranibizumab, and a control group received sham injections. Both treatment groups experienced greater improvement in BCVA than did the control group.12

Similarly, in the VISTA and VIVID studies of patients with central DME, 2 mg of intravitreal aflibercept, administered either every four or eight weeks (the latter after five monthly doses), produced visual gains that were far superior to the results with laser therapy.13

The DRCR.net Protocol T study compared the efficacy of the three anti-VEGF drugs currently in widespread clinical use for DME: ranibizumab, aflibercept, and bevacizumab (used off label). Participants were randomly assigned to one of the three treatment groups. The study concluded that aflibercept is the most effective drug for DME, intravitreal corticosteroid implants have been associated with variable outcomes. For example, in the DRCR.net Protocol U study, patients with persistent DME who received intravitreal dexamethasone implants in combination with ranibizumab had decreased retinal thickening on OCT, although BCVA did not improve.

In the MEAD study of a dexamethasone implant, patients who completed the trial had a 0.9 letter gain in BCVA compared with those who dropped out. Among the participants, 37.5% had no change in BCVA, while 23.2% gained more than 10 letters, and 16.0% lost more than 10 letters.15

Putting it together. These data suggest a stepwise approach to treatment (see Table 2), with anti-VEGF treatment initiated in patients with moderate to severe DME (VA of 20/30 or worse). Approximately three months or more after starting anti-VEGF treatment, the patient should be reevaluated clinically and with OCT, and further treatment options should be considered if VA and/or central macular thickness have not improved or stabilized sufficiently. If the response to anti-VEGF therapy is suboptimal at this point, some retina specialists choose to initiate intravitreal corticosteroid therapy and focal or grid laser photocoagulation, while many others prefer to continue with six months of anti-VEGF injections before considering intravitreal corticosteroid therapy.

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**Table 2: Stepwise Approach to DME Treatment**

<table>
<thead>
<tr>
<th>Is central involvement detected on OCT?</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. If no, recommend tight glycemic control and observe.</td>
</tr>
<tr>
<td>II. If yes, evaluate the patient’s visual acuity.</td>
</tr>
<tr>
<td>A. If VA is better than 20/30, observe or begin treatment with anti-VEGF drugs or focal or grid laser photocoagulation.</td>
</tr>
<tr>
<td>B. If VA is 20/30 to 20/40, begin anti-VEGF therapy with any of the three agents (afibercept, bevacizumab, ranibizumab).</td>
</tr>
<tr>
<td>C. If VA is 20/50 or worse, begin anti-VEGF therapy with aflibercept.</td>
</tr>
<tr>
<td>1. If anti-VEGF treatment fails or response is suboptimal, consider switching to a different anti-VEGF agent.</td>
</tr>
<tr>
<td>2. After 24 weeks of anti-VEGF failure or suboptimal response, consider intravitreal corticosteroid or focal or grid laser photocoagulation.</td>
</tr>
</tbody>
</table>

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Ms. Elyasi is a medical student at the Bruce and Ruth Rappaport Faculty of Medicine at the Technion Israel Institute of Technology, Bat Galim, Haifa, Israel. Dr. Hemmati is a cornea specialist and chief medical officer of Optigo Biotherapeutics, Vancouver, B.C., Canada. Relevant financial disclosures: Ms. Elyasi: None. Dr. Hemmati: Cell Care Therapeutics: C,O; Optigo Biotherapeutics: E,O.

See disclosure key, page 5. For full disclosures, see this article at aao.org/eyenet.
EYLEA® (aflibercept) Injection
For Intravitreal Injection

Inspired by a real patient with DME.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS

• EYLEA is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

WARNINGS AND PRECAUTIONS

• Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.

• Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

• There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the control group compared with 3.3% (19 out of 595) in the ranibizumab group. The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

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777 Old Saw Mill River Road, Tarrytown, NY 10591
EYLEA ACHIEVED RAPID, SUSTAINED OUTCOMES IN DME

Demonstrated efficacy outcomes in VISTA and VIVID, phase 3 anti-VEGF trials in DME (N=862)¹

Mean change in BCVA (ETDRS letters) at Year 1 from baseline²⁻⁵,*

<table>
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<tr>
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<th>Initial Gains (Month 5)</th>
<th>Primary Endpoint (Year 1)</th>
<th>Prespecified Exploratory Endpoint (Year 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VISTA</td>
<td>VIVID</td>
<td>VISTA</td>
</tr>
<tr>
<td>EYLEA Q4</td>
<td>+10.3 (n=154)</td>
<td>+9.3 (n=136)</td>
<td>+12.5 (n=154)</td>
</tr>
<tr>
<td>EYLEA Q8</td>
<td>+9.9 (n=191)</td>
<td>+9.3 (n=135)</td>
<td>+10.7 (n=191)</td>
</tr>
<tr>
<td>Control</td>
<td>+1.8 (n=154)</td>
<td>+1.8 (n=132)</td>
<td>+0.2 (n=154)</td>
</tr>
</tbody>
</table>

P<0.01 vs control at Year 1.

The analyses of these exploratory endpoints were not multiplicity protected and are descriptive only.

Year 2 data was consistent with results seen in Year 1.³

VISTA and VIVID study designs: Two randomized, multicenter, double-masked, controlled clinical studies in which patients with DME (N=862; age range: 23-87 years, with a mean of 63 years) were randomized and received: 1) EYLEA 2 mg Q8 following 5 initial monthly doses; 2) EYLEA 2 mg Q4; or 3) macular laser photocoagulation (control) at baseline and then as needed. From Week 100, laser control patients who had not received EYLEA rescue treatment received EYLEA as needed per re-treatment criteria. Protocol-specified visits occurred every 28 (±7) days.¹

In both clinical studies, the primary efficacy endpoint was the mean change from baseline in BCVA at Week 52, as measured by ETDRS letter score.¹

*Last observation carried forward; full analysis set.

¹Following 5 initial monthly doses.

SEE WHAT EYLEA COULD DO FOR YOUR PATIENTS WITH DME AT HCP.EYLEA.US

anti-VEGF, anti-vascular endothelial growth factor; BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; Q4, every 4 weeks; Q8, every 8 weeks.

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.
- Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

INDICATIONS

EYLEA*(aflibercept) Injection 2 mg (0.05 mL) is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).


Please see Brief Summary of Prescribing Information on the following page.
Intraocular inflammation 2% 3% 3% 4%
Eyelid edema 1% 2% 2% 3%
Cataract 7% 7% 13% 10%
Retinal detachment <1% <1% 1% 1%
Corneal edema 1% 1% 1% 1%
Retinal pigment epithelium tear 2% 1% 2% 2%

The data described below reflect 6 months exposure to EYLEA with a endophthalmitis.

Retinal detachment <1% <1% 1% 1%
Corneal edema 1% 1% 1% 1%
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Attend a free EyeNet® Corporate Lunch during AAO 2021.

Check aao.org/eyenet/corporate-lunches for updated program information.

Ernest N. Morial Convention Center
Room R02-05, 2nd Floor

Check-in and Lunch Pickup
12:15-12:45 p.m.
Lunches are provided on a first-come basis.

Program
12:45-1:45 p.m.

SATURDAY, NOV. 13
First-Line Treatment in Diabetic Retinopathy and Diabetic Macular Edema: A Patient Case-Based Approach
Speaker: Nathan Steinle, MD
Presented by Regeneron Pharmaceuticals and designed for US retina specialists.

SUNDAY, NOV. 14
Navigating Dry Eye Disease: An Audience-Activated Adventure
Speaker: Jay K Mattheis, MD, MSPH, FACS—Director, Peer Education for Novartis - US Ophthalmics
Dr. Mattheis is an employee of Novartis. Presented by Novartis Pharmaceuticals Corporation and designed for US eye care specialists.

MONDAY, NOV. 15
A Difference in Drug Delivery
Speakers: Ike Ahmed, MD (moderator), Oluwatosin Smith, MD, and Savak Teymoorian, MD
Presented by Allergan, an AbbVie Company and designed for US ophthalmologists.

These programs are non-CME and are developed independently by industry. They are not affiliated with the official program of AAO 2021 or Subspecialty Day. By attending a lunch, you may be subject to reporting under the Open Payments Program (Sunshine Act). Also, by attending a lunch, you consent to share your contact data, inclusive of National Provider ID, with the corporate partner.
Developers of biosimilar drugs have been running a fast-moving global race since the first biologic therapies lost their patents in 2015. And the stakes are only increasing, because drug makers now face a second “patent cliff” as the next round of biologics is slated to come off patent in the next few years.1

In ophthalmology, the push to develop biosimilars is taking place amid a rapidly changing landscape. For instance, a 2020 study found 25 ophthalmic biosimilars in development: four for aflibercept (Eylea), eight for bevacizumab (Avastin), six for ranibizumab (Lucentis), and seven for adalimumab (Humira).1 But just a few months after the study was published, multiple mergers and collaborations—and even outright abandonment of several products—had occurred.

Despite this uncertainty, it’s just a matter of time before ophthalmologists will have the option of using one or more of these novel drugs. And as with any pharmaceutical product, biosimilars will have to clear a series of hurdles, from study design to assessments of safety and efficacy, cost issues, and off-label use, before they achieve broad-based acceptance by clinicians.

Biosimilar Basics

**What they are.** Technically, biosimilars are molecules with similarity to existing biologic medications, which are known as their innovator biologics or reference medicines. And as with their related biologic drugs, the development of biosimilars is continuing to evolve along with cell line science, protein expression science, and bioengineering.2

But biosimilars offer a compelling alternative to their preexisting counterparts: With biosimilar product development, pharmaceutical companies are able to create drugs similar enough to proven biotherapeutics in safety and efficacy—and they can do so more quickly and at a lower cost.1

For instance, an average innovator biologic costs $1.2 billion to $2.5 billion (in U.S. dollars) and takes roughly 10 to 15 years to develop. In contrast, research and development (R&D) for a biosimilar takes eight to 12 years—and costs $100 million to $200 million.1 Theoretically, those cost savings are then passed on to patients and insurance companies.

**What they aren’t.** Biosimilars are not generics. Generic drugs are small molecules, relatively simple to duplicate and manufacture. Innovator biologic drugs are 100 to 1,000 times larger than generics and are made up of hundreds of amino acids biochemically married in a particular sequence within a living cellular system.2 Biosimilar versions of biologics are just as complex as their reference medicines.

“A biosimilar is not just a copy of a product like a generic, since much more R&D and scientific study goes into biosimilars than generics,” said
Ashish Sharma, MD, at Lotus Eye Hospital and Institute in Coimbatore, India. “They’re highly researched molecules.”

**From Bench to Clinic**

**The road to approval.** The FDA’s current standard for approving biosimilars is as follows: “A biosimilar is highly similar to, and has no clinically meaningful differences in, safety, purity, and potency (safety and effectiveness) from an existing FDA-approved reference product. The goal of a biosimilar development program is to demonstrate biosimilarity between the proposed biosimilar product and the reference product, not to independently establish the safety and effectiveness of the proposed product.”3 (See “Safety and Efficacy,” below.)

**The road to acceptance.** Biosimilars face a unique challenge in that they may be perceived differently than standard medications and thus can trigger a level of skepticism akin to the “no-cebo effect,” Dr. Ashish Sharma said. He argues that “Physicians shouldn’t be too skeptical [about] using them, since everything about the active molecule—primary structure, dynamics, pharmacokinetics—has been shown [to be] similar” to the reference medicine.

**Study Design**

How should clinicians assess studies of biosimilars?

**Focus on equivalency.** Biosimilar drugs aren’t required to be put through phase 1 or 2 clinical trials with one or two years of follow-up data.

“For a biosimilar, you want to show it’s equivalent—it works the same as—the reference product, not worse and not better,” said Neil M. Bressler, MD, at the Wilmer Eye Institute in Baltimore. “You can’t figure out if it’s exactly the same because it’s a biologic agent; that’s why showing that you have an ‘equivalent’ product is the standard.”

An equivalency study sets out to prove that the biosimilar has equivalent biologic activity, Dr. Bressler said. “If you show that the biosimilar acts the same [as the reference medication] out to eight weeks, you don’t need primary outcomes out to one or two years—though during those eight weeks of testing you have to show that there aren’t any safety issues,” Dr. Bressler said.

**What does this shorter trial mean for ophthalmologists?** “They need to know that the equivalency shown within a [phase 3] randomized clinical trial of the biosimilar and its reference product may be accepted by regulatory agencies as sufficient proof that the biosimilar is the same as the proven product,” said Dr. Bressler.

For instance, this might involve data on anatomic improvement of abnormal retinal thickening or vision outcomes in the short term, he noted. “It may be a new concept to recognize that if you show it’s an equivalent product [for these outcomes] out to four or eight weeks, then you [researchers and clinicians] have confidence that the biosimilar should act as the reference product acted over one or two years.”

**Understand nuances.** What if a biologic is a monoclonal antibody produced by a cell culture? “The aflibercept that was tested in initial phase 3 clinical trials 10 years ago may not be the identical product in 2020, because the cell cultures that produced the aflibercept in 2010 may be different from the cultures producing aflibercept in 2020, even if the methods for producing those cell cultures are kept constant,” said Dr. Bressler. “With a biosimilar, if it acts the same as the reference product on retinal structure or vision, we’re under the presumption that it will continue to act the same as the reference product after two years.”

In the early days of biosimilars, before the development of global regulations on these products, several “biomimics”—that is, noncomparable biotherapeutic products—appeared in some countries.2 With guidelines now in place, a biosimilar may even improve on the potency, half-life, or other characteristic of the innovator molecule and become its “biobetter.”2

**Safety and Efficacy**

Global protocols for biosimilar approval are constantly changing, but in the United States, the FDA generally erects three hurdles: analytical proof of biosimilarity, an animal study on toxicity, and a brief clinical study.4

**Burden of proof.** “What ophthalmologists need to recognize is that the burden of proof is very different with biosimilars,” said Sumit Sharma, MD, at the Cole Eye Institute in Cleveland, Ohio. “The approval process only needs to show that it’s essentially equivalent in activity and side effect...
profile, but it doesn’t need to show that it’s exactly the same. Physicians should have a high index of suspicion if they don’t think it will function the same.”

The underlying assumption for each biosimilar is that safety and efficacy were already proven for the reference product. “All the manufacturer has to show is that it’s biosimilar—similar in absorption, in elimination, in levels that it reaches, and in vitro activity,” Dr. Sumit Sharma said. “They don’t actually have to show safety and effectiveness in a biosimilar, so in most cases, it will be safe, but you don’t know for sure.”

Not an identical twin. The FDA looks for data showing similarity with the reference drug in terms of safety and efficacy, but the data will never be exactly the same as that achieved with the original product, he said. “In the antibody production process, a number of phases need critical purification steps to get to a level of purity and avoid toxicity—for example, when you inject in the eye versus subcutaneously—and they’re not required to show the safety side of that,” he explained.

Research Spotlight

Several biosimilars with ophthalmic potential:

Razumab (Intas) is the first biosimilar of ranibizumab to be available on a global basis. It was approved by the Drug Controller General in India in 2015.

Use for wet AMD. In India, Shashikant Sharma et al. evaluated the long-term use of Razumab injections across 17 sites in the RE-ENACT 2 study.1 The researchers evaluated 103 patients with wet AMD. Improvements were noted in all parameters, including best-corrected visual acuity (BCVA), central subfield thickness, intraretinal fluid, and subretinal fluid. No significant changes in intraocular pressure occurred, and there were no new safety concerns.

Use for other indications. Also in India, Ashish Sharma et al. retrospectively compared outcomes of patients switched from ranibizumab to Razumab.2 This study involved 20 patients with wet AMD, retinal vein occlusion, and diabetic macular edema. No clinical signs of immunogenicity or change in efficacy were noted with the biosimilar.

Renflexis (infliximab-abda; Merck) is one of the biosimilars of infliximab.

Use for uveitis. In the United States, Deaner et al. retrospectively evaluated the frequency of ocular flares in patients with noninfectious uveitis who were switched to Renflexis for nonmedical (i.e., insurance coverage) reasons.3 The researchers assessed 17 patients. The frequency of new or worsening ocular flares increased when patients were switched to the biosimilar, especially within the first 90 days. Most of the ocular flares resolved with increased dosage of Renflexis.

Post-Translational Changes

A variety of post-translational modifications can happen on the way to the clinic. For instance, structural changes can occur between batches of a given biologic, due to oxidation, glycation, and other processes.2 “When a biosimilar antibody is made, the type of bacterial or nonbacterial system it’s made in is proprietary, as are the purification steps taken,” said Dr. Sumit Sharma. Thus, “while the antibody sequence is released to the public, the way it’s made is not.”

Again, not an identical twin. Without a proven blueprint of the entire process, a drug maker is left trying to reverse-engineer a complex, macrocellular product. Almost by definition, a biosimilar may never be exactly the same as its reference product.

Do these minor differences matter? “One of the things we’ve discovered with antibody production is that the process really matters,” Dr. Sumit Sharma said. “If you go back to the beginning of the anti-VEGF era, a number of process improvements were made to reduce inflammation rates. But will all of the biosimilars go through those same process...
improvements, since they’re not required to do a large study on safety?” After all, as with the initial, detailed manufacturing process for a biologic, all of those early improvements are also proprietary.

In her study, Eva R. Kabir, PhD, put it succinctly: Even small variations in process or structure between a biosimilar and its reference biologic can change the safety and efficacy of a biosimilar.2

**True Cost Savings?**

As the global race for biosimilars continues, will the promised cost savings materialize? That may depend on where you practice.

**Location, location, location.** “In India, because we have a big need for cost-effective medications, we’re fine with clinical data from only 120 patients, whereas it’s $2,600 for the originator infliximab, ” said Dr. Ashish Sharma. “Biosimilars help solve the problem of lack of insurance in India, Brazil, and other South American countries, where we pay from the pocket.”

Both biologics—and their biosimilar cousins—are made in an expensive, iterative process. While the innovator molecule bears the financial brunt of development, reverse-engineering a biologic to a biosimilar is still costly.

“A company has to spend a lot of money, so it’s not a big price cut, usually about 30% to 40% in India,” said Dr. Ashish Sharma. “It’s also expensive to enter a new country because regulatory requirements are different.”

Moreover, low-resource countries may already have long-term supplier contracts in place. “A lot of poorer countries already have deals with the big pharmaceutical companies to get access to their medications for much cheaper than what we pay in the United States, sometimes for less than what the biosimilar would cost them,” said Dr. Sumit Sharma. For instance, he said, “When you look at adalimumab [Humira], the average price per dose in the United States is $4,400—but in South Africa, it’s $740.”

Within the United States, some biosimilars may not have dramatic cost savings over their innovator drugs. “With infliximab-dyyb [Inflectra], a biosimilar for infliximab, the eight-week cost is $2,100, whereas it’s $2,600 for the originator infliximab,” said Dr. Sumit Sharma.

“There have been a number of studies looking at the cost savings using biosimilar infliximab in the United States, and while insurance companies may require it, the overall cost saving is not huge,” he said.

**Off-Label Use**

A specific challenge for ophthalmologists is off-label use of biosimilars from other medical disciplines—for example, infliximab for uveitis.

**Ophthalmology is not rheumatology.** “The rheumatologic literature finds the biosimilar Renflexis [infliximab-abda] identical to Remicade [infliximab] in terms of activity, but if you look at activity in the eye, we found that it required higher doses to get the same efficacy,” said Dr. Sumit Sharma (see “Research Spotlight”). “Because it’s off label, there were no studies required from the FDA to approve the biosimilar for [ocular] use, so we have no data on its efficacy in the eye.”

**All for one—and one for all?** A further issue is that “a biosimilar company only has to get approval for one indication, and they’ll get approval for all indications,” said Dr. Sumit Sharma. “You often don’t see the safety signals until you’re looking at hundreds or thousands of patients, so no one has data yet on the safety or efficacy of these medicines. The FDA requires equivalency data in terms of pharmacodynamics and pharmacokinetics. It doesn’t require safety and efficacy data, and that’s the challenge.”

Jennifer K. Sun, MD, MPH, agreed that the core issues are safety and efficacy. “The difficulty with biosimilars is making sure that we have the level of evidence so that we thoroughly understand their efficacy and their safety profile as we start to use them in place of FDA-approved [reference] drugs,” said Dr. Sun, at Harvard. “It may be that while biosimilars are similar to agents accepted for use, there may be small differences in molecular structure or the pathways they influence, so there’s always a possibility of off-target effects that we would want to be aware of.”

**Looking Ahead**

What should you expect in the near future?

**Advent of anti-VEGF biosimilars.** “The biggest change will happen when the anti-VEGF biosimilars enter the market in the next three to five years,” said Dr. Sumit Sharma.

Dr. Sun agreed. In ophthalmology, “a lot of what drives the biosimilar question has to do with the financial burden of anti-VEGF treatment,” she said. “Anything that changes the ability of patients to pay for these medications, with similar safety and efficacy, will be a key

For Further Reading


Sharma A et al. *Eye* (Lond). Published online June 22, 2021.

driver of how they get used.”

**Need for comparative effectiveness studies.** In addition, a different kind of research is needed, said Dr. Sun, who serves as one of the chairs of the DRCR Retina Network, a collaboration of clinical research sites for retinal disease. “It’s going to be critical as these biosimilars come down the pike, both for clinicians and patients, to have good-quality comparative effectiveness studies.”

Dr. Sun suggested several models for high-quality studies: “Comparative effectiveness studies—like the network’s Protocol T (for diabetic macular edema), as well as the CATT study and Ivan study (for neovascular AMD)—have really been essential for us to be able to make individual treatment decisions between medications in these very common retinal diseases with enormous public health impact.”

**Need for MD awareness.** Given the rapidly expanding pipeline of biosimilars, physicians will be challenged to stay up to date—and to do so, they will need evidence from well-designed studies. “That’s why it’s critical for federal and foundation funding to do these objective comparative studies, which may not be the primary interest of any one specific industry player,” Dr. Sun said.

Of note, information on biosimilars is available on the FDA’s website (www.fda.gov). At time of press, 28 biosimilars had been approved (search for “Biosimilar Product Information”).

**The Bottom Line**

Will biosimilars live up to their promise? While the answer is unknown, it’s clear that expert opinions on the pros and cons of biosimilars are as varied as the biotherapeutics themselves—and a number of issues remain to be resolved.

“Having biosimilars is a fantastic idea, but I don’t think [the way that] the approval process, the safety data process, and the pricing have turned out has been enough of a boon in the U.S. market as was hoped for,” Dr. Sumit Sharma concluded.

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**Meet the Experts**

- **Neil M. Bressler, MD** The James P. Gills Professor of Ophthalmology at the Wilmer Eye Institute, Johns Hopkins University School of Medicine in Baltimore and editor-in-chief of *JAMA Ophthalmology*. Relevant financial disclosures: Bayer: S; Biogen: S; Genentech/Roche: S; Novartis: S; Regeneron: S; Samsung Bioepis: S. (Note: All research income is paid to the Johns Hopkins University School of Medicine.)

- **Ashish Sharma, MD** A vitreoretinal specialist at Lotus Eye Hospital and Institute in Coimbatore, India. Relevant financial disclosures: Allergan: C,L; Bayer: C,L; Intas: C,L; Novartis: C,L.

See disclosure key, page 5. For full disclosures, see this article at aao.org/eyenet.
•  Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA.

•  Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments.

WARNINGS AND PRECAUTIONS

•  EYLEA is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

•  Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.

•  Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

•  There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

EYLEA® (aflibercept) Injection

For Intravitreal Injection

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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Proportion of patients who gained ≥15 ETDRS letters (primary endpoint) and mean change in BCVA (ETDRS letters) (secondary endpoint) at Month 6 from baseline vs control1-4.*

<table>
<thead>
<tr>
<th>Study</th>
<th>Gained ≥15 ETDRS letters</th>
<th>Mean change in ETDRS letters</th>
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<tbody>
<tr>
<td>VIBRANT (MEfBRVO)</td>
<td>EYLEA (n=91) 53% vs 27% in the control group (n=90)</td>
<td>+17.0 vs +6.9 in the control group (n=90)</td>
</tr>
<tr>
<td>COPERNICUS (MEfCRVO)</td>
<td>EYLEA (n=114) 56% vs 12% in the sham control group (n=73)</td>
<td>+17.3 vs -4.0 in the sham control group (n=73)</td>
</tr>
<tr>
<td>GALILEO (MEfCRVO)</td>
<td>EYLEA (n=103) 60% vs 22% in the sham control group (n=68)</td>
<td>+18.0 vs +3.3 in the sham control group (n=68)</td>
</tr>
</tbody>
</table>

P<0.01 vs control and sham control.

**VIBRANT study design:** Randomized, multicenter, double-masked, controlled study in which patients with MEfBRVO (N=181; age range: 42-94 years, with a mean of 66 years) were randomized to receive: 1) EYLEA 2 mg Q4 or 2) laser photocoagulation administered at baseline and subsequently as needed (control group). The primary efficacy endpoint was the proportion of patients who gained ≥15 letters in BCVA at Week 24 compared with baseline.1

**COPERNICUS and GALILEO study designs:** Randomized, multicenter, double-masked, sham-controlled studies in patients with MEfCRVO (N=358; age range: 22-89 years, with a mean of 64 years). Patients were assigned in a 3:2 ratio to either: 1) EYLEA 2 mg Q4 for the first 6 months or 2) sham injections (control) Q4 for a total of 6 injections. In both studies, the primary efficacy endpoint was the proportion of patients who gained ≥15 letters in BCVA at Week 24 compared with baseline.1

*Last observation carried forward; full analysis set.

SEE WHAT EYLEA COULD DO FOR YOUR PATIENTS WITH MEfRVO AT HCP.EYLEA.US

BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; Q4, every 4 weeks.

ADVERSE REACTIONS

• Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.

• The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

• Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

INDICATIONS

EYLEA® (aflibercept) Injection 2 mg (0.05 mL) is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).


Please see Brief Summary of Prescribing Information on the following page.
EYLEA (aflibercept) injection
For Intravitreal Use

BRIEF SUMMARY—Please see the EYLEA full Prescribing Information available on HCPEYLEAU.US for additional product information.

1 INDICATIONS AND USAGE
EYLEA is a specific vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of patients with:
- Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema Following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), Diabetic Retinopathy (DR)

2 CONTRAINDICATIONS
- 2.1 Ocular or Perivascular Infections
- 2.2 Active Intraocular Inflammation

3 WARNINGS AND PRECAUTIONS
- 3.1 Endophthalmitis and Retinal Detachment

4 ADVERSE REACTIONS

5 Increase in Intraocular Pressure

6 Adverse Reactions

7 Family History

8.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

8.2 Macular Edema Following Retinal Vein Occlusion (RVO)

8.3 Females and Males of Reproductive Potential

8.5 Pregnancy

8.6 Lactation

8.7 Pediatric Use

8.8 Geriatric Use

8.9 Other populations

8.10 Clinical Trials

8.11 Chemically defined formulation

8.12 Product information

8.13 BRIEF SUMMARY—Please see the EYLEA product information.

9/3/21   8:18 AM
A healthy 17-year-old boy presented with a two-day history of bilateral paracentral “shadows” in his vision, which appeared five days after a flulike illness. Although his visual acuity was preserved bilaterally (20/20), Amsler grid testing confirmed the presence of several bilateral paracentral scotomas.

At presentation, fundus examination showed discrete pigmented perifoveal lesions, associated with perifoveal areas of hyperreflective and thickened outer nuclear layer (ONL) as seen on spectral-domain optical coherence tomography (SD-OCT). These findings, together with his previous illness, suggested a diagnosis of acute macular neuroretinopathy (AMN). A nasopharyngeal swab was positive for influenza type B, a common condition associated with AMN. He also had coexisting *Streptococcus* group A pharyngitis, which has not been linked to AMN.

Within two weeks, the lesions became more evident, particularly on infrared reflectance (IR) imaging. IR images show dark petaloid perifoveal lesions typical of AMN (Figs. 1A, 2A), corresponding to areas of thickened ONL and focal disruption of ellipsoid and interdigitation zones on SD-OCT (arrows, Figs. 1B, 2B).

At the four-month follow-up, the patient still had visual complaints, and there were areas of outer retinal thinning on SD-OCT.

**MORE ONLINE.** Look for this article at aao.org/eyenet to learn more about AMN.

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**WHAT IS THIS MONTH’S MYSTERY CONDITION?** Visit aao.org/eyenet to make your diagnosis in the comments.

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**LAST MONTH’S BLINK**  
**Bilateral Acute Macular Neuroretinopathy**

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9 years of extensive real-world and clinical experience, backed by 8 phase 3 clinical trials\(^1\)

>13 million doses administered to hundreds of thousands of patients\(^2\)

82% of payers offer access to EYLEA first line, covering >272 million patients\(^2, *\)

EYLEA4U\(^*\) provided

>4.4 million support services to eligible patients as of June 30, 2020\(^2\)

*Data represent payers across the following channels: Medicare Part B, Commercial, Medicare Advantage, and VA. Individual patient coverage is subject to patient’s specific plan.


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