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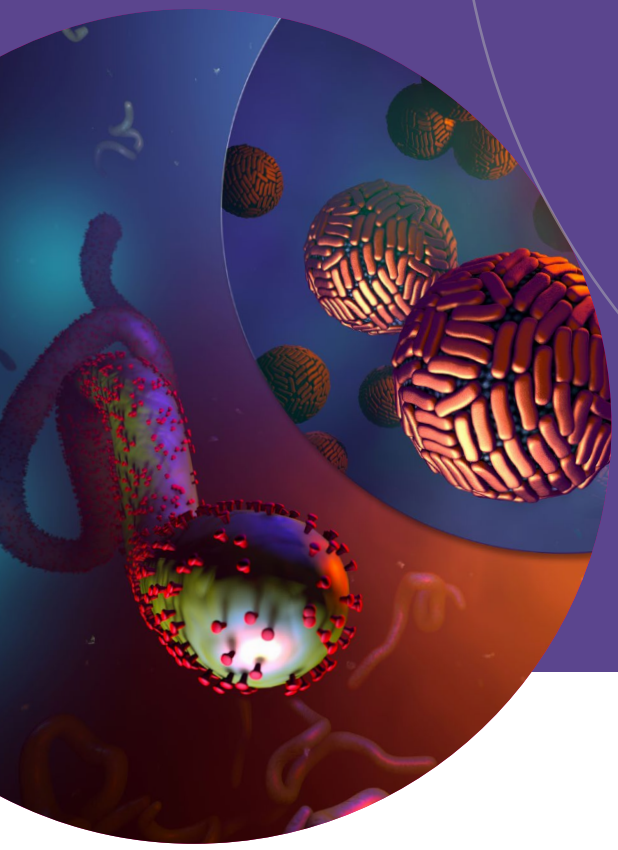

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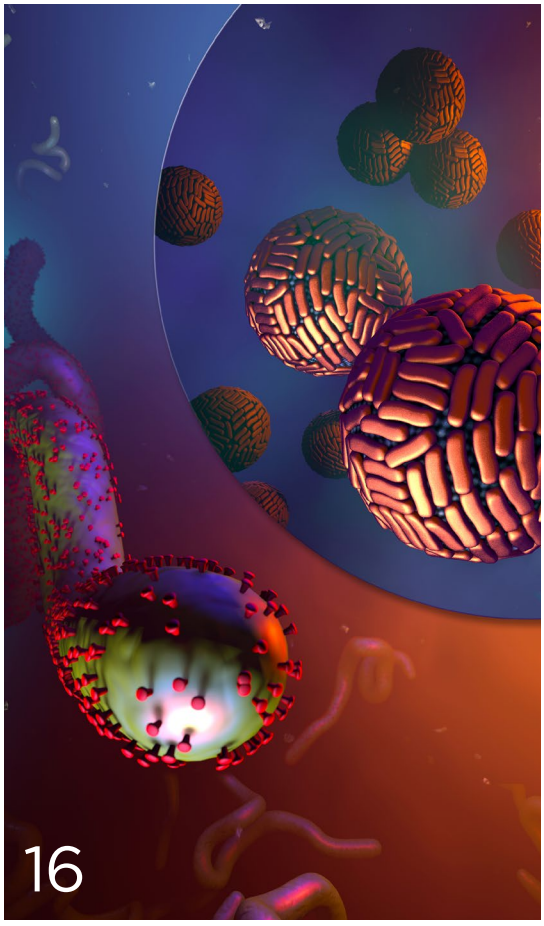

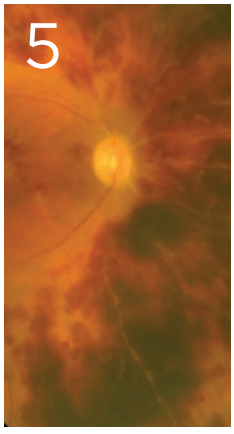

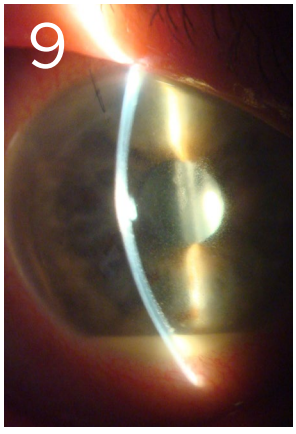

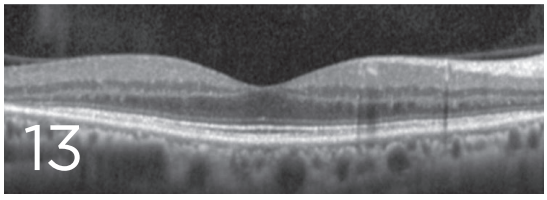

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Programs

Saturday, Nov. 11

The Impact of UWF Imaging on Quality of Care and Practice Efficiency: Leading Anterior and Posterior Segment Specialists Review the Evidence
Speakers: David M. Brown, MD, Jeffrey S. Heier, MD, Warren E. Hill, MD
Presented by Optos

Sunday, Nov. 12

Ligneous Conjunctivitis and Plasminogen-Related Disease: Can We Finally Treat Them?
Speakers: Edward J. Holland, MD, Shira L. Robbins, MD
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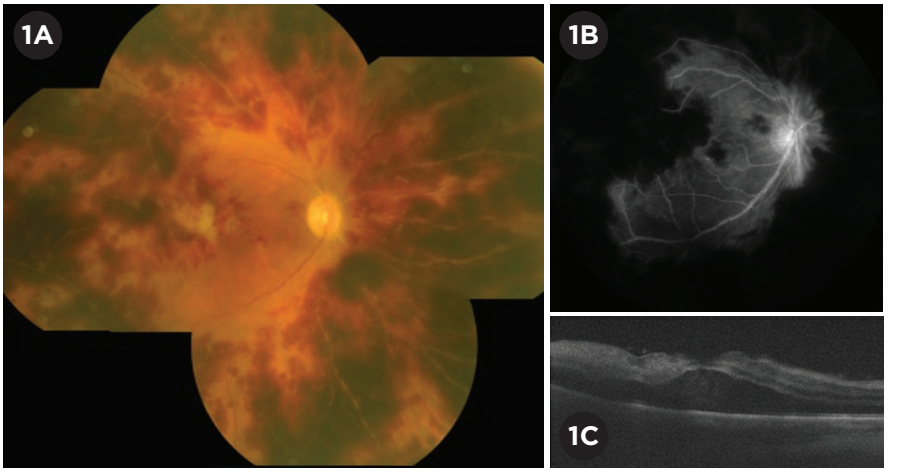
HORV and Cataract Surgery, Part 1: Update on Theories and Tx



RIGHT EYE. *A 66-year-old woman presented with decreased vision 10 days after otherwise uncomplicated bilateral sequential cataract surgery spaced 1 week apart. Intracameral vancomycin (1 mg/0.1 cc) was used at the end of each case. The right eye surgery was first. Despite treatment with systemic corticosteroids and valacyclovir, the patient developed neovascular glaucoma, and her visual outcome was NLP. (1A) The mosaic color photograph demonstrates diffuse peripheral retinal vascular occlusion and associated large patches of retinal hemorrhage. Ischemic macular whitening is evident. The retinal veins are not tortuous or dilated. (1B) Fluorescein angiography (FA) reveals retinal vascular occlusion in areas of retinal hemorrhage. (1C) Optical coherence tomography (OCT) shows a thickened macula and hyperreflectivity of the inner retinal layers, indicating ischemia. Cystoid macular edema is not prominent.*

Fearful of postoperative endophthalmitis, many cataract surgeons in the United States have added intracameral vancomycin to their surgical routines over the last decade.[1,2] But the discovery of a link between vancomycin and a rare, catastrophic disease entity known as hemorrhagic occlusive retinal vasculitis (HORV) has raised doubts about the use of this antibiotic for intracameral surgical prophylaxis.

Although causation has not been proved, HORV is thought to stem from a type III hypersensitivity reaction to intraocular vancomycin. The condition manifests painlessly as a sudden, dramatic decrease in visual acuity, with retinal vascular occlusions, numerous peripheral hemorrhages, and ischemia. Reports to date indicate that this occurs from 1 to 26 days after uneventful cataract surgery.

This delayed presentation led to devastating visual losses in patients with HORV who underwent second-eye cataract surgery before the first eye became symptomatic, said Andre J. Witkin, MD, at the New England Eye Center in Boston. Dr. Witkin is part of a physician task force investigating HORV cases around the nation.

"This disease is really terrible. In some cases, people had their second surgery within a week or two of the first, and only after the second surgery did the disease manifest—and they ended up going blind in both eyes," he said.

Originally published in February 2017

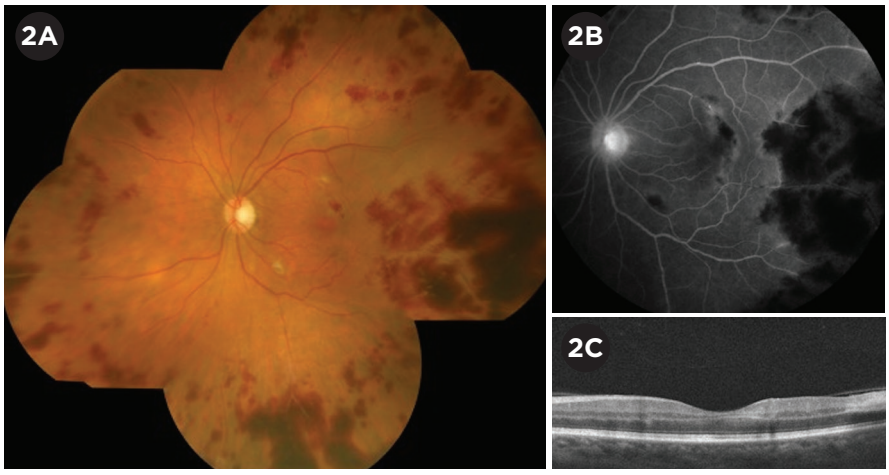
BY LINDA ROACH, CONTRIBUTING WRITER, INTERVIEWING **JENNIFER I. LIM, MD, LUCIA SOBRIN, MD, MPH,** AND **ANDRE J. WITKIN, MD.**

Investigating HORV

In 2015, Dr. Witkin and his colleagues published a case series describing the first 6 known patients with HORV (in 11 eyes).[3] In that report, intracameral vancomycin was the only risk factor in common among all the affected eyes. (No single formulation or manufacturer was implicated.)

Subsequently, a task force convened by the American Society of Cataract and Refractive Surgery (ASCRS) and the American Society of Retina Specialists (ASRS) established a registry (www.asrs.org, click "Report HORV") and learned of additional cases, for a total of 36 eyes in 22 patients.[4] Of these, 14 patients had bilateral disease. Visual

Andre J. Witkin, MD



LEFT EYE. *The patient's second eye became symptomatic 1 week after the first. She received anti-VEGF injections and PRP for neovascular glaucoma, in addition to systemic corticosteroids early in the disease course. Her visual outcome was 20/200. (2A) The mosaic color photograph demonstrates peripheral retinal vascular occlusion with large patches of retinal hemorrhage. There are 2 cotton-wool spots in the macula, but the macula appears otherwise normal. The retinal veins are not tortuous or dilated. (2B) FA reveals retinal vascular occlusion in areas of retinal hemorrhage. Staining of retinal venules is evident. (2C) OCT shows mild hyperreflectivity in the inner retinal layers, indicating macular ischemia.*

acuity was 20/200 or worse in 22 eyes (61%), and 8 eyes (22%) had no light perception (NLP).

When will there be good news? As bad as those reports are, the task force analysis and smaller case studies also contain some good news about HORV.

- **Early signs.** The disease appears to have a wide clinical spectrum, suggesting an opportunity for clinicians to prevent profound vision loss by recognizing early, sometimes nonhemorrhagic signs of a hypersensitivity reaction[4-6] (see "In the Clinic").
- **Treatment strategy.** Severe vision loss might be prevented with intensive topical, oral, and intravitreal corticosteroids; intravitreal anti-VEGF injections to prevent rapid development of neovascular glaucoma; and panretinal photocoagulation (PRP) to stabilize the retina[4,5] (see "Treatment Guidance").

Why now? Investigators have been unable to explain why HORV is showing up only now, said Lucia Sobrin, MD, MPH, at Massachusetts Eye and Ear in Boston. "Ophthalmologists have been using intravitreal [injections of] vancomycin for endophthalmitis for years, without reports of this problem."

However, some observers wonder whether hidden HORV did occur in the past, when ophthalmologists were treating bacterial endophthalmitis with vancomycin, said Jennifer I. Lim, MD, at the University of Illinois at Chicago. "I remember seeing some eyes after intravitreal antibiotic injections for endophthalmitis where there was quite a lot of hemorrhaging, and we said, 'Oh, this is from the endophthalmitis,'" Dr. Lim said. "But maybe, in some cases, the hemorrhage we saw might have been from the vancomycin and we just never knew it, because the vitreous was completely whited out and we could not see the retina prior to treatment. We'll never really know."

Immunologic Clues to HORV

According to the ASCRS/ASRS Clinical Alert, there is evidence of a "strong association" between HORV and intracameral vancomycin use, possibly resulting from a type III hypersensitivity reaction.[4]

In type III hypersensitivity, exposure to an antigen leads to antibody production, and these antibodies bind to the antigen in the circulation, Dr. Sobrin said. "These antibody-antigen complexes are deposited in vessel walls, and then an inflammatory cascade goes along from there. Thrombi also form in the vessels, leading to ischemic injury," she said. "If the immune system has previously 'seen' the precipitating antigen, the reaction can happen very quickly and severely."

Initial hint. In 2014, Dr. Sobrin and her colleagues (including Dean Eliott, MD, Thomas A. Albini, MD, Andrew A. Moshfeghi, MD, and Carmen Santos, MD) published the first report on ischemic retinal vasculitis after cataract surgery with vancomycin.[7]

"One of the 2 patients in our study had a documented reaction to vancomycin with renal failure previously. That was one of the main reasons that vancomycin hypersensitization came to our attention," she said.

Direct toxicity ruled out. Initially, there was speculation that an adjuvant given during surgery, either alone or in combination with the vancomycin, was directly toxic to retinal vessels, Dr. Witkin said.

However, patients who developed HORV had good visual acuity on postop day 1. Visual deterioration was delayed, ranging from 1 to 26 days postoperatively (mean, 8 days).[4] "We would expect toxicity to occur immediately after surgery," Dr. Witkin said. In addition, other studies "haven't shown vancomycin to be toxic to the eyes in animals, unless it's given in really high doses," he said.

Echoes of other immune diseases. HORV presents similarly to leukocytoclastic vasculitis and Henoch-Schönlein purpura, which are type III hypersensitivity reactions in the skin associated rarely with vancomycin.[4]

"Leukocytoclastic vasculitis has a delayed presentation of 1 to 2 weeks, and it tends to affect veins, and that's what we saw in our HORV patients," Dr. Witkin said. "The veins were strikingly affected, out of proportion to the arterioles. There were a lot of hemorrhages surrounding the veins, and the veins were sheathed in a lot of cases."

Dr. Sobrin agreed. "Type III sensitivity reactions typically affect the small venules, the postcapillary venules, and that's what we see in HORV."

Dose-response relationship. Greater exposure to vancomycin in the affected eyes correlated with greater disease

Andre J. Witkin, MD

severity, suggesting a dose-response relationship.

This was tragically apparent in 7 eyes that, before HORV was recognized, were treated presumptively for suspected bacterial endophthalmitis—with intravitreal injections of vancomycin. Five of these 7 eyes were NLP at the most recent follow-up.[4]

"Conversely, there was a patient who had a much lower dose of vancomycin in the infusion bottle, and this person only had a mild reaction," Dr. Witkin said. "There were hemorrhages and vascular occlusions, but the condition resolved on its own without treatment."

In the Clinic

Early recognition of HORV in cataract patients who received vancomycin is crucial to preserving as much retinal function as possible, the experts say. If a cataract surgeon is using intracameral vancomycin and close sequential second-eye surgery is planned, or if a patient who saw well 1 day after surgery suddenly experiences decreased vision, a dilated examination should be done to look for vasculitis and intraretinal hemorrhages, Dr. Witkin said.

Recognize first. Some reports[5,6] suggest that HORV has a wide spectrum of severity, including mild or even asymptomatic disease that can resolve if addressed promptly with topical and oral steroids. "It is important to recognize this entity immediately when the patient presents. You shouldn't waste time treating them for other things," Dr. Sobrin said.

- **HORV vs. endophthalmitis.** Eyes with HORV look very different from those with endophthalmitis, Dr. Witkin said. "In HORV, there's a fairly clear view to the retina, with relatively little anterior chamber reaction or vitritis. That distinguishes it from endophthalmitis, where a lot of the time you don't have a view of the retina at all," he said. "With HORV, the retinal findings are really out of proportion to the amount of inflammation in other parts of the eye."

Treat promptly. For fulminant cases, treatment should be immediate and aggressive to limit the amount of vision lost to severe retinal ischemia.[4] Strategies include 1) topical, oral, and, in some cases, periocular or intravitreal steroids to halt inflammatory processes inside the eye; 2) early use of intravitreal anti-VEGF to block the rapid development of neovascular glaucoma; and 3) early panretinal photocoagulation[4] (see "Treatment Guidance" for further considerations).

In a case described last year, aggressive therapy partially reversed extreme vision loss in one eye of a bilateral HORV patient.[5] Treatment consisted of topical Pred Forte (prednisolone 1%) and oral prednisone 50 mg daily, and 2 injections, given 1 month apart, of intravitreal bevacizumab. The patient initially presented with visual acuity of counting fingers in one eye and NLP in the other; after treatment, she improved to 20/80 in the first eye and counting fingers in the second.

Last but not least. Above all, be wary of using vancomycin if there is any hint that the eye might have HORV. "In terms of what to do in an eye that might have HORV, it is important to avoid using intravitreal vancomycin for suspected endophthalmitis," Dr. Witkin said.

Treatment Guidance

Considerations for using prophylactic vancomycin:

- Weigh the potential risk of HORV, which is extremely rare, against the risk of endophthalmitis.
- Reconsider using vancomycin with close sequential bilateral cataract surgery.
- If using vancomycin with sequential cataract surgery, remember that HORV has delayed onset; further, it may be asymptomatic in the first eye and detectable only with a dilated retinal exam.
- Cefuroxime or moxifloxacin may be alternatives for intracameral prophylaxis.

Recommendations for managing HORV:

- Consider avoiding intravitreal vancomycin if both bacterial endophthalmitis and HORV are in the differential diagnosis.
- Consider an ocular and/or a systemic workup for other syndromes (e.g., viral retinitis).
- Aggressively use systemic and topical corticosteroids; consider periocular or intraocular steroids.
- Employ early anti-VEGF treatment.
- Employ early PRP.

SOURCE: Adapted from Clinical Alert: HORV Association With Intraocular Vancomycin.

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3 Witkin AJ et al. *Ophthalmology.* 2015;122(7): 1438-1451.
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Dr. Lim is professor of ophthalmology and director of the Retina Service at the Illinois Eye and Ear Infirmary at the University of Illinois at Chicago, where she also holds the Marion H. Schenk, Esq., Chair in Ophthalmology for Research of the Aging Eye. *Relevant financial disclosures: Alcon Laboratories: C; Pfizer: C; Santen: C.*

Dr. Sobrin is attending physician and clinician scientist at Massachusetts Eye and Ear and associate professor of ophthalmology at Harvard Medical School in Boston. *Relevant financial disclosures: None.*

Dr. Witkin is assistant professor of ophthalmology and director of clinical research at the New England Eye Center at Tufts Medical Center in Boston. *Relevant financial disclosures: None.*

See the disclosure key, page 3. **For full disclosures,** view this article at aao.org/eyenet.

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Check-in and Lunch Pickup
12:15-12:30 p.m. Lunches are provided on a first-come basis.

Program
12:30-1:30 p.m.

Programs

Saturday, Nov. 11 **Diabetic Eye Disease: Clinical Challenges and Practical Tips for Multidisciplinary Disease Management**

Speakers: Mandeep Brar, MD (endocrinologist), John W. Kitchens, MD

Presented by Regeneron Pharmaceuticals, and designed for U.S. retina specialists.

Sunday, Nov. 12 **Continuous DME Therapy: Clinical Evidence Through Real-World Experience**

Speakers: Nancy M. Holekamp, MD, Daniel F. Kiernan, MD, Fahd Quhill, MD

Presented by Alimera Sciences

Monday, Nov. 13 **Cataract Surgery: Life Is Beautiful When the Pupil Behaves**

Speakers: Johnny L. Gayton, MD, Edward J. Holland, MD, Richard L. Lindstrom, MD, Keith A. Walter, MD, Robert J. Weinstock, MD, Elizabeth Yeu, MD

Presented by Omeros Corporation, and designed for U.S. cataract surgeons.

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HORV and Cataract Surgery, Part 2: Considering Alternatives to Vancomycin

Today, U.S. ophthalmologists who use vancomycin for intracameral antibiotic prophylaxis during cataract surgery must weigh the risk of a rare but potentially blinding complication, hemorrhagic occlusive retinal vasculitis (HORV), against that of endophthalmitis.

Should these surgeons pursue alternatives to vancomycin? In 2013, a large California study confirmed the value, in a U.S. setting, of intracameral cefuroxime to prevent endophthalmitis after cataract surgery[1]—but access to cefuroxime requires a compounding pharmacy. And ophthalmologists who have been successfully accomplishing intracameral prophylaxis with topical, unpreserved moxifloxacin (Vigamox 0.5%) point out that HORV has not been an issue in their patients.

"There are so many reasons not to use vancomycin," said Randy J. Epstein, MD, at Rush University Medical Center in Chicago, who has used moxifloxacin intracamerally since 2007. "The CDC is begging people not to use it indiscriminately because of bacterial resistance. And now you have HORV. I think it's high time to put this issue to bed already."

The Vancomycin-HORV Link

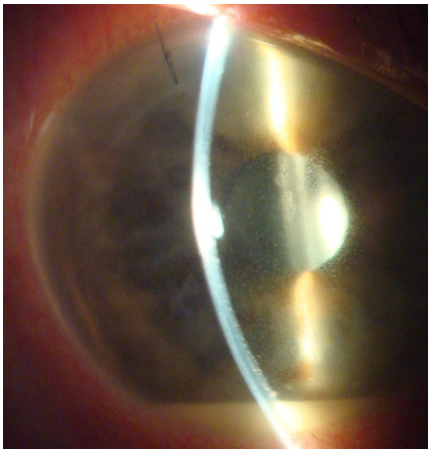
Last summer, a task force of the American Society of Cataract and Refractive Surgery (ASCRS) and the American Society of Retina Specialists (ASRS) reported on a total of 36 eyes diagnosed with postoperative HORV following uncomplicated cataract surgery and concluded that a rare type III hypersensitivity to vancomycin was the most likely cause.[2,3] All but 5 cases occurred since 2013.

The analysis showed that HORV manifests painlessly with a sudden, dramatic decrease in visual acuity, occurring 1 to 26 days (mean, 8 days) after uneventful cataract surgery. The disease is characterized by retinal vascular occlusions, numerous peripheral hemorrhages, and ischemia. The visual outcomes were poor—20/200 or worse in 22 eyes (61%), and no light perception (NLP) in 8 eyes (22%).[2]

No blanket condemnation. Although members of the ASCRS-ASRS Task Force warned that HORV often causes unilateral or bilateral catastrophic visual loss, they did not recommend that surgeons stop using intracameral vancomycin. "We are hesitant to say, 'Absolutely stop using it,' because we think HORV is really rare," explained Andre J. Witkin, MD, a task force member from the New England Eye Center in Boston. "But it's unclear whether it's really worth the risk to use vancomycin in this way."

Individual decisions. Cataract surgeon and task force cochair David F. Chang, MD, of Los Altos, Calif., noted that approximately half of the cataract surgeons who responded to a 2014 ASCRS member survey were using intracameral antibiotic prophylaxis.[4] Among antibiotic users in the United States, vancomycin was the choice of 52%, Dr. Chang said. "Some surgeons believe that vancomycin is more effective against MRSA and other drug-resistant organisms, and they continue to favor this for intraocular antibiotic prophylaxis."

In his own practice, Dr. Chang said, he became concerned about HORV and its delayed presentation. As a result, he no longer uses vancomycin for intracameral prophylaxis. "I used intracameral vancomycin successfully for 18 years with no cases of bacterial endophthalmitis and no known HORV. However,



CALCULATING RISK. *Cataract surgeons who use vancomycin are now in the difficult position of comparing the potential risk of acute postoperative endophthalmitis (shown here) against that of HORV.*

Originally published in March 2017

BY LINDA ROACH, CONTRIBUTING WRITER, INTERVIEWING **DAVID F. CHANG, MD, RANDY J. EPSTEIN, MD,** AND **ANDRE J. WITKIN, MD.**

because I frequently operate on the second eye within 2 weeks of the first, I decided to switch to intracameral moxifloxacin," he said.

What Now?

As the ASCRS survey indicates, half of U.S. surgeons use no intracameral antibiotic prophylaxis.[4] But for those who do—and who are now looking to transition away from using vancomycin—here are their current options.

The leading alternative: Vigamox. The second most popular antibiotic for intraocular prophylaxis (31% of those using intracameral antibiotics) in the United States is moxifloxacin, a broad-spectrum, fourth-generation fluoroquinolone.[4]

In the ASCRS survey, "The majority using intracameral moxifloxacin were injecting unpreserved topical Vigamox by a 7:1 margin over compounded moxifloxacin," Dr. Chang said.

Dr. Epstein said he regards the decision to repurpose Vigamox in this way as a "no-brainer." He pointed out, "It's preservative-free, you know it's sterile, and there's no mystery about what's in the bottle. It's already compounded to the right concentration for us to use in the operating room. It has a very broad spectrum. And it's not that expensive." (See "Overcoming Cost Considerations of Vigamox.")

Supporting evidence. When cataract surgeons who lacked easy access to cefuroxime began looking for alternatives a decade ago, moxifloxacin's easy availability and its rapid, potent bactericidal activity against the most common gram-positive postoperative endophthalmitis pathogens made it an attractive candidate.[5] Early clinical studies found that it is well tolerated in the anterior chamber,[6-8] and safety issues have not emerged subsequently.

Evidence that moxifloxacin usage reduces the incidence of endophthalmitis includes the following studies.

- Cataract surgeons at Kaiser Permanente in California analyzed outcomes of 315,246 surgeries and found that intracameral doses of cefuroxime and moxifloxacin were equivalent at reducing incidence of postoperative endophthalmitis.[9]
- In a study conducted by Dr. Chang and Aravind Haripriya, MD, at the Aravind Eye Hospital system in southern India, instituting routine intracameral moxifloxacin prophylaxis in manual small-incision cataract surgeries reduced the incidence of endophthalmitis 4-fold.[10]
- In a follow-up Aravind study, Dr. Chang said that he and Dr. Haripriya compared endophthalmitis rates in 617,453 cataract surgeries, approximately half with and half without intracameral moxifloxacin.[11] "Compared to the 302,815 eyes that didn't receive intracameral antibiotic, intracameral moxifloxacin reduced the endophthalmitis rate by a factor of 3.5—from 0.07% to 0.02%. This is the strongest clinical evidence to date that intracameral moxifloxacin is effective," Dr. Chang said.

Caution: No preservatives! It is important to ensure that the moxifloxacin product to be injected is at the proper concentration (1 mg/0.1 mL) and contains no preservatives, in order to avoid toxic anterior segment syndrome (TASS), Dr. Witkin said. "Vigamox is the only one that's preservative-free, so it's the only one that you could use," he said.

What about other fluoroquinolones? It is unknown whether any other fluoroquinolone could be used safely and effectively in the anterior chamber, and Dr. Epstein cautions against trying them. "If you use one of the competing branded fourth-generation fluoroquinolones, they're not preservative-free," he said. "With unpreserved moxifloxacin, there's peer-reviewed literature that documents its safety. Why would you want to put your patients at risk by using something that hasn't got that kind of a track record?"

What about compounded antibiotics? American ophthalmologists have had access to cefuroxime for intraocular use—but only if they were willing to have it prepared by a compounding pharmacy. Compounded preservative-free moxifloxacin also can be purchased by this route.

Continuing concerns. However, persistent concerns about ensuring sterility, as well as the potential for dilution errors with compounded cefuroxime, has made many surgeons leery of pursuing this option, Dr. Epstein said.

Positive experiences. "I work both in hospital and surgery center settings. One of the hospitals has a system for using compounded moxifloxacin, because it's cheaper for them than going with Vigamox. And I've had no problem with that," Dr. Epstein said. "In others, I ask the patients to bring in an unopened bottle of Vigamox that I can use for the intracameral injection [see "Overcoming Cost Concerns for Vigamox"]. I have found that either system works well for my patients."

Dr. Chang said he uses moxifloxacin

Overcoming Cost Concerns for Vigamox

Dr. Epstein said that the most common reason that other ophthalmologists give for not using intracameral moxifloxacin is economic. "I'm sensitive to the fact that some people are operating in environments where they've been told that the cost of providing Vigamox for use during surgeries is an issue."

Dr. Epstein offered a straightforward solution: "Give the patient a prescription for the Vigamox, and have the patient bring the unopened bottle to the OR on the day of surgery. This way, you get around not only the surgery center's economic concerns but also all the issues about prescribing and dispensing and [concerns regarding] whether the drug is sterile or not."

In the OR, the circulating nurse opens that bottle in a sterile manner and squeezes some out from the bottle into a sterile specimen cup. The scrub nurse then aspirates 0.2 cc into a TB syringe, using sterile technique. "At the end of the case, I administer 0.05 cc intracamerally from the sterile syringe, and the patient is given the remainder of the bottle to take home and use topically," Dr. Epstein said.

(1 mg/0.1 mL) specifically formulated for intracameral injection by a 503b-certified compounding pharmacy. "I use compounded moxifloxacin from Leiter's compounding pharmacy, which has a very stable shelf life and is less expensive than a bottle of Vigamox."

Stay Tuned

This is by no means the end of the vancomycin dilemma, and surgeons will need to keep abreast of the unfolding HORV story. In the meantime, any cases of HORV should be reported to the ASCRS-ASRS Task Force's registry (www.asrs.org; click "Report HORV").

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Plaquenil Guidelines Point Out New Risks, New Presentation

Despite the advent of newer drugs, hydroxychloroquine (HCQ) continues to be a mainstay in the treatment of systemic lupus erythematosis (SLE), rheumatoid arthritis (RA), and other connective tissue diseases. Moreover, it is used as an adjunct in chemotherapy, and it is being investigated as a treatment for diabetes and heart disease, thanks to its anti-inflammatory, lipid-lowering, and antithrombotic properties.[1]

But as ophthalmologists know, excessive HCQ dosages can result in toxic damage to the eye. In an effort to reduce the incidence of HCQ retinopathy, the Academy published screening guidelines in 2002. These were updated in 2011 and again last year.[2]

Here's an overview of the latest guidelines—and troubling evidence that far too many patients are still receiving too high a dose of HCQ (see "Excessive Dosing Still a Problem," box).

Rethinking Risk

Highlights of the 2016 guidelines include the following.

Use real body weight. "The bottom line is that the daily dose should be 5.0 mg per kg or less, using real body weight," said Michael F. Marmor, MD, at Stanford University in Palo Alto, Calif.

This represents a significant change from the 2011 guidelines, which recommended using ideal body weight to determine dosages. The change was prompted in part by a 2014 study of 2,361 people who had used HCQ continuously for at least 5 years. In this study, Dr. Marmor and his coauthor, Ronald B. Melles, MD, found that real body weight was a better predictor of the risk of toxicity.[3]

One problem with using ideal body weight to determine HCQ dosages was that doing so placed smaller patients at risk of being overdosed, said Dr. Marmor. "These connective tissue diseases disproportionately affect women, and many of them are very slight in stature."

Using real body weight "corrects the problem of overdosing the smaller women and is equally good as a predictor across a broad range of body types," he said. As a practical bonus, the guideline of 5 mg/kg is much easier to calculate, he added.

Adjusting doses. HCQ only comes in 200-mg tablets, so how does one prescribe the proper dose? Dr. Marmor points out that blood levels of HCQ stabilize slowly, so the weeklong dose can be achieved by varying the number of pills on different days of the week.

Think dose plus duration. Dose is only part of the equation, however. "Risk is a function of daily dose plus length of time," said Dr. Marmor.

Patients who have been taking HCQ for 5 or more years are at increased risk of developing HCQ retinopathy, even if they have no other risk factors. For instance, in the 2014 study, the risk of HCQ retinopathy remained low during the first 10 years of use (less than 2%), even for patients who took the recom-

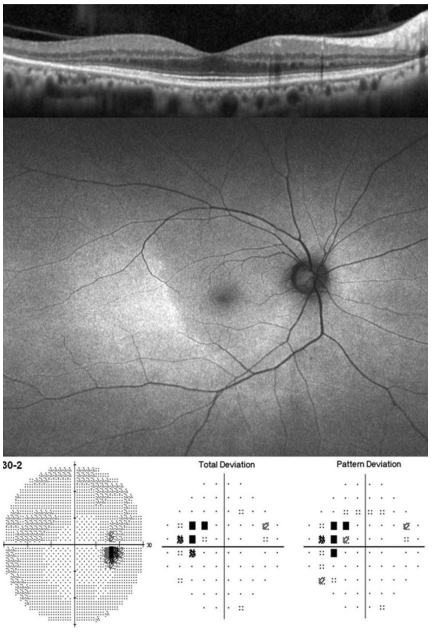

FIG. 1: PERICENTRAL PRESENTATION. *(Top) Horizontal spectral-domain optical coherence tomography, showing temporal loss of the outer retina (ellipsoid zone and interdigitation zone). (Middle) Wide-field fundus autofluorescence showing a broad area of hyperfluorescence extending beyond the outer edge of the inferotemporal macula. (Bottom) 30-2 visual field (VF) with superonasal scotoma corresponding to the retinal changes. A 10-2 VF test showed normal results.*

Originally published in June 2017

BY JEAN SHAW, SENIOR EDITOR, INTERVIEWING **REBEKAH A. BRASLOW, MD, SANG JIN KIM, MD,** AND **MICHAEL F. MARMOR, MD.**

mended dose of 4.0-5.0 mg/kg of the drug—and then rose to almost 20% after 20 years of use.[3]

What about cumulative dose? "We used to think in terms of cumulative exposure to HCQ," Dr. Marmor said. Specifically, 1,000 g of cumulative exposure was considered the cutoff. "But that just doesn't hold up any more," he said, "because some patients will take smaller or larger daily amounts. Risk depends on the balance of dose/kg with duration of use."[2,3]

Consider additional risk factors. Other risk factors include the following.

Renal disease. "The big risk factor that complicates things is kidney disease," Dr. Marmor said. Because HCQ is cleared by the kidneys, renal disease raises the risk of toxicity, and both dosage and screening frequency may need to be adjusted in these patients.[2]

Tamoxifen use. Concomitant use of HCQ and tamoxifen, which is prescribed to treat and prevent breast cancer, raises the risk of HCQ toxicity approximately 5-fold. "Tamoxifen is also retinotoxic, and there may be some metabolic synergy," Dr. Marmor said. Thus, patients who are taking HCQ and tamoxifen concomitantly need to be carefully screened.

Nuances in Presentation

One startling fact that has recently emerged is that HCQ retinopathy tends to present atypically in Asian patients.

"While most patients of European descent show initial photoreceptor damage in the classic parafoveal distribution, most patients of Asian descent will show initial damage in a more peripheral extramacular distribution (Fig. 1) near the arcades," the 2016 guidelines explain.[2]

In his own practice, Dr. Marmor said, "We're in Northern California, and we began to realize that there's a different pattern of damage in Asian patients—that we were at risk of missing early toxicity further out."

In a retrospective study published at the end of 2014, Drs. Marmor and Melles found that 50% of California patients of Asian heritage who had HCQ retinopathy showed degenerative changes near the vascular arcades rather than in the "typical" parafoveal region (and another 30% showed a mix of parafoveal and pericentral damage).[4] Two parallel studies on Korean patients, one of which was published earlier this year, showed similar prevalence of a pericentral pattern.[5,6]

"Pericentral retinal damage seems more common in Asian patients," commented Sang Jin Kim, MD, a coauthor of the 2017 study. In that series, 9 of 174 patients who had taken HCQ for more than 5 years (5.2%) had HCQ retinopathy.[6] And of those 9 patients, Dr. Kim said, 6 [66.7%] "were determined to have a pericentral or mixed pericentral and parafoveal pattern."

The question of why this is the case remains unanswered at present. "We haven't the foggiest idea," Dr. Marmor said. "We presume that it's genetic."

Screening Recommendations

Because HCQ retinopathy cannot be reversed, proper screening is critical. The 2016 guidelines recommend the following.

Screening intervals. All patients who are placed on long-term HCQ treatment should have a baseline screening within the first year of beginning treatment. An initial fundus evaluation of the macula is critical to rule out preexisting disease that might make the retina more susceptible or screening difficult. Baseline visual fields (VFs) and spectral-domain optical coherence tomography (SD-OCT) scans are useful but not essential, unless abnormalities are present at baseline.

Excessive Dosing Still a Problem

Rebekah A. Braslow, MD, had been out of general ophthalmology practice for a few years before she moved to her current position north of Chicago. "I used my spare time to review some of the pertinent practice guidelines, including those on HCQ dosing. Once I started practicing, I realized that quite a few patients were overdosed."

Initially, she thought that those patients were the exception. "However, after a few months, I saw a consistent pattern emerging, suggesting that the guidelines were not widely followed at our institution," she said.

This prompted her to do a system-wide analysis on the entire patient population of her institution, using the electronic health record (EHR) system to identify and analyze patient data. The result: Of 554 patients on HCQ, some 50% had been placed on excess initial doses according to the 2011 guidelines, and 47% were on excess initial doses according to the 2016 guidelines.[1]

"Following the carefully conceived and validated HCQ dosing guidelines seemed like a very straightforward and natural strategy to keep our patients safe," Dr. Braslow commented. "The fact that this was not done suggested a disconnect between our desire to protect our patients from medication toxicity and our day-to-day-practice."

EHR to the rescue? Dr. Braslow came up with a potential solution: Use the same EHR system. "I thought it might be possible to translate the guidelines into a simple set of EHR alerts that would 'take the remembering and thinking out of HCQ dosing' to improve adherence, without requiring extra efforts from the prescribing physicians."

Her idea has been well received, she said. "Once we had their attention, our rheumatology colleagues put together an HCQ task force of physicians and IT staff, with the goal of developing an easy-to-follow EHR alert that provides a guideline-compliant dose recommendation for each patient at the point of care."

Unsurprisingly, there have been some EHR-related hurdles. "Tweaking the EHR seemed conceptually straightforward but proved surprisingly tricky to implement," Dr. Braslow acknowledged. But a pilot program is now up and running, and the task force looks forward to implementing the final version this year.

1 Braslow RA et al. *Ophthalmology*. 2017;124(5):604-608.

Initially, annual screening can be deferred, unless the patient is in a high-risk group. But beginning at the 5-year mark, all patients should be screened every year. And as the guidelines note, during each patient visit, the ophthalmologist should check the HCQ dosage relative to the patient's weight and ask about any changes in systemic status, notably weight loss, kidney disease, and/or tamoxifen use.

Screening technology. Modern examination tools allow ophthalmologists to catch retinal damage at the earliest stage. Once regular screening for HCQ toxicity begins, the most important tests are SD-OCT and automated VFs.[2] Additional tests include fundus autofluorescence (FAF), which can show damage topographically, and the multifocal electroretinogram (mfERG), which can provide corroboration for VFs.

"FAF is hard to interpret sometimes, but you can pick up a glow as toxicity develops," Dr. Marmor said. "You hope to catch changes before you see any black areas."

Screening Asian patients. Regarding VFs, "the 10-2 field is a very intense examination of the central degrees; that's where damage occurs in most non-Asian patients," Dr. Marmor said. "With Asians, damage may occur outside the range of a 10-2 field, so you should do both 10-2 and 24-2 fields."

The problem with doing both 10-2 and 24-2 fields is that "they take time and are very fatiguing," he acknowledged. "As a result, I do SITA Fast fields on my Asian patients, and doing both takes about the same time as one conventional 10-2. The pattern deviation plot is printed out, and I can see the areas that are relatively insensitive."

Ultra-widefield imaging also holds promise for screening Asian patients, Dr. Marmor said. With regard to SD-OCT, Dr. Kim said, "In our series, we could detect all cases with pericentral or mixed parafoveal and pericentral types of HCQ retinopathy by eccentric 6-mm SD-OCT scans. I think SD-OCT scans with broad coverage are a good screening method for Asian patients."

Not recommended. Photography and direct exams are not sensitive and thus are not recommended for annual screening, Dr. Marmor said. "You can't see changes reliably or early enough."

And a patient's self-reported symptoms also cannot serve as a reliable guide to the extent of damage, Dr. Kim said. Even though 4 of the 9 patients with HCQ retinopathy in his study had advanced damage, "only 1 of the 9 patients complained of visual disturbances at the time of diagnosis."

Summing Up

The main point of the revised guidelines is that "you want to get people on the right dose," Dr. Marmor said. "You need to inform the rheumatologist—and you need to inform the patient as well."

But he cautioned against abandoning HCQ altogether. It's important to remember that HCQ is "a remarkably safe drug to use if the dose is correct and you're screening properly," he said. For many patients with SLE, RA, and other connective tissue diseases, "it's much safer than steroids and immunosuppressives."

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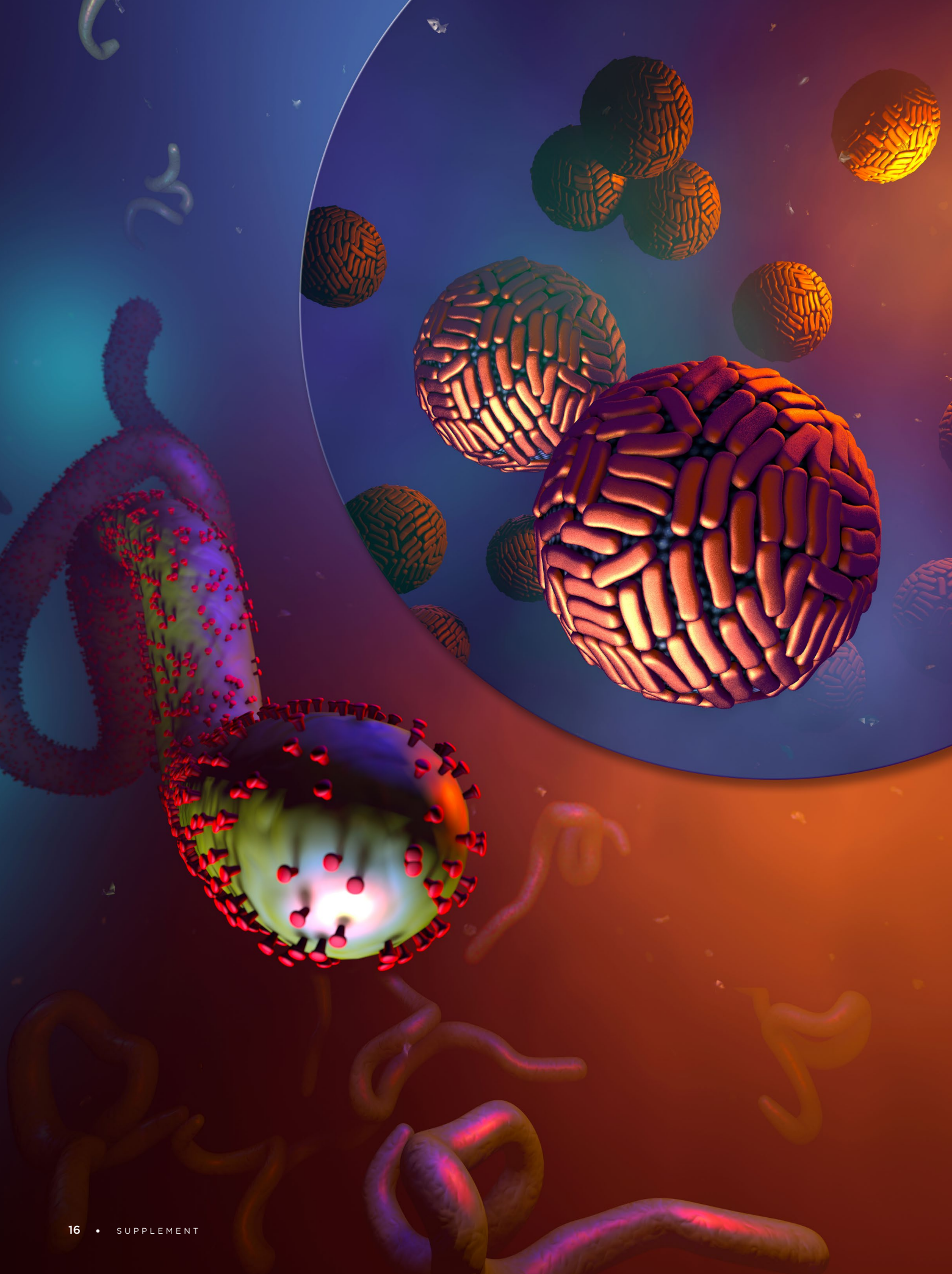
See disclosure key, page 3.



Emerging Viral Infections

Lessons from the Ebola and Zika outbreaks.

By Annie Stuart, Contributing Writer

GLOBAL INTERCONNECTION, accelerating climate change, and viral evolution—the confluence of these and other factors may be magnifying the impact of certain viral infections that affect the eye.

"What we've seen with the spread of Zika and Ebola is that diseases thought to be limited in geographic scope are actually quite broad in their effect and, through travel, can potentially impact individuals on any continent," said Allen O. Eghrari, MD, at the Wilmer Eye Institute in Baltimore.

A Look at Ebola

Ebola virus disease (EVD) is a viral hemorrhagic fever that can cause a range of severe symptoms, including high fevers, myalgias, severe diarrhea, and vomiting, said Steven Yeh, MD, at the Emory Eye Center in Atlanta. The outbreak of 2013-2016 was the largest and most fatal ever—leading to more than 11,000 deaths among more than 28,600 people affected.[1]

Ophthalmology in the trenches. Dr. Yeh was part of a team at Emory Eye Center that cared for the sight-threatening eye disease of Ian Crozier, MD, who contracted life-threatening EVD while treating patients in Sierra Leone. (At the time, the Emory team included Dr. Yeh's colleagues Jessica G. Shantha, MD, and Brent Hayek, MD.)

Dr. Eghrari and Rachael J. Bishop, MD, MPH, from the National Eye Institute, each spent 4 to 5 months on the ground examining patients in Liberia during and after the Ebola outbreaks, and they now lead an eye program there.

A perfect storm. With EVD, "patients develop severe electrolyte abnormalities [due to volume loss] and subsequently can have cardiac arrest as well as septic or hypotensive shock from a severe inflammatory reaction and high viral load," said Dr. Yeh. "Patients develop a cytokine storm, which can develop into an intravascular process leading to bleeding and mucosal or cerebral hemorrhages."

Making the diagnosis. Polymerase chain reaction (PCR) testing of serum can confirm the diagnosis in the initial stages of the disease, said Dr. Yeh. Other tests, which require validation and further study, include virus-specific testing for immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies.

Ebola and the Eye

During the acute stage of the illness, which occurs anywhere from 2 to 21 days following exposure, common ocular signs and symptoms include pain, light sensitivity, blurred vision, floaters, inflammation, and conjunctival hemorrhage, said Dr. Yeh. "Some of our patients reported profound vision loss at the time they were hospitalized in Ebola treatment units." However, during this acute phase, vision issues may be less urgent than the supportive care needed to save lives, he added.

Sicker patients, sicker eyes? With Ebola, uveitis is the most common finding, and it can be sight-threatening or even blinding, said Dr. Yeh. A high concentration of virus during the acute disease is associated with development of uveitis. Conjunctival injection during the acute phase of EVD has also been associated with uveitis.[2]

"The longer [that] survivors were in the Ebola treatment unit," added Dr. Eghrari, "the more likely they were to develop uveitis and associated complications, suggesting that those who were sicker were more at risk for uveitis."

Alfred T. Kamajian

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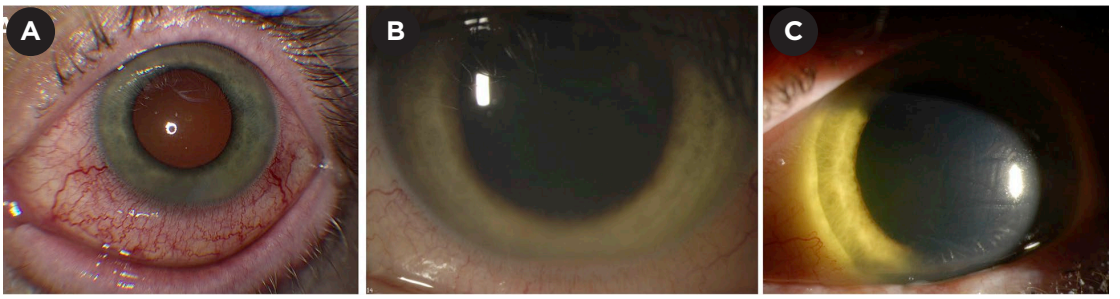


EBOLA. *As panuveitis developed in this Ebola survivor, the slit-lamp photo showed diffuse anterior scleritis as inflammation worsened (A). This was followed by a layered hypopyon uveitis (B) and corneal edema with iris heterochromia (C).*

However, a recent study out of Liberia found a weak correlation between patient-reported symptoms and ocular manifestations, said Dr. Yeh. "What that tells us is that all survivors should have an ophthalmic evaluation to identify the possibility of uveitis, not just those who are symptomatic."

Sequelae. The Emory ophthalmologists found that 25% of Ebola survivors developed uveitis or optic nerve disease, and 40% had severe vision impairment or blindness, according to World Health Organization (WHO) criteria.

"In survivor after survivor, we've seen that virtually any part of the eye can be affected," said Dr. Eghrari. For example, inflammatory changes in the eye can induce posterior synechiae, cataract, epiretinal membrane, macular chorioretinal scarring, or optic disc swelling—all of which can cause vision changes in Ebola survivors. Neurological deficits can also contribute to vision loss, he said.

Unique to Ebola. Patterns of macular edema—some focal, some diffuse—appear unique to Ebola survivors compared with controls, said Dr. Eghrari. "We also see multifocal retinal lesions that appear specific to Ebola virus disease and whose features change over time."

Caring for Survivors

Many survivors of EVD are quite young, said Dr. Eghrari. This makes it particularly important to holistically address a wide range of eye problems that can occur in the setting of the disease.

"Treating people with Ebola eye disease has to be comprehensive," Dr. Eghrari said. For instance, some survivors experience changes that may cause an increase or decrease in intraocular pressure, while others may have conditions such as syphilis or herpetic eye disease that may be exacerbated in the presence of an acute illness.

Drug therapy. In West Africa, patients have responded to corticosteroids, said Dr. Yeh. "If an active infection is present, it may require an anti-infective agent as well as the steroids to treat the inflammation. We treated Dr. Crozier with a combination of topical and systemic corticosteroids and local corticosteroid injections in addition to an experimental antiviral drug."

Some patients have irreversible vision loss, said Dr. Yeh. Others have developed mild or moderate impairment. "But some of the patients we treated with topical and systemic corticosteroids have recovered vision, which is really gratifying."

Ongoing monitoring. The Partnership for Research on Ebola Virus in Liberia (PREVAIL) has recruited a group of 3,000 Liberian Ebola survivors and their close contacts who will be followed for 5 years until 2020. The Liberia-U.S. clinical research partnership will specifically evaluate long-term health consequences, development of immunity, and transmission of the disease. The study will also provide the largest-ever pool for studying Ebola eye disease, said Dr. Eghrari.[3]

Using serology. All participants in the PREVAIL study have been tested for the presence of antibodies, said Dr. Eghrari. This can confirm contact with the virus and makes it possible to specifically associate changes with the virus.

Serology also allows the physicians to rule out co-infection with other viral diseases and screen for other causes of eye problems. For instance, Dr. Eghrari said, "Ocular surface disease is very common in West Africa, and many symptoms such as ocular discomfort, sensitivity to light, irritation, redness, or even discharge have been found in a high proportion of our control participants."

Tracking changes. During annual follow-up of patients in Liberia, the clinic staff use optical coherence tomography (OCT) to look for any subtle changes, said Dr. Eghrari. "This allows us to look for any changes and for responses to treatment, even when subjective measures of visual acuity might remain quite good. With OCT, we've been able to identify objective decreases in intraocular inflammation after treatment with steroids."

Hiding in plain sight. As was the case with Dr. Crozier, high concentrations of the virus can persist in the eye, an immune-privileged system.[4] (Ebola virus can also persist in semen for 12 months or more.[5]) "Although we know the virus can persist

in the eye for some time, it's unclear where the virus is sequestered, because a number of structures could serve as havens," said Dr. Eghrari.

This viral persistence may increase the risk of Ebola exposure to care providers who perform surgeries such as cataract or vitreoretinal surgery, said Dr. Yeh. "To address this question, we initiated a study in Sierra Leone called Ebola Virus Persistence in Ocular Tissues and Fluids [EVICT] Study."

A Look at Zika

Present in Africa for about 60 years, Zika virus (ZIKV) is among a group of RNA-based flaviviruses that are transmitted to humans mostly by the *Aedes aegypti* and *A. albopictus* mosquitoes. It has the ability to spread quickly, said Rubens Belfort Jr., MD, PhD, at the Federal University of São Paulo in Brazil.

Potent strain. Responsible for the most recent epidemic, an Asian strain of the virus likely made its way to northeastern Brazil from Micronesia, possibly by way of an athletic competition, Dr. Belfort said (see "Understanding Zika Strains").

There are "no reports in the literature that ZIKV caused microcephaly in Africa," said Camila Ventura, MD, at the Bascom Palmer Eye Institute in Miami. However, in Brazil, the damage in newborns has been devastating, causing neurological, skeletal, ocular, and hearing abnormalities, she said. This cluster of abnormalities is now known as congenital Zika syndrome (CZS).

Epicenter: Brazil. The virus started to infect people in Brazil about 2 years ago, said Dr. Belfort, and then in the fall of 2015, a large number of children were born with CZS.

"We were screening for retinopathy of prematurity when we started seeing babies with ocular lesions and smaller-than-normal heads," said Dr. Ventura. "Given the new, more serious manifestations of the disease, it was first necessary to prove that Zika was causing it, and then show that the virus was capable of replicating in and crossing the placenta using trophoblasts as the reservoir."

Milder elsewhere? Although cases of ZIKV have been reported throughout the world, the outcomes have thus far been less devastating than in Brazil. For instance, in the United States, the Zika Pregnancy Registry recently estimated that only 6% of infants exposed to Zika during pregnancy have developed birth defects, said Dr.

The Malevolent Mosquito

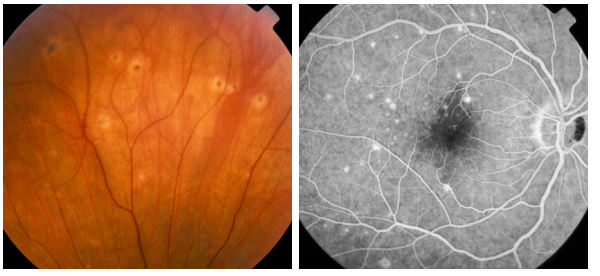
Ebola and ZIKV aren't the only mosquito-borne viruses that pose a threat to the eye.

Epidemiologists are tracking the spread of chikungunya, dengue fever, yellow fever, and West Nile disease around the world. While dengue fever, yellow fever, and West Nile are closely related to ZIKV, chikungunya is not, although it is transmitted by the same mosquito that transmits ZIKV.

"Most of these diseases originated in East Africa," said Lee M. Jampol, MD, at Northwestern University in Chicago. And with the possible exception of yellow fever, all are possible causes of inflammation in the eye, he said. There are no systemic treatments for these particular viral infections, Dr. Jampol said. All the clinician can do is provide supportive therapy.

A note on West Nile. West Nile is now present throughout the continental United States, said Dr. Jampol. His research group was the first to describe its effects on the retina in adults as the disease spread across the United States in the late 1990s.

Characteristic ocular pattern. Most patients with West Nile are asymptomatic, and lesions in the retina tend to heal, Dr. Jampol said. The ophthalmologist may see tiny foci of inflammation. These foci may occur in a linear pattern; alternatively, they may be scattered, said Dr. Jampol. "Most uveitis and retinal specialists can diagnose West Nile based on its appearance."



CHORIORETINAL SCARS FROM WEST NILE VIRUS, *in fundus photo and autofluorescence. According to the CDC, 2,038 cases of West Nile disease were reported in 2016 in the United States. Of those, 56% were neuroinvasive in nature.*

It's critical to note that in diabetic patients, the virus can produce a much more severe effect on the retina and can cause retinal ischemia. People with diabetes may develop severe retinopathy and need treatment, either with laser or anti-VEGF treatments.

Threat to the brain. Spotting signs of West Nile in the eye helps with diagnosis in the brain, said Dr. Jampol. "No one has isolated it [the virus] from the eye, but we are quite certain it is there because an active process in the eye coincides with the presence of encephalitis."

Lee M. Jampol, MD

Ventura. Some researchers have hypothesized that birth defects in Brazil may be worse due to prior exposure to dengue virus.[6]

Zika in adults. The acquired infection in adults looks very different from that in babies with CZS. During the first trimester, some mothers have reported systemic symptoms such as skin rash, arthralgia, and fever, said Dr. Ventura, but among 100 mothers examined by her team in Brazil, none reported ocular symptoms during pregnancy. "We have, however, seen reports of conjunctivitis, anterior uveitis, acute maculopathy, and posterior uveitis in adults," she said. "As soon as the viremia is gone, however, patients recover their vision completely and experience no sequelae."

Complete recovery also occurred in a 64-year-old U.S. resident who was diagnosed with ZIKV retinopathy following a mission trip to the Caribbean. The patient's disease course and clinical appearance were consistent with unilateral acute idiopathic maculopathy; the diagnosis was pinned down via use of the serum plaque reduction neutralization technique (PRNT) assay.[7]

Zika in infants. Today, a multidisciplinary team in Recife, Brazil, is following about 300 babies who have a range of manifestations. In infants, some systemic findings are shared with other infections such as cytomegalovirus (CMV) and toxoplasmosis, said Dr. Ventura, including intracranial complications, microcephaly, seizures, developmental delays, and hearing loss. However, she said, the following combination of findings is unique to CZS: 1) severe microcephaly with partially collapsed skull; 2) brain abnormalities, including thin cerebral cortices, ventriculomegaly, and subcortical calcifications; 3) macular scarring and focal pigmentary retinal mottling; 4) congenital contractures, including arthrogryposis and clubfoot; and 5) marked early hypertonia and symptoms of extrapyramidal involvement.

Some children who were born without microcephaly later developed this finding, as well as other neurodevelopmental problems, said Dr. Belfort. "Therefore, [congenital] microcephaly is no longer needed to make a diagnosis."

Making the diagnosis. PCR can help diagnose ZIKV during the first 2 weeks of acquired infection, but this is rarely done given that symptoms are often mild in adults, said Dr. Belfort. However, if a pregnant woman is diagnosed with the disease, clinical and ultrasound exams can be used to identify microcephaly and other neurological malformations in the fetus, he added.

Diagnostic challenges. After the acute phase, IgM testing for antibodies in blood, urine, cord blood, or cerebrospinal fluid can suggest exposure, but Zika has high cross-reactivity with other flaviviruses.[8] Thus, presumed positive, equivocal, or inconclusive tests must be forwarded to the CDC or a CDC-designated lab for confirmation with PRNT testing.[8]

ONGOING DIFFICULTIES. *Severe microcephaly, as seen in this infant, presents clinicians with a unique set of challenges.*

In addition to missed diagnoses in adults, there are economic barriers to diagnosis, said Dr. Belfort, because all the tests are very expensive. Finally, with Zika, it's also important to rule out other conditions, he added, such as syphilis, toxoplasmosis, herpes, and HIV.

Congenital Zika and the Eye

What to look for. Ocular findings are more common in infants who have severe microcephaly and were infected during the first trimester of pregnancy.[9] Both the posterior and anterior parts of the eye may be affected, said Dr. Belfort. However, the most common ocular findings identified in these children are a well-demarcated chorioretinal scar in the macular region and focal pigment mottling, not an active uveitis, said Dr. Ventura.

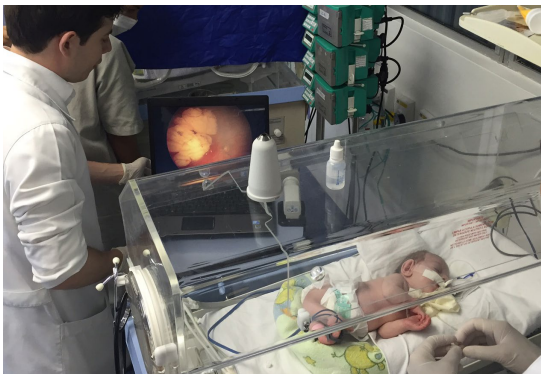
"Although not common, retinal hemorrhages, abnormal retinal vessels, microphthalmia, iris changes, and cataracts may also be present," Dr. Ventura said. In addition, Dr. Belfort and his colleagues published a case report of congenital glaucoma associated with Zika infection.[10]

Optic nerve involvement. Van den Pol et al.[11] analyzed the eyes of infected mice to better understand the pathophysiology of microcephaly and ocular involvement in CZS, said Dr. Ventura. "The first cells infected were astrocytes in the brain and the glial cells in the optic nerve and retina. The same study showed that ZIKV spreads to other parts of the brain, including the central nervous visual system [retina, optic chiasm, suprachiasmatic nucleus, lateral geniculate nucleus, and/or superior colliculus] by axonal transportation."

In another mouse study, Singh et al. found that several types of retinal cells are permissive to ZIKV replication and express receptors for entry.[12]

Vision loss and rehab. "Virtually all the babies

Rubens Belfort Jr., MD, PhD



EXAM FINDINGS. *ZIKV can affect both the anterior and posterior parts of the eye. In this instance, a large ZIKV lesion is evident in the posterior pole of the infant's eye.*

we have seen present with severe visual loss," said Dr. Ventura. "We have also observed that many develop strabismus and nystagmus with time. Surprisingly, [some] babies present with visual impairment even in the absence of ocular findings. Thus, vision loss appears more related to brain damage than to ocular damage itself."

Since children have a high level of neuroplasticity, the main goal of visual rehabilitation, Dr. Ventura added, is to encourage new brain connections to better develop vision.

Long-term outcomes. "The clinical picture of Zika is probably more complex than we first knew," said Dr. Belfort. "These kids are now 1 year old, and we do not know what will happen with them—whether their retinal lesions will reactivate or whether they will present with new lesions. It will be important to continue to follow them."

Impact on corneal grafts. Now that ZIKV has been isolated in tears, and organ transplants have been reported as a mode of transmission of ZIKV, said Dr. Ventura, ophthalmologists have become concerned about corneal transplants. Research is now under way on the risk of contracting the virus from a corneal graft, she said.

What the Future Holds

The newer outbreaks of both Zika and Ebola appear to be greater both in severity and in magnitude than previous outbreaks, said Dr. Eghrari. That realization is generating support for a number of strategies, including the following.

Monitoring systems. Building systems to support lab and genetic evaluation of viruses may prove extremely valuable for identifying genetic markers that can be followed during and after an epidemic, Dr. Eghrari said. "Subtle changes that occur over the course of transmission from person to person make it possible to link cases to previous outbreaks."

Collaboration. "We've seen collaboration among individuals and institutions working together to research Ebola and Zika eye disease," said Dr. Eghrari. "This has helped in building capacity and pooling information, human resources, and medications, in addition to developing vaccines." The hope is that lessons from recent outbreaks will contribute to the understanding of future problems, he said, making it possible to address issues as they arise and prevent outbreaks from causing pathology on a larger scale.

Hector the vector. Without prevention, the WHO estimates that around 4 million people could be affected by ZIKV by 2020. Prevention is the only way to control diseases like this, said Dr. Belfort. "We've been fighting mosquitos for more than 100 years, but the mosquitos are winning. Malaria continues to be out of control. Yellow

Understanding Zika Strains

The African and Asian strains of ZIKV are genetically similar, said Dr. Ventura.

However, in a mouse model experiment, the Asian strain caused a higher upregulation of p53, a protein that regulates the cell cycle.[1] "This finding suggests that p53 plays a pivotal role inducing apoptosis in human cortical neural progenitor cells, affecting the normal development of the central nervous system," said Dr. Ventura. "It may help explain why brain injuries are more prevalent in babies with this strain of Zika."

In other mouse model experiments,[2,3] only the mice that lacked type I interferon (IFN) receptor presented with severe neurological disease after being exposed to ZIKV, a finding that is compatible with those seen in humans. During development, type I IFN response rises with age and is considered the first line of defense against viral infections in the brain. Thus, scientists currently think that type I IFN is key to understanding the pathophysiology behind congenital Zika syndrome, Dr. Ventura said.

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3 Rossi SL et al. *Am J Trop Med Hyg.* 2016;94(6):1362-1369.

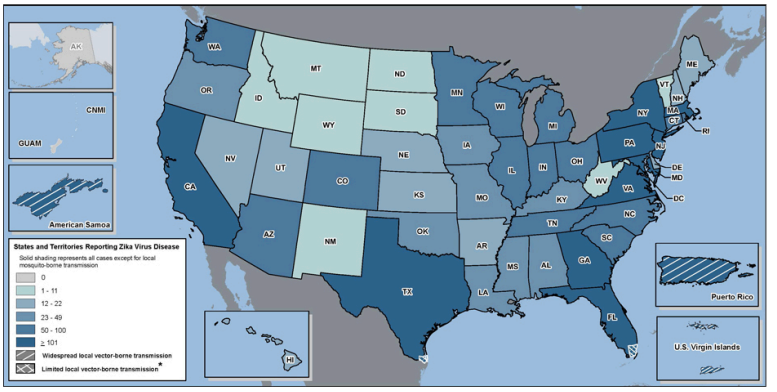
Rubens Belfort Jr., MD, PhD

fever is back in Africa, and, we had a new outbreak of yellow fever in Brazil. Unless we win against mosquitos and improve social and economic conditions, we'll have an outbreak a month."

Vaccines. In addition to mosquito abatement, the other critical preventive approach is vaccination. A vaccine trial for ZIKV is under way.[13]

And, led by the WHO and partners, an Ebola vaccine trial in Guinea and Sierra Leone showed significant efficacy with a vaccine using a ring vaccination algorithm, said Dr. Yeh. "People who had close contact and contacts of those who had close contact with Ebola [i.e., drawing a ring around the index case] were vaccinated. Ten days after the vaccination, there were no cases of Ebola."

The role of ophthalmology. It's important to remind clinicians that they can play an important role in diagnosis, Dr. Ventura said. "With Zika, many people were speculating at first that a batch of expired rubella vaccine was responsible for the brain injuries in newborns. After publishing the first article describing the ocular findings[14]—which were completely different from those caused by congenital rubella—we could say, 'We don't know what this is yet, but it is not rubella.'"



ZIKA IN THE UNITED STATES. *Laboratory-confirmed ZIKV cases reported to ArboNET by state or territory (as of March 8, 2017).*

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9 Ventura CV et al. *JAMA Ophthalmol.* 2016;134(8):912-918.
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12 Singh PK et al. *JCI Insight.* 2017;2(4):e92340. doi:10.1172/jci.insight.92340.
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EXTRA **MORE ONLINE.** For a video interview with Dr. Yeh, images from the PREVAIL study in Liberia, and further reading, view this article online at aao.org/eyenet. For the Academy's 2016 Webinar on EVD and ZIKV, go to store.aao.org and shop by media type.

Meet the Experts

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Lee M. Jampol, MD Professor of ophthalmology at Northwestern University in Chicago. *Relevant financial disclosures: None.*

Camila Ventura, MD Pediatric retina research fellow at the Bascom Palmer Eye Institute in Miami and retina specialist at the Altino Ventura Foundation in Recife, Brazil. *Relevant financial disclosures: None.*

Steven Yeh, MD Louis M. Simpson Professor of Ophthalmology and director of the Uveitis and Vasculitis Section at the Emory Eye Center in Atlanta. *Relevant financial disclosures: Santen: C.*

See disclosure key, page 3. **For full disclosures,** view this article at aao.org/eyenet.

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY—Please see the EYLEA package insert for full Prescribing Information.

1 INDICATIONS AND USAGE

EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of:

Neovascular (Wet) Age-Related Macular Degeneration (AMD); Macular Edema Following Retinal Vein Occlusion (RVO); Diabetic Macular Edema (DME); Diabetic Retinopathy (DR) in Patients with DME

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments. Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. 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 [*see Dosage and Administration (2.7) and Patient Counseling Information (17)*].

5.2 Increase in Intraocular Pressure. Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately [*see Dosage and Administration (2.7)*].

5.3 Thromboembolic Events. 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. 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.

6 ADVERSE REACTIONS

The following potentially serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.

A total of 2711 patients treated with EYLEA constituted the safety population in seven phase 3 studies. Among those, 2110 patients were treated with the recommended dose of 2 mg. 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 floaters, intraocular pressure increased, and vitreous detachment.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, active-controlled clinical studies (VIEW1 and VIEW2) for 12 months.

Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

Adverse Reactions	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%
Eye pain	9%	9%
Cataract	7%	7%
Vitreous detachment	6%	6%
Vitreous floaters	6%	7%
Intraocular pressure increased	5%	7%
Ocular hyperemia	4%	8%
Corneal epithelium defect	4%	5%
Detachment of the retinal pigment epithelium	3%	3%
Injection site pain	3%	3%
Foreign body sensation in eyes	3%	4%
Lacrimation increased	3%	1%
Vision blurred	2%	2%
Intraocular inflammation	2%	3%
Retinal pigment epithelium tear	2%	1%
Injection site hemorrhage	1%	2%
Eyelid edema	1%	2%
Corneal edema	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, and endophthalmitis.

Macular Edema Following Retinal Vein Occlusion (RVO). The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following BRVO in one clinical study (VIBRANT).

Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies

Adverse Reactions	CRVO		BRVO	
	EYLEA (N=218)	Control (N=142)	EYLEA (N=91)	Control (N=92)
Eye pain	13%	5%	4%	5%
Conjunctival hemorrhage	12%	11%	20%	4%
Intraocular pressure increased	8%	6%	2%	0%
Corneal epithelium defect	5%	4%	2%	0%
Vitreous floaters	5%	1%	1%	0%
Ocular hyperemia	5%	3%	2%	2%
Foreign body sensation in eyes	3%	5%	3%	0%
Vitreous detachment	3%	4%	2%	0%
Lacrimation increased	3%	4%	3%	0%
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

Diabetic Macular Edema (DME). The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100.

Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

Adverse Reactions	Baseline to Week 52		Baseline to Week 100	
	EYLEA (N=578)	Control (N=287)	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.

6.2 Immunogenicity. As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.

In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose [*see Animal Data*].

Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept [*see Clinical Pharmacology (12.1)*], treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg.

Adverse embryofetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free aflibercept was approximately 6 times higher than systemic exposure (AUC) observed in humans after a single intravitreal dose of 2 mg.

8.2 Lactation

Risk Summary

There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, EYLEA is not recommended during breastfeeding.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA and any potential adverse effects on the breastfed child from EYLEA.

8.3 Females and Males of Reproductive Potential

Contraception

Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

Infertility

There are no data regarding the effects of EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose approximately 1500 times higher than the systemic level observed humans with an intravitreal dose of 2 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment [*see Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use. The safety and effectiveness of EYLEA in pediatric patients have not been established.

8.5 Geriatric Use. In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

17 PATIENT COUNSELING INFORMATION

In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].

Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

Manufactured by:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591

Issue Date: June 2017
Initial U.S. Approval: 2011

Based on the May 2017 EYLEA® (aflibercept) Injection full Prescribing Information.

REGENERON

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

Feel the Power at AAO 2017. Regeneron Booth 4239

POWER TO PREVAIL

As demonstrated in phase 3 clinical trials evaluating BCVA,* as measured by ETDRS letters, in patients with Wet AMD, Macular Edema following RVO, DME, and by ETDRS-DRSS† in DR in Patients with DME,[1] as well as your clinical experience

Start with EYLEA for proven efficacy outcomes[1]

AMD = Age-related Macular Degeneration; DME = Diabetic Macular Edema; DR = Diabetic Retinopathy.

INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

- EYLEA® (aflibercept) Injection 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) in Patients with DME.

CONTRAINDICATIONS

- EYLEA® (aflibercept) Injection 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. 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.

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 floaters, intraocular pressure increased, and vitreous detachment.

Please see adjacent Brief Summary.

*Best-corrected visual acuity.
†Early Treatment Diabetic Retinopathy Study–Diabetic Retinopathy Severity Scale: an established grading scale for measuring the severity of DR.

Reference: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. May 2017.

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