REVIEW® of Ophthalmology

September 2020

reviewofophthalmology.com

SHOULD YOU OPEN A DRY-EYE CLINIC?

Experts help you weigh the pros and cons. *P. 28*

ALSO INSIDE:

*In some patients with continued daily use. One drop in each eye, twice daily (approximately 12 hours apart).[3]

†Xiidra is an LFA-1 antagonist for the treatment of dry eye disease. Pivotal trial data: The safety and efficacy of Xiidra were assessed in four 12-week, randomized, multicenter, double-masked, vehicle-controlled studies (N=2133). Patients were dosed twice daily. Use of artificial tears was not allowed during the studies. The study end points included assessment of signs (based on Inferior fluorescein Corneal Staining Score [ICSS] on a scale of 0 to 4) and symptoms (based on patient-reported Eye Dryness Score [EDS] on a visual analogue scale of 0 to 100).[3] A larger reduction in EDS favoring Xiidra was observed in all studies at day 42 and day 84. Xiidra reduced symptoms of eye dryness at 2 weeks (based on EDS) compared to vehicle in 2 out of 4 clinical trials. Effects on signs of dry eye disease ICSS (on a scale from 0-4; 0=no staining; 4=coalescent) was recorded at each study visit. At day 84, a larger reduction in inferior corneal staining favoring Xiidra was observed in 3 of the 4 studies.[3]

Indication

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of signs and symptoms of dry eye disease (DED).

Important Safety Information

- Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients.

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

Important Safety Information (cont)

- In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.
- To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.
- Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.
- Safety and efficacy in pediatric patients below the age of 17 years have not been established.

For additional safety information about XIIDRA®, please refer to the brief summary of Full Prescribing Information on adjacent page.

References: 1. US Food and Drug Administration. Code of Federal Regulations, Title 21, Volume 5 (21CFR349). Accessed April 17, 2020. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=349&showFR=1 **2.** Jones L, Downie LE, Korb D, et al. TFOS DEWS II Management and Therapy Report. *Ocul Surf.* 2017;15(3):575-628. **3.** Xiidra [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; June 2020.

XIIDRA® (lifitegrast ophthalmic solution), for topical ophthalmic use
Initial U.S. Approval: 2016

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

4 CONTRAINDICATIONS

Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation *[see Adverse Reactions (6.2)]*.

6 ADVERSE REACTIONS

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

- Hypersensitivity *[see Contraindications (4)]*

6.1 Clinical Trials Experience

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

In five clinical trials of DED conducted with lifitegrast ophthalmic solution, 1401 patients received at least one dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had less than or equal to 3 months of treatment exposure. One hundred-seventy patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5%-25% of patients were instillation-site irritation, dysgeusia, and reduced visual acuity.

Other adverse reactions reported in 1%-5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus, and sinusitis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Xiidra. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Rare serious cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, urticaria, allergic conjunctivitis, dyspnea, angioedema, and allergic dermatitis have been reported. Eye swelling and rash have also been reported *[see Contraindications (4)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on Xiidra use in pregnant women to inform any drug-associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from premating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

Data

Animal Data

Lifitegrast administered daily by IV injection to rats, from premating through gestation day 17, caused an increase in mean pre-implantation loss and an increased incidence of several minor skeletal anomalies at 30 mg/kg/day, representing 5,400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg/kg/day (460-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation days 7 through 19. A fetal no observed adverse effect level (NOAEL) was not identified in the rabbit.

8.2 Lactation

Risk Summary

There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low *[see Clinical Pharmacology (12.3) in the full prescribing information]*. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

8.4 Pediatric Use

Safety and efficacy in pediatric patients below the age of 17 years have not been established.

8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

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REVIEW NEWS
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Pandemic: Challenges Still Lie Ahead for Clinics

In May, *Review* interviewed doctors across the country about their states' elective surgery reopening protocols. Most reported slow increases in patient volume and expressed hope for flattening the curve. Recently, we checked in again to see what new challenges are afoot.

"COVID-19 cases have gone up markedly in Utah since May," says Nick Mamalis, MD, of the Moran Eye Center in Salt Lake City. "We had on the order of about 150 cases a day, and then in June and July cases increased rapidly and peaked at about 900 cases a day. Fortunately in the Salt Lake City area, we've peaked and are starting to come down again, thanks to the institution of masking and social distancing. We're down to around 300 daily cases now."

"In California, we benefited from the large-scale early shutdown, but as the state began reopening, we saw case numbers climbing," adds Michele C. Lim, MD, of the University of California, Davis in Sacramento. She points out, conversely, that "when the case load was low in the beginning, we were completely shut down, but now as time goes on and cases are surging, everything is going full steam ahead."

The Moran Eye Center requires pre-surgical COVID testing within 72 hours of cataract surgery. "We've blocked off part of our parking garage and set up a testing center, so we can do our own testing here," says Dr. Mamalis. The patients are then instructed to stay home until their surgery.

In May, Vanderbilt Eye Institute's Paul Sternberg Jr., MD, who's also the physician lead for its COVID-19 Response Command Center, said Vanderbilt had set up its own PCR test and was running about 700 to 800 tests a day. Now he reports that tests have been as high as 1,200 a day. "We anticipate an uptick in patient requests for testing since school is about to start," he says.

Rishi Singh, MD, in practice at the Cole Eye Institute in Cleveland, Ohio, says, "Our numbers for both eye-related and systemic issues like cancer and heart disease all went down over the past few months. I think people probably ignored many of their disease symptoms and waited to see if they'd resolve on their own, rather than risk coming into the clinic and being potentially exposed to COVID."

Delays in seeking care have affected many during the pandemic. Dr. Lim reports that she recently had a few patients come in with very high pressures who'd been previously well-controlled, but hadn't been seen in months. "These patients went to the OR urgently to get their pressures under control," she says.

"The cases we've been seeing recently have been more significant in nature," Dr. Singh agrees. "Those with diabetes whom we're following for proliferative diabetic retinopathy have been coming back worse than before. Patients with AMD who hadn't been seen for months have lost vision, some of which is almost irreparable at this point."

Patients are returning to the clinic, though. Dr. Mamalis reports that his practice is back to about 90 percent of its pre-pandemic clinic volume. "The pandemic has really affected patient flow and how we see patients, and it's put a burden on our technicians," he says. "We no longer move patients from room to room. Now, they're taken to one room for both the workup and for the doctor to see them. Afterwards, the entire room is cleaned, including the chair, slit lamp, door and counters. If the patients need to go somewhere else for a test, that room is closed afterwards."

Maintaining adequate social distancing in the clinic is another challenge that comes with increasing patient volume. "We're holding our clinic volume at 80 percent because we don't have enough space to physically distance at our pre-pandemic volume," says Dr. Lim. Her Saturday imaging clinics took the place of her drive-thru exams. "I have patients come in for visual fields, OCT imaging and pressure checks on Saturdays, and I follow up with a video visit," she says. "It's worked out well—the hospital is mostly empty on Saturdays and patients don't need to take time off work."

"The other big challenge we're facing now is the fact that some of these returning patients are COVID-positive," Dr. Singh says. "How do you see them? Do you see them

alongside your other clinic patients? Do you distance them differently? The protocols are constantly evolving; it seems to change from week to week as far as recommendations go."

Daniel Chang, MD, of Bakersfield, California, whose practice has ramped up to 75 to 80 percent of its pre-pandemic patient volume, adds that some of his staff members have come down with COVID. "With contact tracing, we found that no infections were transmitted at the office; they came from outside contacts, like at family events and parties. Fortunately, most of the affected staff are young and healthy, and bounced back quickly." Per the CDC guidelines on aerosol transmission, many clinics have begun using eye protection in addition to N-95 masks.

But challenges also come from beyond the medical realm. "We initially thought staff infections would be the biggest challenge, but another thing we're currently facing in California is the schools having only distance learning," says Dr. Chang.

Dr. Sternberg echoes these concerns. "We're working on creating more flexibility for our schedules so that parents can balance their childcare and professional responsibilities," he says.

On the bright side, Dr. Chang points out that this pandemic has pushed doctors to work more efficiently. "We've also created a safer, cleaner environment for our patients, which will prove better in the long run," Dr. Sternberg adds. "The safest place in your community is the doctor's office—it's the only place you'll go where everyone has a mask on. Patients need to come back and feel comfortable; they need their preventive care."

Face-Mask Difficulties

An article, published online ahead of print in the *Journal of Glaucoma,* reports that improperly fitted face masks can cause artifacts on standard automated perimetry.

In the case study, a 32-year-old female underwent SAP with the 24-2 SITA Fast test of the Humphrey Field Analyzer while wearing an ear-loop surgical mask. Post-testing, it was noted that the mask had ridden up on the woman's face. Condensate was noted on the perimeter lens.

SAP demonstrated good reliability indices, but there was a marked reduction in sensitivity inferiorly in both eyes. In addition, the Glaucoma Hemifield Test was outside normal limits. As a result, the staff made sure that the upper border of the patient's mask was well-sealed, with the loops secured around the ears and the nasal strip of the mask pinched down. Repeat visual fields were found to be normal.

The authors suggest that adjustments to the fit of face masks may help prevent fogging or mask slippage and increase test reliability. REVIEW

1. Young SL, Smith ML, Tatham AJ. Visual field artifacts from face mask use. J Glaucoma 2020; Jul 14. [Epub ahead of print].

Correction

In the August issue of *Review*, on page 28 of the article titled "An Extra Push for Wet AMD Patients," focal macular laser should have been identified as the treatment used to seal leaking vessels in the past, not panretinal photocoagulation. Also, on page 30 of the same article, Beovu should have been described as drying at a greater degree and faster degree than Eylea in a subgroup analysis from Phase III studies, not in a subgroup analysis from one practice.

REVIEW of Ophthalmology

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DEXYCU®
(dexamethasone intraocular suspension) 9%

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INDICATION AND USAGE

DEXYCU® (dexamethasone intraocular suspension) 9% is indicated for the treatment of postoperative inflammation.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Increase in Intraocular Pressure

- Prolonged use of corticosteroids, including DEXYCU, may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision
- Steroids should be used with caution in the presence of glaucoma

Delayed Healing

- The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation
- In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of corticosteroids

Exacerbation of Infection

- The use of DEXYCU, as with other ophthalmic corticosteroids, is not recommended in the presence of most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal disease of ocular structures

WARNINGS AND PRECAUTIONS (cont'd)

Exacerbation of Infection (cont'd)

- Use of a corticosteroid in the treatment of patients with a history of herpes simplex requires caution and may prolong the course and may exacerbate the severity of many viral infections
- Fungal infections of the cornea are particularly prone to coincidentally develop with long-term local steroid application and must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate
- Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection

Cataract Progression

- The use of corticosteroids in phakic individuals may promote the development of posterior subcapsular cataracts

ADVERSE REACTIONS

- The most commonly reported adverse reactions occurred in 5-15% of subjects and included increases in intraocular pressure, corneal edema and iritis

Please see brief summary of full Prescribing Information on adjacent page.

EyePoint PHARMACEUTICALS

07/2020
US-DEX-2000097

DEXYCU (dexamethasone intraocular suspension) 9%,
for intraocular administration
Initial U.S. Approval: 1958

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE

DEXYCU (dexamethasone intraocular suspension) 9% is indicated for the treatment of postoperative inflammation.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Increase in Intraocular Pressure

Prolonged use of corticosteroids including DEXYCU may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma.

5.2 Delayed Healing

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of corticosteroids.

5.3 Exacerbation of Infection

The use of DEXYCU, as with other ophthalmic corticosteroids, is not recommended in the presence of most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal disease of ocular structures.

Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate.

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection.

5.4 Cataract Progression

The use of corticosteroids in phakic individuals may promote the development of posterior subcapsular cataracts.

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

- Increase in Intraocular Pressure *[see Warnings and Precautions (5.1)]*
- Delayed Healing *[see Warnings and Precautions (5.2)]*
- Infection Exacerbation *[see Warnings and Precautions (5.3)]*
- Cataract Progression *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The following adverse events rates are derived from three clinical trials in which 339 patients received the 517 microgram dose of DEXYCU. The most commonly reported adverse reactions occurred in 5-15% of subjects and included increases in intraocular pressure, corneal edema and iritis. Other ocular adverse reactions occurring in 1-5% of subjects included, corneal endothelial cell loss, blepharitis, eye pain, cystoid macular edema, dry eye, ocular inflammation, posterior capsule opacification, blurred vision, reduced visual acuity, vitreous floaters, foreign body sensation, photophobia, and vitreous detachment.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of DEXYCU (dexamethasone intraocular suspension) in pregnant women. Topical ocular administration of dexamethasone in mice and rabbits during the period of organogenesis produced cleft palate and embryofetal death in mice and malformations of abdominal wall/intestines and kidneys in rabbits at doses 7 and 5 times higher than the injected recommended human ophthalmic dose (RHOD) of DEXYCU (517 micrograms dexamethasone), respectively *[see Data in the full prescribing information].*

In the US general population the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

8.2 Lactation

Risk Summary

Systemically administered corticosteroids are present in human milk and can suppress growth, interfere with endogenous corticosteroid production, or cause other unwanted effects. There is no information regarding the presence of injected DEXYCU in human milk, the effects on breastfed infants, or the effects on milk production to inform risk of DEXYCU to an infant during lactation. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for DEXYCU and any potential adverse effects on the breastfed child from DEXYCU.

8.4 Pediatric Use

Safety and effectiveness of DEXYCU in pediatric patients have not been established.

8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between older and younger patients.

Manufactured for: EyePoint Pharmaceuticals US, Inc. Watertown, MA 02472

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Ophthalmic Product Development Insights

Matthew Chapin *Andover, Mass.*

Considerations for the New Entrepreneur: FDA Pre-IND Meetings

In this installment of this quarterly column, we'll discuss some key issues that tie into strategic planning for regulatory meetings, with a focus on the FDA Pre-Investigational New Drug (pre-IND) meeting for drugs and biologics. The pre-IND meeting, or PIND, with FDA is a critical milestone for development companies prior to filing the IND, the approval of which allows the conducting of your first clinical trial. Here, we'll focus on how the meeting feeds into business planning, development strategy, fundraising process and key elements we've found useful to keep in mind after years of supporting clients and partners through this process.

We are fortunate in ophthalmology to have ophthalmologists as clinical reviewers at FDA, and a review team that has been very open to meeting with sponsors at any stage to provide guidance and recommendations. The Division of Ophthalmology is part of the Center for Drug Evaluation and Research (CDER), which reviews trial programs involving small molecules, peptides, antibodies, fusion proteins and the like as active pharmaceutical ingredients (APIs). Gene therapies, cell-based therapies, tissue-based therapies and the like are reviewed by the Center for Biologics Evaluation and Research (CBER). Furthermore, over-the-counter products are reviewed by a separate division within CDER—the Office of Nonprescription Drugs. Generic products are reviewed in the Office of Generic Drugs. Despite the different divisions, the clinical review team from CDER's Division of Ophthalmology is generally consulted for PIND meetings and reviews across the other CDER and CBER divisions to ensure consistency on approach for clinical requirements, treatment endpoints, data review, etc.

Our discussion will look at the "When, What, Why and How" of this process. The key question we often receive from new entrepreneurs and start-ups is "When should we meet with the FDA?" The answer to this depends on what you want to ask the FDA and accomplish with the meeting. In addition, the follow-up question that actually helps you address the "How" of the process is, "When will you be ready for the meeting?"

When to Meet with the FDA

Let's start by answering the question of why you want to see the FDA and/or what you want to accomplish by meeting with the agency. The reason will usually fall into one or more of the following categories:

- for increased clarity before moving ahead in the near term with certain IND-enabling activities (such as toxicology, PK or formulation/manufacturing);
- to clarify development plans and budgets for preparing financing through the IND and your planned clinical trial(s);
- to de-risk development pathways and confirm development plans and budgets for a follow-on future round, such as a Series B to cover clinical studies;
- to help in discussions with investors or answer questions from your board prior to funding the next stages (or for later programs, questions that you will receive from strategic partners, and especially end-of-Phase-II meetings to plan for Phase III); or
- questions with answers that have strategic value, or will help with overall conceptualization of the future program.

What Are You Going to Ask the FDA?

Here are some general examples of the types of questions entrepreneurs typically have. Hopefully this sparks some thoughts on what you may want to ask. (This isn't an exhaustive list.)

- **Questions related to Chemistry, Manufacturing and Controls (CMC):**

— are the planned specifications for the proposed product appropriate?

— adequacy of the starting material for the API (the active drug ingredient);

— manufacturing process for first-in-human POC/Phase I, compared with later stages of development;

— approach to sterility, discussion on container closure system for the first trial; and

— qualification and support for a new ingredient in the formulation, or new component to the product.

- **Toxicology-related questions.** A final determination on the toxicology requirements will come down to formulation, nature of the excipients, how much drug is being released (e.g., in cases involving drug delivery), how you plan to correlate data on the drug pharmacokinetics and ocular and systemic levels of the drug, with known preclinical and clinical safety data (i.e., the safety margins), etc. Thus, the more information you have to provide in your meeting briefing package, the more specific the confirmation can be on various requirements for your program.

Here are some common topics for questions:

— The need for a single or two different species. Two species are typically required for local ocular toxicology. For those new to ophthalmology development, rats and mice aren't acceptable species for GLP ocular toxicology because their ocular anatomy isn't sufficiently similar to a human's (although they still can be used for systemic toxicology with systemic administration). We get this question often from new start-ups. Species selection is also based on cross-reactivity of biological products. For example, humanized antibodies may only be cross-reactive in primates.

— If your product is being repurposed from a currently available drug, it's possible that a single species may be appropriate to suggest. But this is situational and a good question for the pre-IND meeting.

— Changes in formulations of existing ophthalmic products may also impact the need for new toxicology studies. The key is if the change in formulation is expected to impact the drug absorption or pharmacokinetics and thus the safety profile of the product.

— Dosing plan for the first clinical trial(s) which will be supported by the toxicology testing.

— For a sustained-release product, the length of toxicology required to support the intended release period of the delivery system in the planned first clinical trial, and relation to the animal PK data. Also, the appropriate dosing frequency required in the toxicology to support the intended dosing regimen in the clinical trial(s).

— General planning for subsequent development, including Phase III studies, based on assumptions from your early toxicology and clinical trials.

— Strategies for incorporating the interim sacrifice of animals and interim reports from your toxicology studies to support an earlier filing of your IND and the start of clinical trial dosing while the full toxicology study is being completed.

- **Clinical-related questions:**

— questions about endpoints, patient selection, sub-groups, and duration of follow-up;

— requirements for the safety database which may be different from the treatment and follow-up needed for efficacy; (in some situations, the FDA will ask to see follow-up data

(Continued on page 32)

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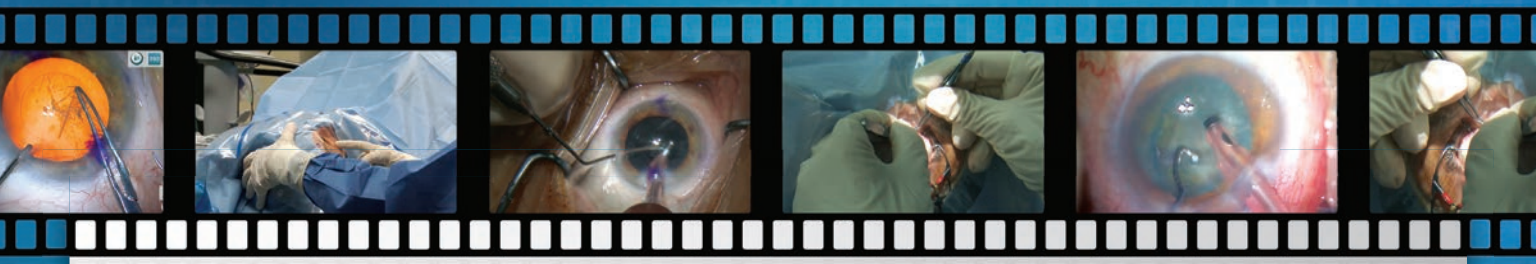

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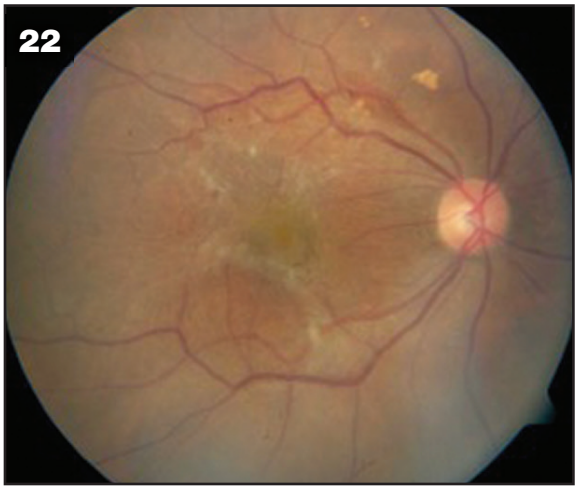

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Retinal Imaging On the Go

Although handheld fundus cameras require close contact, they may still be viable for some clinics and teleophthalmology.

Christine Leonard, Associate Editor

COVID-19 is changing the role of portable retinal imaging devices. With restricted clinic options, telemedicine, and the need to maintain social distance and reduce both staff and patient volume, handheld devices have found an expanding niche. "We've had to deploy services in spaces without standard imaging devices due to space limitations," says Delia Carbrera DeBuc, PhD, a research associate professor of ophthalmology at Bascom Palmer in Miami. "Portable devices are penetrating the markets now. We're also seeing an increase in demand for virtual and hybrid visits at Bascom Palmer."

Here, Dr. Cabrera DeBuc shares some insight on portable retinal cameras in today's clinic, and we'll review 10 options for visualizing the retina in atypical clinic settings.

Handheld Retinal Cameras

Handheld retinal cameras have a number of applications, from community screening and triage to pediatric and geriatric care, where patients may not be able to sit comfortably at a slit lamp or traditional fundus camera. The image quality and field of view of a portable device are variable and generally held to be inferior to those of standard fundus cameras, but some studies have shown that portable fundus cameras can yield professional-quality fundus images.[1]

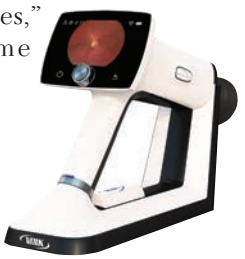
Dr. Cabrera DeBuc says the main issue with handheld cameras is stability. "Getting a good image can be difficult," she says. "It's best if you have a trained technician. Many of the portable cameras I've used have slit lamp attachments, which I prefer when I use them."

Additionally, handheld cameras provide a smaller field of view, so you may have to take multiple photos, and some details may be skewed. "You can't see all the details like you can on a standard fundus machine," she explains. "Portable cameras are good for a first indication to have an idea of whether or not you should refer the patient for better analysis."

If you need a handheld retinal camera during COVID-19, Dr. Cabrera DeBuc says that sanitation and safety are key. "The main concern is contact," she says. "We haven't yet developed an at-home device for retinal selfie imaging, like the at-home tonometers. The technician needs to face the patient, so you should use a shield if possible."

Though portable retinal cameras are smaller than traditional fundus cameras, they require more direct contact for imaging. "Most portable cameras have an eye cup, which comes in direct contact with the patient," she says. "Other fundus machines have a lens that you just move forward and back to focus, but the eye cup sits against the patient's eye the entire time to ensure the correct positioning. From a sanitation standpoint, I think the handheld cameras require more careful cleaning."

Dr. Cabrera DeBuc says that if you're thinking of incorporating a portable retinal camera in your clinic to accommodate COVID-19 restrictions or for teleophthalmology, becoming comfortable with the camera or having training is key. "The main complaint with handhelds is that we're not able to get good images," she says. "Some



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people are better with the cameras than others, though. Your ophthalmic technician may be the right person to get properly trained on a handheld camera. It's also a good idea to ask the product developer for assistance. They know a lot of tips and tricks for using the camera that you may not be familiar with."

Here's a brief overview of five portable fundus cameras.

• ***Dragonfly*** (Eyefficient; Aurora, Ohio) is a lightweight, handheld fundus camera. Its nonmydriatic technology eliminates 20 minutes of patient dilation time, says the company. The Dragonfly offers a 45-degree field of view for checking critical areas of the retina and includes a 3.97-inch touch screen and five internal fixation targets for capturing retinal images. With built-in Wi-Fi, micro SD and Miracast connectivity, the Dragonfly offers quick and easy dissemination of retinal images through the Web from remote locations, says Eyefficient. A rechargeable lithium-ion battery is included. For information, visit eyefficient.com.

• ***Pictor Prestige*** (Volk) is a portable retinal camera specifically designed for imaging small pupils—as small as 3 mm—with a 50-degree field of view. Volk says the device's image quality analysis ensures that you won't need a repeat imaging visit. The Pictor Prestige features a user-friendly interface, a battery lasting a full day in the clinic and a backup battery for overtime use. For information, visit volk.com.

• ***VersaCam α*** (Nidek) is a portable fundus imaging unit with autofocus and autoshot options for button-free use, in addition to a manual capture mode. The VersaCam weighs 445 g (about 1 lb.) and comes with a rechargeable battery that holds a charge for about three hours of continuous operation, according to Nidek. The camera itself is a 5-megapixel clear-color camera with 45-degree horizontal by 40-degree angles of view and seven internal fixation lamps for stable fixation during measurement. Data and image review appears on a 3.5-inch touch screen, and data can be saved on an SD card or transferred to image software for Nidek devices. There's also an optional slit lamp attachment. For information, visit nidek.intl.com.

• ***Signal*** (Topcon) is a lightweight, compact retinal camera, making it ideal for visiting bedridden patients or those in their own homes, the company says. Signal enables ophthalmologists to perform non-mydriatic retinal examinations with a 50 x 40-degree field of view. The camera produces true-color fundus images and features nine fixation targets for central and peripheral imaging. The autofocus function features speed image acquisition, says Topcon. The device can operate for approximately five continuous hours and images can be uploaded to the cloud or stored in the device's memory. In addition to being mobile, Topcon says Signal has low brightness and intensity that can help when working with small children, who are often scared by the bright lights of stationary retinal cameras. Optional slit lamp adapters are available. For information, visit topconmedical.com.

• ***VisuScout 100*** (Zeiss) features a 5-megapixel handheld fundus camera that takes color and red-free images with a 40-degree field of view and meets all relevant ISO 10940 fundus camera standard requirements. The VisuScout's nonmydriatic operation (minimum pupil size 3.5 mm) and autofocus capabilities make dilation unnecessary, says the company. Nine internal fixation LEDs facilitate patient alignment and the capture of peripheral images. Zeiss says the VisuScout is easy to operate, requiring only a brief training session, and that examinations can be performed quickly. The device comes with a rechargeable lithium-ion battery. Data and images can be uploaded with Wi-Fi or by USB, or saved on an SD card. For information, visit zeiss.com.

Smartphone Retinal Imaging

Smartphone ophthalmic imaging has become increasingly popular, especially in less-advantaged regions, due to phones' portability, ubiquity, low cost and diagnostic quality that's comparable to that of traditional fundus camera images.[2] "Many places around the world don't have enough specialists or resources, so these tools are helpful," Dr. Cabrera DeBuc says. "If they can use a lens adapter with a 20-degree field of view to see the back of the eye, they can at least have an idea of whether or not the patient needs to be referred."

Smartphone retinal imaging's potential in teleophthalmology is also growing, with integrated smartphone apps that allow image and file sharing paired to EHRs. Here are a few adapter options for your smartphone.

• ***iExaminer*** (Welch Allyn; Skaneateles Falls, New York) is a nonmydriatic fundus imaging device for iPhone 6, 6s and 6-plus models. The iExaminer incorporates the company's PanOptic ophthalmoscope for capturing high-resolution images with a view of the fundus five-times larger than the standard Welch Allyn ophthalmoscope, and a 25-degree field of view of the fundus. An accompanying app enables file storage, sharing via email and printing. Free and pro versions of the app are available in the App Store. For information, visit welchallyn.com.

The iExaminer (Welch Allyn) is iPhone-compatible.

• ***Peek Retina*** (Peek Vision, London) is a small, three-part modular adapter for Android-based devices that can be applied to a phone in less than 30 seconds, according to the company. With Peek, doctors can immediately share files, transfer them

(Continued on page 36)

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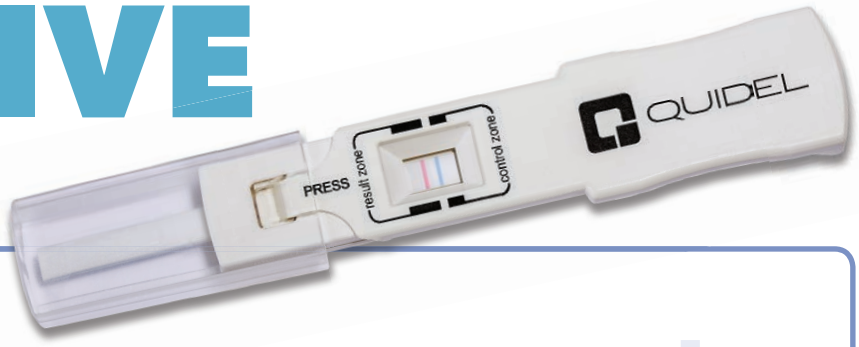

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1. Kabat A, Jasper AL, Lonsberry B, Sindt C. Improving recognition of viral and bacterial conjunctivitis [CE monograph]. *Review of Optometry.* March 2018.
2. O'Brien TP, Jeng BH, McDonald M, Raizman MB. Acute conjunctivitis: truth and misconceptions. *Curr Med Res Opin.* 2009;25(8):1953-1961.

Paul M. Larson, MBA, MMSc, COMT, COE, CPC, CPMA

Signifcant Changes to The ABN Are Coming

Clearing up potential areas of confusion regarding Medicare's Advance Beneficiary Notice of Noncoverage form.

Q I just saw the Advance Beneficiary Notice of Noncoverage forms being used in my office have a 3/2020 expiration. Am I going to have to give back the money I collected for the noncovered charges since then?

A If you executed the forms properly, you should be fine to use the "older" version of the ABN form. Specific CMS forms have to get approval periodically before they can be presented for official use. Forms that aren't re-approved in a timely fashion mean that use continues until retirement or replacement. Since there was no updated version to use, your use of the 03/2020 version is fine and considered a valid notice until a new version is made available.

Q Is there a newer version of the ABN? How will I know I am using the newest version?

A Yes. While there was a significant delay in approval of the new version, it's available for use now. Importantly, you can use either the old or new version until the "mandatory use" date for the new version arrives. Use of an older version after this date could make the notice invalid and you might be forced to give the patient his money back.

The original date for mandatory use of the new version was August 31, 2020, but that was pushed back to January 1, 2021 due to COVID-19. CMS noted the following in boldface type on their ABN Fee-for-Service website page (https://www.cms.gov/Medicare/Medicare-General-Information/BNI/ABN):

"The ABN, Form CMS-R-131, and instructions have been approved by the Office of Management and Budget (OMB) for renewal. Due to COVID-19 concerns, CMS has expanded the deadline for use of the renewed ABN, Form CMS-R-131 (exp. 6/30/2023). At this time, the renewed ABN will be mandatory for use on 1/1/2021. The renewed form may be implemented prior to the mandatory deadline. The ABN form and instructions may be found in the download section."

At the bottom of the most recent version of the form, you will see this: "Exp. 06/30/2023." Any other date might make use invalid.

Q What's different about the new ABN?

A The government has long operated under the dictates of the Paperwork Reduction Act of 1995. That's partly why forms must be reviewed periodically. The form itself didn't change, except that in some cases you will have to change the "Option 1" area, and there is a new date version in the form's footer. In the new ABN version "Instructions for Use" document (https://www.cms.gov/Medicare/Medicare-General-Information/BNI/Downloads/ABN-Form-Instructions.pdf), it notes the single change as follows: "… guidelines for Dual Eligible (Medicare/Medicaid) beneficiaries have been added to the ABN form instructions." In the official instructions on page 5, it notes:

"Special guidance for people who

are dually enrolled in both Medicare and Medicaid, also known as dually eligible individuals (has a Qualified Medicare Beneficiary [QMB]Program and/or Medicaid coverage) ONLY:

Dually Eligible beneficiaries must be instructed to check Option Box 1 on the ABN in order for a claim to be submitted for Medicare adjudication."

Q If the beneficiary isn't dual-eligible, it sounds like the only real change is the date?

A Yes, the remainder of the guidance on filling in the boxes for regular Part B beneficiaries is unchanged. The guidelines for when to issue the ABN (or not) is the same. Remember that the ABN itself is an official form for Medicare Part B and isn't for use with Medicare Advantage or Part C Medicare. Check with those plans for specifics.

Q Other than telling the dual-eligibles they can only mark Option Box 1, is there anything else I need to know?

A Yes, and it's an important change: Medicare asks you to strike through some of the words in Option Box 1 if the beneficiary is Dual-eligible. In the Instructions, they show this:

"Strike through Option Box 1 as provided below: OPTION 1. I want the (D) listed above. ~~You may ask to be paid now~~, but I ~~also~~ want Medicare billed for an official decision on payment, which is sent to me on a Medicare Summary Notice (MSN). ~~I understand that if Medicare doesn't pay, I am responsible for payment, but I can appeal to Medicare by following the directions on the MSN~~."

They also go on to state:

"These edits are required because the provider cannot bill the dual-eligible beneficiary when the ABN is furnished. Providers must refrain from billing the beneficiary pending adjudication by both Medicare and Medicaid in light of federal law affecting coverage and billing of dual-eligible beneficiaries."

Medicare also reviews the other considerations related only to dual-eligible beneficiaries and how those claims are processed. Perhaps most important for this specific group of beneficiaries, the instructions also note when it's acceptable to charge and collect from the beneficiary in advance and when it's not. REVIEW

Mr. Larson is a senior consultant at the Corcoran Consulting Group and is based in Tucson, Arizona. He can be reached at plarson@corcoranccg.com.

Avoiding Unhappiness After Cataract Surgery

Follow these five tips to ensure patient satisfaction and avoid undesirable outcomes.

Sean McKinney, Senior Editor

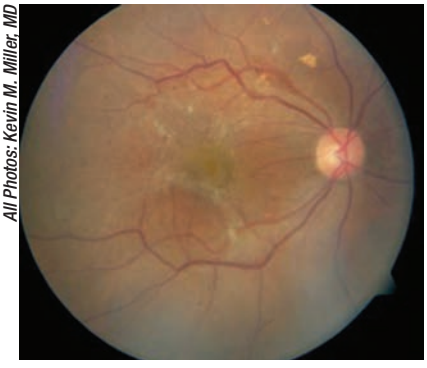
Perhaps you didn't pay enough attention to the retina before implanting a premium IOL, got fooled by a patient's masked corneal astigmatism, committed to a wound size that was too small, struggled with small pupils or made an intumescent cataract burst from an ill-advised approach. If any of these problems sound familiar—or if you don't want them to become familiar—follow these five tips to steer clear of trouble.

1 *Don't forget the retina.*

"It should go without saying that if you can't see the back of the eye, you're not going to implant a premium IOL because patients won't be happy with their vision afterward," says Kevin M. Miller, MD, Kolokotrones Chair in Ophthalmology at the University of California, Los Angeles. "You also need to obtain an OCT before considering a premium IOL."

Below are some of the conditions that Dr. Miller says should rule out the use of these lenses:

- vitreomacular traction;
- epiretinal membrane;
- full-thickness macular holes;
- severe macular degeneration; and



All Photos: Kevin M. Miller, MD

If an epiretinal membrane, obvious here on ophthalmoscopy, is behind a dense cataract, pursuing an OCT and multifocal IOL is ill-advised.

- pigment epithelial detachments close to the center of the fovea.

"Remember, also, that if you're planning to implant a premium IOL, you need to examine the retinas of both eyes, because eventually both eyes must be acceptable for the premium lens," says Dr. Miller. "If you need to do regular cataract surgery, you'll want to do an ultrasound to also rule out pathology in the retina, such as a mass, a tumor or a detached retina."

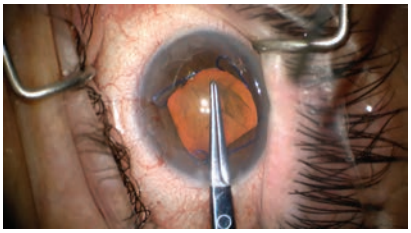
Kathryn M. Hatch, MD, director of the refractive surgery service at Massachusetts Eye & Ear and an assistant professor of ophthalmology at Harvard Medical School, agrees that implanting premium IOLs in the presence of AMD isn't worth the risk. "I worry about degrading the patient's vision," she says. "If the patient's vision gets worse after you put in a multifocal, that could create some serious unwanted issues."

Alan S. Crandall, MD, senior vice-chair, Department of Ophthalmology & Visual Sciences at the University of Utah's Moran Eye Center, orders an OCT on every cataract surgery candidate. "I often pick up on an epiretinal membrane that's pretty hard to see without an OCT scan. I think it's important to capture any findings that may affect a patient's surgery and his postop vision in the future. And it helps me set reasonable postop expectations for my patient," he says.

2 *Manage cases of astigmatism realistically.*

Dr. Hatch says she analyzes corneal topography—and more—on every preop patient by using an OPD-Scan III (Marco/Nidek). "I'm checking for pathology and astigmatism,"

This article has no commercial sponsorship.



It may be wise to use the Malyugin Ring or other tools and treatments, even in modestly undersized pupils, to avoid a traumatized iris, intraoperative floppy iris syndrome, photophobia and other potential problems.

she notes. "We'll diagnose irregular astigmatism or keratoconus in patients who didn't know they had these issues. This is critical if your goal is to reduce spectacle dependence after surgery. Even three-quarters or a half of a diopter of astigmatism after surgery can really degrade the quality of vision. We keep all options available, including limbal relaxing incisions or a toric IOL."

Mindful of patients' frequent disappointment over astigmatism, Dr. Miller tries to improve it as much as he can. "My cut-off is 20/200 or better," he says. "They must have the potential to see the big E on the eye chart after surgery. You can do limbal relaxing incisions, phaco incisions and use a toric lens. Even if the potential visual gain isn't great, or if the patient has a small epiretinal membrane or a little drusen, it can be worth the effort."

Dr. Miller recommends using the words "manage" instead of "correct" astigmatism, noting that "we surgeons can't make everybody better. Sometimes, we're going to deliberately make them worse to give them the best long-term result."

For example: Your patient has no astigmatism preop, but certainly will postop. "So what can you do?" asks Dr. Miller. "You can make a temporal incision and their postop astigmatism will be vertical. Or you can create a superior incision and make the astigmatism horizontal. Let's say it's 0.3 D vertical or 0.3 D horizontal. The vertical residual astigmatism will actually go to zero over time. The 0.3 D residual horizontal is going to get worse, going from 0.3 D, to 0.4 D, to 0.5 D and worse. So there's a best approach, which is to make a small temporal incision, with-the-rule, vertically. This will yield the best long-term result, even though the patient is worse in the beginning."

Dr. Miller recalls a patient who had no astigmatism in his prescription but 2.5 D of astigmatism in the cornea that wasn't initially apparent. "I took out the lens and I implanted a spherical IOL, unaware of the astigmatism in the cornea," he says. "All of a sudden, this patient who had no history of astigmatism had 2.5 D of astigmatism that had been masked by lenticular astigmatism. The patient never needed a correction for astigmatism in his glasses and now I had to put in a high-powered toric lens. That's a difficult conversation to have."

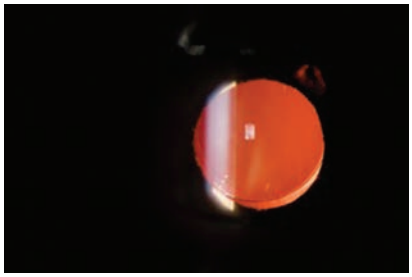
Dr. Miller recommends remaining mindful of the limitations of astigmatism management—and the interventions that can maximize results, including:

- a phaco incision on the steep axis to cut down on astigmatism by 0.2 D to 0.5 D;
- a toric IOL; and/or
- limbal relaxing incisions, including after toric implantation if more than 4 D of astigmatism correction is needed.

"After surgery, if the patient still has residual astigmatism, I wouldn't try to rotate or change the lens," he adds. "Laser refractive correction can address residual cylinder."

3 *Ensure appropriate wound size.*

"Your incision can't be too tight, or too loose," says Dr. Miller. "If you make it too tight, you end up having to stretch it to get the phaco tip and lens inside the eye and the wound will leak. These are the incisions you end up needing to put a stitch into. This can become very counterproductive."



A toric IOL can often work well as part of a combination of solutions for managing postop astigmatism. This retro-illumination photograph shows steep toric axis marks in the red reflex.

Dr. Hatch says she generally doesn't vary the size of her incisions, unless she enlarges one to implant a large IOL or to use a different cartridge. "This happens only occasionally," she adds.

Dr. Crandall explains that he always measures before he makes his incision. He chooses his wound size based on the spherical aberrations of the cornea, lens power (in most cases) and cartridge size.

"You want your wounds to be reproducible," he says. "I always calculate based on the sizes of different lenses, which will determine the size of my incision. If you don't measure, you risk making an incision that's too small, which can easily cause you to strip Descemet's membrane."

4 *Manage small pupil size.*

Confronting the small pupil is a regular occurrence for Dr. Crandall. "Because a lot of folks here in Utah were originally from Sweden, Norway and Denmark, you could say I live in the land of pseudoexfoliation," he says dryly. "Just about everybody's pupils are small. As a result, I've become a big believer in managing the pupil. I use the Malyugin Ring 2.0 (MicroSurgical Technology), the capsule expander (XpandNT Iris Specu-

TRUST THE POWER OF

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

EYLEA Offers Dosing Flexibility in Wet AMD[1]

3 FDA-Approved Dosing Regimens in Wet AMD[1]

Q4

Q8
following 3 initial monthly doses

After one year of effective therapy
Q12

The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).[1]

AMD = Age-related Macular Degeneration; Q4 = every 4 weeks; Q8 = every 8 weeks; Q12 = every 12 weeks.

IMPORTANT SAFETY INFORMATION AND INDICATIONS

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.

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2019. **2.** Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. *Ophthalmology*. 2014;121(1):193-201. **3.** Khurana RN, Rahimy E, Joseph WA, et al. Extended (every 12 weeks or longer) dosing interval with intravitreal aflibercept and ranibizumab in neovascular age-related macular degeneration: post hoc analysis of VIEW trials. *Am J Ophthalmol*. 2019;200:161-168.

Please see Brief Summary of Prescribing Information on the following page.

Q12 DOSING REGIMEN IN WET AMD[1-3]

As Demonstrated in Phase 3 Clinical Trials[1-3]

Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every-4-week (monthly) dosing after the first 12 weeks (3 months).

Although not as effective as the recommended every-8-week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. Patients should be assessed regularly.

Visit HCP.EYLEA.US to see the data.

WARNINGS AND PRECAUTIONS (cont'd)

- 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.

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.

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).

REGENERON

777 Old Saw Mill River Road, Tarrytown, NY 10591

04/2020
EYL.20.04.0009

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

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

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 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.

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 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.

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 2980 patients treated with EYLEA constituted the safety population in eight phase 3 studies. Among those, 2379 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 detachment, vitreous floaters, and intraocular pressure increased.

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, controlled clinical studies (VIEW1 and VIEW2) for 24 months (with active control in year 1).
Safety data observed in the EYLEA group in a 52-week, double-masked, Phase 2 study were consistent with these results.

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

	Baseline to Week 52		Baseline to Week 96	
Adverse Reactions	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)	EYLEA (N=1824)	Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%	27%	30%
Eye pain	9%	9%	10%	10%
Cataract	7%	7%	13%	10%
Vitreous detachment	6%	6%	8%	8%
Vitreous floaters	6%	7%	8%	10%
Intraocular pressure increased	5%	7%	7%	11%
Ocular hyperemia	4%	8%	5%	10%
Corneal epithelium defect	4%	5%	5%	6%
Detachment of the retinal pigment epithelium	3%	3%	5%	5%
Injection site pain	3%	3%	3%	4%
Foreign body sensation in eyes	3%	4%	4%	4%
Lacrimation increased	3%	1%	4%	2%
Vision blurred	2%	2%	4%	3%
Intraocular inflammation	2%	3%	3%	4%
Retinal pigment epithelium tear	2%	1%	2%	2%
Injection site hemorrhage	1%	2%	2%	2%
Eyelid edema	1%	2%	2%	3%
Corneal edema	1%	1%	1%	1%
Retinal detachment	<1%	<1%	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, 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

	CRVO		BRVO	
Adverse Reactions	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) and Diabetic Retinopathy (DR). 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

	Baseline to Week 52		Baseline to Week 100	
Adverse Reactions	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.
Safety data observed in 269 patients with nonproliferative diabetic retinopathy (NPDR) through week 52 in the PANORAMA trial were consistent with those seen in the phase 3 VIVID and VISTA trials (see Table 3 above).

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, 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.

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.

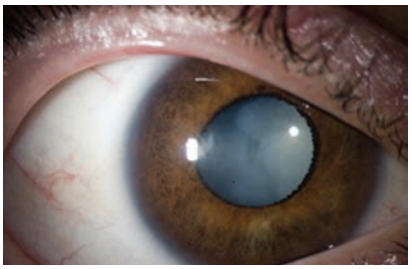
REGENERON

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

Issue Date: 08/2019
Initial U.S. Approval: 2011

Based on the August 2019 EYLEA® (aflibercept) Injection full Prescribing Information.

EYL.19.07.0306



White, intumescent cataracts are often under pressure. Equalize the pressure gradient before puncturing the capsule.

lum, Diamatrix) and the MST capsule hooks (MicroSurgical Technology). I have three or four different devices I use, depending on the rigidity of the pupil." Other devices that can be applied in these situations include the Iris Expander (Oasis Medical) and the I-Ring (Beaver-Visitec International).

Dr. Crandall recommends making sure your patient's pupil size is at least 5 mm. "There's no question that I can do cataract surgery through a 3-mm pupil," he says. "But the cost of doing that is increased inflammation. You're needlessly moving the pupil. In some respects, you're going back 15 years, when we weren't so elegant in these cases and we often left cortex behind."

Despite today's tools and treatments for safely managing small pupils, surgeons note that this anatomical challenge can too easily lead to a traumatized iris, intraoperative floppy iris syndrome, photophobia and other potential problems. When she sees a small pupil, Dr. Hatch prepares for worst case scenarios. "If a patient has a small pupil in the office," she says, "I know I may need to use a Malyugin Ring or iris hooks or mydriatic agents." These include:

- phenylephrine 1% and ketorolac 0.3% (Omidria);
- tropicamide (Mydriacyl); and
- cyclopentolate (Cyclogyl).

"If a patient is on the borderline of a small pupil, I usually err on the side of caution, and just put in the ring or use a mydriatic agent," she adds.

Besides using dilating agents, Dr. Miller says he'll dilate a small pupil with high-viscosity (cohesive) viscoelastics, such as VisCoat (Alcon), EndoCoat (Johnson & Johnson Vision or OcuCoat (B + L). "And then, of course, you can use the rings and devices," he says. Alternatively, some surgeons use a mixture of epinephrine 0.025%/lidocaine 0.75% in a fortified BSS solution ("epi-Shugarcaine").

5 *Approach an intumescent cataract with caution.*

Through the University of Utah's Ghana Exchange Program and his role as co-director of the International Outreach Division at the John A. Moran Eye Center, Dr. Crandall removes 100 to 200 intumescent cataracts per year, performing surgeries in India, Nepal, Ethiopia, Tanzania, Ghana, South Sudan, Guatemala, Haiti and Micronesia. He's also involved in the Himalayan Cataract Project and operates on patients in the Navajo Nation in southern Utah. He says he's learned techniques that could help his colleagues who struggle with these cases.

"The first step is to figure out if the lens is very intumescent," he explains. "The minute you open it up, is it going to try to split? I always stain the capsule, 100 percent of the time. I make a micropuncture centrally, maintaining the ability to immediately remove flocculant material via a cannula. The main thing is that you have to pressurize the eye so that the fluid doesn't come out in a burst.

"What most surgeons do that's incorrect," Dr. Crandall continues, "is when they start their rhexis, they inadvertently hit the wounds, releasing viscoelastic, which immediately creates a fluid wave of power toward the cornea, and that's usually what generates the burst that you don't want. So what I do is stain the capsule and put in my viscoelastic. I don't even make my main wound until I get a puncture in the lens and we can remove all the flocculant material. Then I make the main wound and go in through a sideport."

When the patient has an intumescent cataract, Dr. Miller says he takes the simplest approach possible. "We just want to get in, implant a monofocal lens and get out without experiencing a big problem," he says. "I also use a toric lens if the capsular bag is intact after cataract removal and the patient has a lot of astigmatism."

Dr. Hatch says these cases sometimes prompt her to alter her technique, especially when she's making a capsulorhexis and opening the capsule. Like Dr. Crandall, she uses a needle to puncture the capsule, withdrawing it in the same motion. She never uses her femtosecond laser on these cataracts. "You can't use the laser to soften white cataracts, either, because the femtosecond laser can't image them," she says. "Often, the best you can do is just use a lot of trypan blue."

Everyday Challenges

Although most cataract surgery cases go smoothly, these situations can be unsettling and rattle your confidence. Like her colleagues, Dr. Hatch says taking extra time and preparing for unusual circumstances can turn potential problems into everyday challenges and help you avoid disappointment afterward. "It's all about thinking it through and planning your steps," she says. "You have to have a plan." REVIEW

Drs. Miller, Hatch and Crandall are consultants for Johnson & Johnson Vision. Drs. Miller and Crandall are also consultants for Alcon. In addition, Dr. Crandall is a consultant for ASICO, Excel–Lens, Carl Zeiss Meditec, Mastel Surgical, MicroSurgical Technology, New World Medical, Omeros and iVeena.

Should You Open a Dry-eye Clinic?

Christopher Kent, Senior Editor

Doctors with extensive dry-eye experience answer 10 frequently-asked questions.

As many have noted, dry eye ain't what it used to be. Just a few decades ago, with little existing knowledge about the causes and treatment of dry-eye disease, doctors were at a loss to do much for these patients. Today, the situation has changed drastically, with a proliferation of tests and treatments. Now, these changes have led to the appearance of specialty clinics designed to treat dry eye.

Paul Karpecki, OD, of iOR Partners, director of cornea services at Kentucky Eye Institute in Lexington and an associate professor at the University of Pikeville Kentucky College of Optometry, has served as a research investigator for numerous clinical studies relating to ocular surface disease, and has helped set up eight dry-eye clinics in different practices (all of which he says are doing well). "Dry-eye treatment has evolved a lot," he points out. "At the outset, only about half of our dry-eye patients ended up satisfied; we didn't have the knowledge or diagnostics or therapeutics to really help them. Fast-forward 20 years, and we now have numerous resources. Today, the majority of our patients end up highly satisfied."

As more practices have decided to open dry-eye clinics, others are wondering if they should follow suit. Here, doctors deeply involved in treating dry eye—most with their own specialty clinics—answer 10 questions frequently asked about opening a dry-eye clinic.

1 ***Who should do this?***

Vance Thompson, MD, founder of Vance Thompson Vision in Sioux Falls, South Dakota, and a professor of ophthalmology at the University of South Dakota School of Medicine, argues that there's definitely a need for this kind of specialty dry-eye treatment. "Dry eye is one of the most underdiagnosed conditions in eye care today, and one of the most undertreated," he says. "If you want to embrace dry-eye care, it can definitely be a full-time practice."

"I don't think there's any criteria that makes a given practice a good or bad place to open a dry-eye clinic," says Dr. Karpecki. "Every practice, large or small, has plenty of dry-eye patients. No type of practice is immune to dry eye—although a retina specialist might find this too far afield."

Treating dry eye can be especially helpful for refractive surgeons, making a dry-eye clinic worth considering. "Focusing on dry-eye treatment improves biometry and IOL calculations,[1] surgical outcomes, and most important, it improves patient qual-

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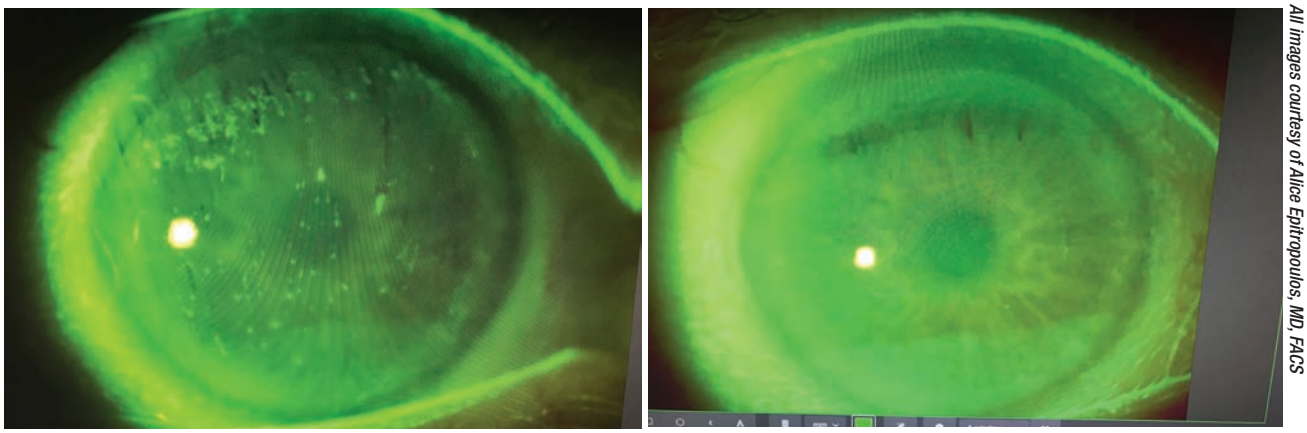

All images courtesy of Alice Epitropoulos, MD, FACS

This patient presented with significant keratitis and an unstable tear film, with reduced tear-fim break-up time and meibomian gland atrophy (above, left). She was diagnosed with meibomian gland disease and evaporative dry eye. She underwent a Blephex treatment (microblepharoexfoliation) and thermal pulsation, and was started on re-esterified omega-3 supplements and preservative-free lipid-containing artificial tears. She showed much improvement post-treatment (above, right).

ity of life," notes Alice Epitropoulos, MD, FACS, a partner at Ophthalmic Surgeons and Consultants of Ohio and a clinical assistant professor at The Ohio State University. She runs the Dry Eye Center of Excellence for the group practice, while also performing cataract and refractive surgery.

John D. Sheppard, MD, MMSc, president of Virginia Eye Consultants and a professor of ophthalmology at Eastern Virginia Medical School, who set up a dry-eye specialty clinic in his practice about six years ago, agrees. "Premium IOL surgeons understand the value of this," he notes. "The one thing everybody hates is an angry multifocal lens patient who paid $3,000 for a new IOL and then can't see optimally." (Dr. Thompson adds that measuring and treating dry eye prior to surgery not only can make your outcomes more accurate, it can also help prevent patients from blaming postop problems on your surgery.)

Some reasons for deciding not to pursue this may relate to the surgeon's personal interests. Preeya K. Gupta, MD, who specializes in cornea and refractive surgery and is an associate professor of ophthalmology at Duke University Eye Center in Durham, North Carolina, says that although her academic practice offers many of the high-tech diagnostic and treatment options for dry eye, they've opted not to separate out their dry-eye treatment into its own clinical entity.

"I had mixed feelings about focusing exclusively on treating dry eye," she explains. "It's an emotional challenge to manage many of these patients, some of whom are very frustrated. But even without a dedicated dry-eye clinic, our volume of dry-eye patients has grown over the years. Patients are eager to get care for their dry-eye condition."

2 *How risky a proposition is this?*

"I think opening a dedicated dry-eye center is a low-risk proposition," says Dr. Gupta. "You're offering your patients a service that's in high demand. Plenty of patients out there have dry eye but haven't been treated—including many of your existing patients. If you screen for this, you'll find a high incidence of dry eye, and many of those patients are looking for specialized care."

"Many ophthalmologists avoid treating dry-eye disease because they feel that doing so would slow them down," says Dr. Epitropoulos. "Some also believe that treating dry-eye disease has low profit margins. Some worry that it would distract them from their surgical practices. But those are myths; they're not true. Having a dry-eye center is a practice-builder. Remember that most commercial payers and Medicare will reimburse for tear osmolarity and InflammaDry." Dr. Sheppard notes that even the latest therapeutic devices, which require a considerable investment, have the potential to bring in significant patient-pay revenue.

"Creating a dry-eye center involves a multidimensional approach," adds Dr. Epitropoulos, "but it's something that any practice can accomplish if it's committed to doing it."

3 *Will having a dry-eye clinic bring in extra patients?*

Dr. Thompson says a dry-eye clinic will definitely bring in more patients. "In addition," he says, "when patients come in for dry-eye treatment, they're likely to have other problems as well, such as cataract, glaucoma, corneal issues and other concerns."

Dr. Sheppard says his dry-eye clinic draws in extra patients. "I think it's most useful for attracting the attention of internet surfers, and referral by word of mouth," he says. "I think it impresses people who have a dry-eye

problem; it tells them they're coming to the right place. Patients who come to our clinic have often seen other doctors and been unhappy with the outcome. When they realize that you respect their complaints and you're not making fun of them, they like that. They'll refer other patients to you as well."

Dr. Thompson adds that a dry-eye clinic can be a great source of referrals. "We like to work with the doctors in our region," he says. "We make sure they know that we have a dry eye center of excellence, and that we're here for them if they have dry-eye cases that they're not making headway on, or if they want help with more serious things such as making serum tears or working with amniotic membrane tissue." Dr. Epitropoulos concurs, noting that a large percentage of her patients come from referrals, from both doctors and patients.

Dr. Karpecki points out that although a dry-eye clinic should bring in new patients, that might not happen at the outset. "It takes a while," he says. "In the beginning, your dry-eye patients will mostly come from your existing patient pool, so internal marketing will be key. But you'll be increasing the number of exams, because you're getting patients into your specialty clinic, and many of these patients will need procedures. The new patients will come later."

A patient undergoes LipiFlow treatment for meibomian gland dysfunction.

4 *Will we need specialized personnel?*

Dr. Karpecki says that running a dry-eye clinic does involve a skill set, so you shouldn't jump in without training your staff—and possibly bringing in a specialist.

"Figuring this out by trial and error would be a waste of your time and effort," he says. "To get a good dry-eye clinic up and running, get help from those who've already done it. Often this requires bringing in a different doctor—an MD or an OD—who can focus on building it up and taking it to the next level. Find a doctor who has the passion and drive to be dedicated to it, even if he or she doesn't yet have all the knowledge and experience that comes with running this type of clinic. That can be obtained."

"If you set up your own clinic you'll need to have ancillary personnel to help you out," Dr. Sheppard agrees. "A number of the point-of-service dry-eye tests are useful diagnostics—but only if they're done correctly. You want to have staff who are specifically trained so they can perform the procedures and testing properly. Usually, the companies that make the tests will send in personnel to train your staff; then, those staff members can help train the rest of your staff."

Dr. Epitropoulos notes that you may also want to enlist a clinical research coordinator. "Having a dry eye center of excellence and a clinical research coordinator who's organized and experienced gives us the opportunity to participate in clinical trials. Being able to do that gives our patients access to new cutting-edge treatments and technologies that may not be available in private practice," she says.

5 *Can a dry-eye clinc produce useful data?*

Doctors with dry-eye clinics agree that it allows them to collect data that's often helpful—sometimes in surprising ways.

"The data clinical staff can gather has been very useful clinically, and the data our publicity team gathers has been very constructive for our business," says Dr. Sheppard. "Of course, you have to actually look for the data, but you can do many useful internal studies if you're predisposed to do so."

Dr. Karpecki believes that monitoring the data from such a clinic is essential. "The future of dry-eye treatment—and successful clinics—is going to center around using big data and artificial intelligence," he says. "We've already started doing that in our clinics. We've create a simple algorithm for the doctors; they put in the patient's information and get back a recommendation for treatment. Then, to refine this, we have the patient fill out a form detailing the response to each treatment.

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Ophthalmic Product Development Insights

(Continued from page 10)

after dosing cessation);

— confirmation of statistical analysis plans;

— If this a new indication with no currently approved drug and thus no precedent for what has been previously required for safety or efficacy, are you ready to discuss approvable endpoints at the PIND meeting? Sometimes this may be best done in more detail at the end of a Phase II (EOP2) meeting to plan for Phase III, once you have clinical data in hand. But at least you can use the PIND meeting to get insights into the FDA's thinking and approach. Keep in mind, the agency follows the "So what?" test—i.e., what impact does your product have on visual function and daily living? You can review your validation plan for novel endpoints.

— the best approach to powering non-inferiority, clinical equivalence or bioequivalence studies. It's wise to review your approach to the statistics, related confidence intervals and the potential need for vehicle control arms early on in your planning, as this will drive the number of patients required, and ultimately the budget needs, for your trials.

— the best approach to first-in-human studies. Is there a need for a traditional Phase I safety study (and appropriate dose escalation), or can you go straight into Phase II in target patients with efficacy assessments? You could review possible approaches to a first clinical trial that's a combined Phase I/II with two parts: Part I being safety and Part II being dose expansion into a randomized study.

The follow-up question you need to then ask is, "Do we have enough information to ask the question we want to ask?" and "When will we have that information?" That will then drive the "When" for submitting a request for a meeting. There's no magic answer about when to meet; some companies go in very early while others choose to go post-funding with a lot of data and a package that almost resembles a full IND. When you choose to meet is just a matter of what your objective is and what's most appropriate for your program.

Typical Steps for Pre-IND Meetings

The meeting request will have initial draft questions, so the FDA can ensure that the appropriate reviewers attend (you'll submit your final questions in your briefing package). It's key to keep in mind that once the meeting date is scheduled, the full briefing document is to be submitted one month prior to the meeting; it needs to have sufficient information to support the questions and level of specificity you want from the FDA. Often, we see companies who initially want to rush to request a meeting so they can say to investors that they have a meeting on the books. This isn't always advisable. Before doing something like that, make sure you have a list of the questions to ask, and that the information for your briefing package will be ready in time for the deadline to get it to the agency.

In conclusion, we hope this summary helps you structure the thought process involved with the pre-IND meeting process and provides a few pearls to consider. The answer to, "When do we meet with the FDA?" is based on your specific program, and available information and data to support your intended agency queries. The best advice: "Don't request a meeting with the FDA too early, and don't meet with the agency too late."

Mr. Chapin is a senior vice president of corporate development at Ora, which offers drug, biologic, and device consulting, clinical research, and development strategy and support to catalyze new client and partner initiatives. The author welcomes your comments or questions regarding product development. Please send correspondence to mchapin@oraclinical.com or visit www.oraclinical.com.

Review and comments on this column were supported by Aron Shapiro, a senior vice president in the corporate development group at Ora.

"The information we gain from doing this is sometimes counterintuitive," he continues. "For example, I used to teach students that if your patient has an evaporative dry eye related to meibomian gland issues or lipid deficiency you should recommend an oil-based tear. When we analyzed our data it turned out that I was only partly right. In the mild-to-moderate cases that was good advice. However, the really severe patients—those with rosacea, a minimal number of glands, high osmolarity or more advanced forms of the disease—actually preferred osmolarity-lowering tears. This experience taught me that big data—the data we capture—is going to be critical. It may reveal that our assumptions and anecdotal experience aren't always right."

6 *How much diagnostic equipment do you need?*

"Concerns about having to invest in equipment undoubtedly discourage many doctors from opening a dry-eye clinic," notes Dr. Karpecki. "The tests and treatment options out there are excellent, and the companies obviously want us to buy them, but that doesn't mean you have to have them to run a successful clinic."

Dr. Sheppard points out that ophthalmologists already have the most important dry-eye diagnostic equipment. "The most important device is your slit lamp," he says. "Then, you need fluorescein to stain the cornea. A topographer is important, but almost everybody has one."

"In addition to doing a great exam and taking a thorough history and having the right dyes to stain the ocular surface, other equipment can be helpful," notes Dr. Thompson. "Tools like the HD Analyzer can give you an objective tear-film breakup time. Many topographers can tell you a lot about the condition of the tear film, since the air-tear interface is what reflects the placido disc that helps provide you with the corneal curvature information. Often, an irregular topography indicates a dry eye."

Dr. Karpecki says he'd recommend one piece of equipment beyond the recently available testing and treating technologies. "Having a slit lamp imaging system—essentially a slit lamp with a camera built into it—can be really helpful," he says. "First, this gives you an easy and efficient way to show patients that they have a problem. Second, when I write down a staining score, I don't know exactly what I saw when the patient returns. But if I have a picture of the staining, or a picture showing what the patient's meibomian gland expression looked like, I'll be able to tell how much they've improved."

Dr. Epitropoulos agrees that a lot of equipment isn't required for evaluating dry eye. "However, if you want to become a dry eye center of excellence, I think it's important to incorporate the latest state-of-the-art technology," she says.

"In terms of the higher-tech devices," Dr. Sheppard notes, "you can invest in them one at a time if you're inclined, such as an inflammation test, an osmolarity test or a meibography device like the LipiScan. Even if you decide you want to have all three, bringing them in all at once can become a headache because you have to learn to use them, as well as getting the billing straight. So if you're going to purchase or adopt them, procure one technology at a time."

"Key pieces of equipment to have in your practice, in my opinion, include some kind of point-of-care testing, such as osmolarity or MMP-9 measurement, and meibography," says Dr. Gupta. "I find meibography to be essential because meibomian gland disease is a significant contributor to dry eye. The images are crucial."

7 *How much treatment technology do you need?*

Dr. Karpecki says you don't

need to have every piece of high-tech equipment. "You probably need a debrider for the eyelid margins," he says. "You should have 180-day dissolving punctal plugs, and the instruments designed to work with them. Then, you probably want to have a tool for expressing the oil glands. You can do that manually, or using a thermal pulsation or expression technology, low-level light therapy or IPL. You'll need a device to clean the lid margins and remove the biofilm, such as Blephex, and access to amniotic membrane and autologous serum. I do think it's useful to have at least one or two high-tech devices—at the very least to set yourself apart from other clinics."

"I believe it's good to have something that will help you treat the meibomian glands," says Dr. Thompson. "I don't believe in pushing on eyes after warming the eyelids, the way we used to teach people to do. I prefer to use devices that express the glands without pushing on the eye, like LipiFlow, which creates a 'sandwich' on either side of the eyelid to create the compression, or the TearCare system from Sight Sciences, where you warm the eyelid and then use forceps to express the meibomian glands."

"Therapies such as LipiFlow, Blephex, iLux and IPL really do help to optimize the health of the tear film, improve patient symptoms and improve surgical outcomes," notes Dr. Epitropoulos. "Cynthia Matossian, MD, presented her data at the 2019 ASCRS meeting, which showed that thermal pulsation treatment prior to cataract surgery improves the accuracy of keratometry and subsequent surgical decision making.[2] That's been true in my practice as well."

"You should approach this the same way you'd set up a LASIK practice," says Dr. Sheppard. "With these new instruments you're selling patients a cash procedure, and you can't do that in a flippant way. You have to have a whole coordinated setup with a counselor, technicians, billing, a friendly, sales-minded scheduler and a patient credit program that lets patients pay for a procedure on credit, the same way they'd buy a car. Taking that step is a big decision."

Dry-eye Clinic Treatment Pearls

These strategies can help make your dry-eye clinic a success:

• ***Don't get too focused on treating one part of the problem at a time.*** "There are multiple parts to this disease," notes Paul Karpecki, OD, director of cornea services at Kentucky Eye Institute in Lexington. "For example, when managing evaporative dry eye you have to control the inflammation; you have to treat the obstructed glands; often, you have to control blepharitis or biofilm; and then you have to manage the tear film. If you just focus on managing the tear film and don't treat the inflammation and bacterial biofilm and the obstructed glands, you won't get anywhere. The dry eye will continue to get worse. And if you address these problems one step at a time, by the third step the patient will be gone.

"You have to do something about all of these elements right away," he concludes. "Everything you see, you need to treat. You need to treat the blepharitis on day one, the obstructed glands on day one, the inflammation on day one and the tear film on day one."

• ***Assume everyone who comes in has ocular surface disease until you rule it out.*** "Even if a patient is asymptomatic, we'll look for signs of dry-eye disease," says Alice Epitropoulos, MD, FACS, a partner at Ophthalmic Surgeons and Consultants of Ohio and a clinical assistant professor at The Ohio State University. "That's because a high percentage of asymptomatic patients actually do have dry-eye disease—which can become symptomatic after surgery. William Trattler, MD, did a study of incoming cataract patients that showed that close to 80 percent of patients scheduled for cataract surgery had a component of dry-eye disease, but only a small percentage had a previous diagnosis.[3] This is important because dry eye can affect the accuracy of our measurements when determining what strength implant to put in, which can ultimately affect surgical outcomes and patient satisfaction. In addition, if you don't diagnose the problem and it gets worse after surgery, the patient is going to blame your surgery for causing it. So it's really important to make sure you're checking everybody for dry-eye disease."

• ***Follow the DEWS II diagnostic guidelines.*** "Those guidelines, created by the Tear Film & Ocular Surface Society, are documented and they've been shown to work," says Dr. Karpecki. "I know that doctors may shy away from this, thinking that it's a complicated system, but it's not. It's quite straightforward and easy to use.

"Specifically, the algorithm says that to diagnose dry eye you need to find a sign and a symptom," he explains. "To find a symptom, you can use a questionnaire like the DEQ-5 or SPEED questionnaires. Then, you need a global test that can find evidence that dry eye is present. (The document says you only need to perform one test, but I prefer to do two, for confirmation.) Then, you need to differentiate between aqueous-deficient dry eye and evaporative dry eye. That's important because the treatments are different.

"Our clinic manages 45 to 65 patients a day," he says. "Doctors sometimes assume we have an incredibly complex dry-eye algorithm, but you don't need anything more complex than what I've described. We're only doing four things: having the patient fill out a questionnaire; measuring osmolarity; performing corneal staining (which can also reveal tear-film breakup time and meniscus height); and expressing the glands. If you can do that, you'll do an excellent job of diagnosing these patients."

— CK

8 *Should you advertise your clinic?*

If you're opening a dry-eye clinic, Dr. Thompson suggests a number of ways to spread the word. "Meet with your potential referring doctors and show them case presentations illustrating how you've helped patients with mild, moderate and severe dry eye," he says. "Show how you've helped them not only deal with ocular surface issues, but also image-quality issues. We talk with local rheumatolo-

gists and internists and family doctors, because we know that patients with collagen vascular diseases like rheumatoid arthritis often have dry eye along with their systemic disease.

"In addition, you can include news about your dry-eye center in your patient newsletter," he says. "Hold webinars. When new technologies or drugs are approved, send a press release to your local press media outlets. All of these strategies will help generate referrals and bring in new patients."

Dr. Karpecki says it's perfectly reasonable to do some marketing of your dry-eye clinic, especially using social media and similar avenues. "However," he notes, "you have to be successful internally first, for two reasons: First, you already have that patient base, so there's almost no expense involved. Second, being successful internally first gives you the chance to get really proficient with managing these patients before getting outside referrals. I've seen practices try to build referral ocular surface clinics without doing this; then the first few referrals didn't turn out well, and they never got another referral."

9 *How do I get started?*

Dr. Epitropoulos says many doctors ask her how to start a dry eye center of excellence. "If you're thinking about building a dry-eye center, reach out and talk to other doctors who've done it," she advises. "That way you don't have to reinvent the wheel. Visit other dry-eye clinics to get a first-hand view of how a dry eye center of excellence is run. Consider taking courses, such as Dry Eye University in Jacksonville, Florida, set up by Frank Bowden III, MD. You can also take online courses and those offered at the major meetings.

"Another key to building a successful dry eye center of excellence is staffing," she continues. "Doing this requires a team of trained, dedicated technicians. They also need to be caring and empathetic, because these patients are frustrated and often depressed about their disease; they often need someone to listen to them and understand what they're going through.

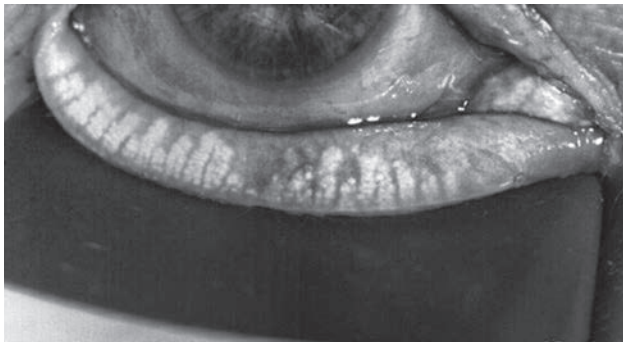
"You also want to find a lead technician and coordinator to be your quarterback," she notes. "This should be someone who can work with you and oversee your patient flow, workups, patient education and overall problem-solving. And if you're going to participate in clinical trials for dry-eye treatments, you'll also need to have an organized, efficient and experienced clinical research coordinator.

"Once you're up and running, you'll need to keep up with the latest technology for diagnosing and treating dry eye," she adds. "And, it's crucial to continuously educate both your patients and your staff. Having your staff visit other dry-eye clinics and attend courses will ensure that they're well-educated about dry eye so they can communicate with patients effectively."

10 *Should I wait for the pandemic to end?*

There are three good reasons to create your dry-eye clinic now, during the pandemic," says Dr. Karpecki. "First, it takes a little time to get your system in place and understand patient flow. Since most of us are seeing fewer patients right now, that gives us more time to set this up and learn to make it work efficiently.

"Second," he says, "the dry-eye patients coming in right now will be the more serious cases. They'll require treatments like amniotic membrane, punctal occlusion and so forth, so they'll generate more revenue for your practice than other patients might. That's been the case in our clinic; our patient volume is down 15 to 30 percent, but because we're seeing more significant cases, our revenue hasn't dropped at all.



Moderate meibomian gland atrophy associated with dry-eye disease.

"Third," he says, "no one can rely on insurance reimbursement alone, and dry-eye patients often need out-of-pocket procedures. In addition, we found that even during the COVID shutdown, our dry-eye patients continued to order products they needed from us, generating some additional revenue. Those are three good reasons to start a dry-eye clinic right now, rather than waiting for things to return to some semblance of normalcy after the pandemic is over."

Dr. Gupta adds another point. "During the pandemic, the one population that's been willing to come back into our clinic is our dry-eye patients," she says. "So I wouldn't wait for the pandemic to end to set up a dry-eye clinic, if you're thinking about doing it."

Making a Difference

"Millions of Americans suffer from dry-eye disease," notes Dr. Epitropoulos. "These are some of the most frustrated patients I come across. A lot of them have suffered for years, and we're their last hope. Really helping them is one of the most gratifying parts of practicing medicine for me—sometimes even more than performing cataract or refractive surgery." REVIEW

Dr. Sheppard reports financial ties to Quidel, TearLab, TearScience and Johnson & Johnson Vision. Dr. Thompson is a consultant for Visiometrics, Johnson & Johnson Vision and TearCare. Dr. Karpecki consults for more than 40 dry eye-related companies. Dr. Gupta is a consultant for Johnson & Johnson Vision, TearLab and Quidel. Dr. Epitropoulos is a consultant for Allergan, Sun, Novartis, Johnson & Johnson Vision, PRN, BioTissue and Blephex.

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(Continued from page 18)

to EHRs or show patients what they've seen for an educational experience.

The Peek Retina device underwent a validation trial of 2,152 optic nerve images in 2016. The researchers found that nonclinical photographers were able to use the low-cost smartphone adapter to acquire images sufficient to enable independent remote grading comparable to that done using images acquired by an ophthalmic assistant using a desktop retinal camera. For information, visit peekvision.org.

• ***D-Eye*** (D-Eye; Padova, Italy) is a digital direct ophthalmoscope that attaches to a smartphone (iPhone 5s, SE, 6-generations, 7 or 8) and takes high-quality photos and video of the fundus. D-Eye doesn't require dilation, and offers a 6-degree field of view with undilated pupils for viewing the optic nerve and posterior pole. With dilated pupils, users can achieve a 20-degree field of view. The adapter fits over a smartphone's camera aperture and uses the phone's LED light. A companion D-Eye app allows doctors to enter patient information, focus the retinal camera and record, archive, view and transmit images.

The company says that D-Eye is ideal for telemedicine diagnoses and consultations. The FDA-approved device also uses a HIPPA-compliant cloud-based data management platform to store and share images for evaluation and screening. For information, visit d-eyecare.com.

• ***Paxos Scope*** (DigiSight Technologies; San Francisco) is an FDA-registered portable ophthalmic camera that enables image capture of the anterior segment and retina. Paired with the Paxos mobile app, ophthalmologists can coordinate with others in real-time by using the team collaboration features and also perform documentation in EHRs. The Paxos platform enables provider-to-provider teleconsultations for eye-related disease, says the company.

• ***Fundus on Phone*** (Remidio; Bangalore, India) is a nonmydriatic, smartphone-enabled retinal camera with integrated artificial intelligence. Its optics design is FDA-approved, and the device comes with a user-friendly app for accessing patient data and EHRs. This fundus camera also includes a diabetic retinopathy screening solution with an offline AI for DR detection within 10 seconds, according to the company. One study concluded that the FOP can be an initial tool for mass retinal screening for those with diabetes.[3] For information, visit remidio.us/fop.php. REVIEW

Dr. Cabrera DeBuc has no financial interests in any of the products mentioned.

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Techniques & Tools for Managing Dry Eye

Christine Leonard, Associate Editor

An update on the latest drugs and devices, with tips for managing all severities of dry-eye disease.

Due to its variable presentation, dry eye can be a multilayered, complex problem, and there are a number of different ways of addressing each aspect of the disease. Typical treatments range from lifestyle changes and OTC and prescription drops to punctal plugs, scleral lenses and devices that stimulate tear production. Here, we'll discuss treatment strategies, and review the latest drugs and devices for managing the various components of dry eye.

The State of Dry Eye

"When I was a resident, treating dry eye was mainly a matter of giving a patient some drops," says Douglas K. Grayson, MD, of Omni Eye Services, which has multiple offices in the New Jersey-New York City area. "In the past 10 years, however, it's been taken more seriously. There are more treatments available today. Multifocal lens use has also made us more conscious of treating dry eye, both preliminarily and afterward. You're not going to get good results otherwise; dry eye will decrease the accuracy of measurements like keratometry."

"Dry eye is a tough disease to treat because it's multifactorial and has many possible causes," says Sydney L. Tyson, MD, MPH, of Wills Eye Hospital in Philadelphia. "The disease may be related to evaporation, systemic illness or meibomian gland dysfunction, for example. When you have that type of multifactorial issue going on, it makes it difficult to nail down one treatment that will work for everybody."

That may be one of the reasons dry-eye treatments have been slower to develop, relative to other areas in ophthalmology, Dr. Tyson reasons. "For the longest time, we had cyclosporine, and then we added lifitegrast," he says. "But dry-eye medications just haven't had a technological renaissance like cataract surgery or glaucoma with MIGS devices."

"I think we're just beginning to understand dry eye," says Mitchell P. Weikert, MD, MS, professor of ophthalmology at Baylor College of Medicine in Houston. "In the past decade we've realized there's a major inflammatory component to dry eye. That seems to be where several of the breakthroughs have been, in terms of management. Now we have access to different formulations of cyclosporine."

Cyclosporine has been around for many years and forms the basis for most prescription dry-eye medications such as Klarity-C (Imprimis-Rx), Restasis (Allergan) and a new drug formulation called Cequa (Sun

A Brief Summary of Dry-Eye Options (Products in italics are still in clinical trials)

Artificial Tears		
Blink Moisturizing	J&J Vision	A hypo-osmolar viscoelastic formula that mimics human tears to restore the tear film and provide relief from dry-eye symptoms by regulating osmolarity levels.
Retain HPMC	Ocusoft	A hypromellose ophthalmic solution 0.3% that relieves dry-eye symptoms by resembling natural tears.
Freshkote	Eyevance	Supports the eye's tear film with antimicrobials and a blend of polyvinyl alcohol 2.7% and povidone 2%, which results in high oncotic pressure on the ocular surface to draw excess water from epithelial cells. Preservative-free.
Systane Complete	Alcon	Provides hydration and tear evaporation protection to relieve dry-eye symptoms. Nano-sized droplets form a protective matrix across the eye's surface. Preservative-free options are also available.
Soothe XP Emollient	Bausch + Lomb	Restores the lipid layers with mineral oils to seal in moisture and protect against irritation.
Advanced Eye Relief	Bausch + Lomb	Glycerin 0.3% and propylene glycol 1% replenish tears and prevent irritation.
Refresh Optive Mega-3	Allergan	Restores the lipid layer with a natural oil blend and relieves MGD symptoms. Includes carboxymethylcellulose sodium 0.5%, glycerin 1% and polysorbate 80 0.5%. Preservative-free.
Refresh Celluvisc	Allergan	A preservative-free artificial tear gel that contains carboxymethylcellulose sodium 1%.
Lubricin	Lμbris BioPharma; Novartis	An endogenous human protein that functions as an anti-adhesive, anti-inflammatory biologic lubricant. Lubricin is a developing (Phase II trials completed) therapeutic approach for prescription dry-eye treatment.
TheraTears	TheraTears	A hypotonic, electrolyte-balanced formula that replicates healthy tears.
Optase	Scope	A three-step regimen for dry eye, blepharitis and MGD that includes a moist-heat mask, eyelid cleansing wipes, dry-eye spray and a preservative-free eye drop.
For Treating Inflammation & Promoting Tear Production		
Restasis	Allergan	A prescription ophthalmic emulsion (cyclosporine 0.05%) that increases the eye's natural ability to produce tears and reduces inflammation.
Xiidra	Novartis	A prescription drop (lifitegrast ophthalmic solution 5%) that targets the source of dry-eye inflammation.
Klarity-C	ImprimisRx	A preservative-free cyclosporine ophthalmic emulsion 0.1%.
Cequa	Sun Ophthalmics	A cyclosporine ophthalmic solution 0.09%; this prescription drop increases tear production using nano micellar technology.
Cyclokat	Novagali; Santen	A cationic emulsion of cyclosporine A approved in Europe and in Phase III trials in the U.S.
TOP1630	TopiVert	A non-systemic kinase inhibitor that treats chronic ocular inflammation. Currently in Phase 1/2a proof-of-concept study for dry-eye treatment.
CyclASol	Novaliq	A preservative-free cyclosporine A ophthalmic solution 0.1%, currently under clinical evaluation.
Klarity-L	ImprimisRx	A preservative-free loteprednol ophthalmic suspension 0.5%.
Lotemax	Bausch + Lomb	A loteprednol etabonate ophthalmic suspension 0.5% often used off-label for treating dry eye.
Alrex	Bausch + Lomb	A loteprednol etabonate ophthalmic suspension 0.2%.
Inveltys	Kala Pharmaceuticals	A loteprednol etabonate ophthalmic suspension 1% often used off-label for treating dry eye.
Eysuvis (KPI-121)	Kala Pharmaceuticals	A loteprednol etabonate ophthalmic suspension 0.25% in the FDA approval process.
Reproxalap	Aldeyra Therapeutics	A novel, small-molecule drug candidate for dry eye, currently in Phase III trials of the 0.25% topical concentration. Inhibits reactive aldehyde species, a novel anti-inflammatory target.
Fonadelpar (SJP-0035)	Senju Pharmaceuticals	An ophthalmic solution that facilitates corneal epithelial wound healing with a new mechanism of action: peroxisome proflierator-activated receptor delta agonist. Currently in Phase III development.
DNase	Dr. Sandeep Jain, University of Illinois, Chicago; supported in part by Genentech	A recombinant DNA drop (0.1%) that may reduce symptoms of severe dry eye by breaking up DNA webs that form on the ocular surface as a result of dry eye. Currently FDA-approved for treating cystic fibrosis (Pulmozyme, Genentech) and classified as experimental for dry eye. DNase recently finished a Phase I/II clinical trial.
Genesis 2.0, ACE and Renaissance	Ocular Science	Three amnion-derived eyedrops with a proprietary combination of cytokines, growth factors and molecules to relieve dry-eye symptoms. Currently in commercialization.
iTear	Olympic Ophthalmics	A handheld, noninvasive neurostimulator that stimulates the trigeminal nerve to increase tear production. Currently in clinical trials.

A Brief Summary of Dry-Eye Options

For Blepharitis & Lid Hygiene		
BlephEx	BlephEx	A painless in-office device that helps maintain and clean the eyelid margins. Removes bacteria, biofilm and bacterial toxins. Replacement tips available.
Ocusoft Lid Scrub	Ocusoft	Contains a non-irritating formula that removes dirt, oil, debris and pollen from the eyelids.
Sterilid	TheraTears	An eyelid cleanser for removing external irritants from lids and lashes.
Cliradex	Tissue-Tech	A tea tree-oil-based cleanser that relieves symptoms associated with Demodex, blepharitis, MGD, rosacea, dry eye, chalazion and other lid margin diseases. Comes in towelettes and light foam. Preservative-free.
I-Lid 'N Lash Pro	I-MED Pharma	A professional-use hydrating cleansing gel with 20% tea tree oil for removing ocular debris and intensive cleaning of the lids and lashes. Available in a 50-mL metered dose pump.
TheraPearl Eye Mask	Bausch + Lomb	A hot-and-cold therapy that helps to alleviate dry eye.
For Meibomian Gland Dysfunction		
LacryStim IPL	Quantel Medical	Intense pulsed light system that uses a unique wavelength spectrum and train of pulses to stimulate the lachrymal and meibomian glands, reduce inflammation and improve tear film quality.
LipiFlow	J&J Vision	A vector thermal pulsation system for treating MGD in the office. Delivers therapeutic pulsation energies to meibomian glands to liquefy and evacuate meibum.
iLux	Alcon	A handheld, portable device that targets the meibomian glands with light-based heat and compression under direct visualization in less than 12 minutes.
TearCare	SightSciences	An open-eye, blink-associated device suite that delivers consistent thermal energy to lid structure.
eyeXpress	Holbar Medical Products	An eye hydration system for in-office therapy. A goggle system delivers uniform, regulated heat to the lid structure.
MiBo Thermoflo	MiBo Medical Group	Treats dry eye by delivering consistent, emissive heat and ocular massage to the meibomian glands.
NuLids	NuSight Medical	An at-home treatment for dry eye and lid hygiene. An oscillating tip stimulates the meibomian glands and cleans away debris.
Avenova	NovaBay Pharmaceuticals	A hypochlorous acid wash 0.01% for long-term hygiene management of MGD. Kills a broad spectrum of bacteria. Recently confirmed to kill SARS-CoV-2
Epi-C PLUS	Espansione Group	A no-gel IPL with low-level laser therapy approved for dermatological use in the U.S. For ophthalmic use, white and yellow masks stimulate lymphatics and increase drainage. Wavelength: 633 ±10 nm; emission power: 100 mW per cm^2.
TempSure	Cynosure	A 4-MHz radiofrequency device for reducing wrinkles around the eyes and forehead, sometimes used off-label for treating MGD.
Punctal Plugs		
Vera180	Lacrivera	Synthetic, absorbable lacrimal plugs (poly-p-dioxanone) designed to provide temporary occlusion for approximately 180 days. Available in sizes of 0.2 to 0.5 mm.
Soft Plug Extended Duration	Oasis Medical	A short-term plug (less than three months). Available in sizes of 0.2 to 0.5 mm. Also available: absorbable collagen and permanent intracanalicular plugs.
Scleral Lenses & Amniotic Membrane		
PROSE	BostonSight	A gas-permeable prosthetic device that reduces dry-eye symptoms of pain and light sensitivity and supports ocular surface healing.
DigiForm	TruForm Optics & Contamac	A scleral lens made of material with a low wetting angle to alleviate dry-eye symptoms, corneal distortion and surface irregularities. Also available in Optimum Extra and Optimum Extreme.
Onefit	Blanchard Contact Lenses	A scleral lens to help alleviate end-of-day dryness symptoms and intolerance of environmental effects with soft lenses. Provides a thin fluid cushion over the eye.
Boston IV	Bausch + Lomb	A rigid, gas-permeable contact lens with a non-stick surface that resists dirt and debris. B+L says it's an economical choice for vision correction and dry eye. Other options such as the Boston XO2, XO, EO and ES have B+L's Tangible Hydra-PEG coating technology, which increases surface water retention and lubricity and minimizes deposits on the lens.
Prokera	Tissue-Tech	A cryopreserved amniotic membrane that can serve as a biological bandage for severe dry eye and help restore the corneal epithelium.
AmbioDisk	Katena	A 12-mm sutureless dehydrated amniotic membrane for in-office applications. May be used to treat severe dry eye and ocular surface diseases.
BioDOptix	BioD	A dehydrated, extracellular membrane allograft derived from human amniotic tissue for use as a scaffold for ocular repair.
Oxervate	Dompe	An ophthalmic solution (0.002%) containing a recombinant nerve growth factor that supports corneal innervation.

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Ophthalmics), whose novel mechanism of action employs nanomicellar technology to keep the cyclosporine suspended in solution and aid in cell absorption. "Packaging the individual molecules of cyclosporine in micelles is a fairly innovative delivery system for the medication," Dr. Weikert notes.

A lifitegrast formulation like Xiidra (Novartis) approaches dry eye differently from cyclosporine. "Lifitegrast uses cellular adhesion molecules to interrupt the inflammatory cascade of dry eye," says Dr. Weikert. "It blocks the interactions between T-cells, ocular surface cells and the antigen-presenting cells to dampen the inflammatory cascade that can happen with dry eye. When you decrease T-cell activation, you decrease the release of pro-inflammatory cytokines."

"Drops are a first-line therapy for dry eye, but patients have variable responses and side effects," Dr. Tyson points out. "In addition to occasional burning, drops can be expensive, so we sometimes use compounded medication instead, which is a little less expensive. Some patients report that the drops taste bad. Even though they're in the eye, these medications can still cause a metallic taste in the mouth. Other options include omega-3 fatty acid pills, which can be taken orally by patients to help dry-eye symptoms as well."

Treatment Approaches

Treating dry eye is a matter of finding the right combination of therapies, Dr. Tyson explains. "It's a long-term treatment, not a cure," he says. "As dry eye worsens, we up the ante in terms of therapy. A stepwise approach is necessary."

Dr. Weikert divides his dry-eye management strategies into four categories: increase tear production; tear replacement; improve tear quality; and protect the ocular surface. "Anti-inflammatory medication helps to increase tear production," he says. "In terms of replacing tears, there are many artificial tears available with different compositions, and they're better than what we had in the past. They don't address the root cause of inflammation, however."

Inflammation lies at the heart of most dry-eye disease, physicians say, so identifying the source or sources of inflammation is key to formulating your approach. "Evaporation and meibomian gland dysfunction are two ways that inflammation processes affect the lacrimal gland," Dr. Tyson explains. For mild to moderate forms of dry eye, Dr. Tyson often turns to artificial tears or punctal plugs.

"If the dry eye is related to evaporation, there are only two ways to fix it: You can either increase tear production or increase the supply and retain more tears," he continues. "That's where punctal plugs come in. If the dry eye is more of a meibomian gland issue, we do warm compresses, lid hygiene and use devices like BlephEx (BlephEx), which exfoliates the biofilm on the lid surface to remove bacteria and exotoxins. We can also use heating treatments or intense pulsed light therapies like LipiFlow (Johnson & Johnson Vision) or iLux (Alcon) for meibomian gland dysfunction.

"Using tears is a major part of the dry-eye regimen," agrees Dr. Grayson. "A short course of Lotemax (Bausch + Lomb) or a steroid drop for a while is another option. More serious cases may warrant something like Restasis, Xiidra or Cequa for a few weeks. For very severe cases, you may want to use an amniotic membrane graft such as Prokera (Bio-Tissue) [a cryopreserved AMG] or BioDOptix (BioD) [a dehydrated AMG]." AmbioDisk (Katena) is another dehydrated amniotic membrane option.

Expressing Meibomian Glands

A recently published study of dry-eye disease symptoms found that in the sample population (n=2,346; 77.4 percent female, 87.1 percent Chinese), meibomian gland dysfunction, along with lower forniceal papillary reaction, was the primary determinant of symptoms, contributing significantly to symptom severity compared to traditional dry-eye signs.[1]

Poor tear quality is often secondary to blepharitis, resulting from blocked meibomian glands. "Doxycycline and azithromycin are classic treatments for blepharitis," Dr. Weikert says. "They have some anti-inflammatory properties as well."

Manual therapies are also suitable for blepharitis. Dr. Grayson says he recommends using warm washcloths, baby shampoo or lid-scrub pads to help clear up symptoms.

For more serious cases, heating the meibomian glands with a device is a common way to express the glands and return the meibum to the proper consistency for better tear film quality. "LipiFlow (J&J Vision) clips around the eyelids and heats the meibomian glands to express them and mobilize the oils out of the glands," says Dr. Weikert. The iLux (Alcon) and the MiBo Thermoflo (MiBo Medical Group) work in a similar manner. The NuLids device, which patients can use at home, also helps treat MGD by massaging the glands.

However, Dr. Weikert points out that in order to improve the meibomian glands and their secretions, your patient has to have meibomian glands. "Those with very advanced blepharitis may have lost their meibomian glands and therefore won't be candidates for treatment because there's nothing left to treat, or it's substantially reduced," he says.

Supplementing Tears

"Artificial tears still play a valuable role by supplementing tears," Dr. Weikert says. "They're a low-cost al-

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ternative that can help people with mild dry eye. Some people do get by with only a little tear replacement once a day, but those are very mild cases; anything more than that requires additional therapy.

"We blink every six to 10 seconds, so you need tears that don't evaporate for at least that amount of time," Dr. Weikert continues. "Many patients have tear instability, and their tears evaporate in only two to three seconds, so before their next blink, their ocular surface is exposed to the air for several seconds. That exacerbates surface damage."

Dr. Grayson points out that there's a new over-the-counter eye drop called Optase, which has hyaluronic acid and artificial tears in it. He has yet to try it out. Optase (Scope) is part of a dry-eye regimen that includes a moist-heat mask and eyelid cleansing wipes along with a dry-eye spray.

Popular among Dr. Grayon and his colleagues is Freshkote (Eyevance), another OTC artificial tear. "It's more of a milky drop," Dr. Grayson says. "It has antimicrobial properties as well." Freshkote consists of a blend of polyvinyl alcohol 2.7% and povidone 2%, which Eyevance says results in a high oncotic pressure on the ocular surface that draws excess water from epithelial cells.

Another way to increase tear production is through nerve stimulation, the mechanism of action behind Allergan's now-defunct intranasal tear stimulator, TrueTear. The TrueTear device activated the nasolacrimal reflex by delivering electrical currents to the neurons in the nasal cavity to temporarily increase tear production. Allergan stopped manufacturing TrueTear recently and is offering full refunds for devices purchased within the last three years. The company says the decision has nothing to do with the safety or efficacy of the product.

There are also some at-home methods, including a forthcoming medication in development by Oyster Point Pharmaceuticals in the form of a preservative-free nasal spray. This spray is a nicotinic acetylcholine receptor agonist that helps the parasympathetic nervous system promote natural tear-film production and re-establish tear-film homeostasis.

Clinical evidence for a handheld device called iTear (Olympic Ophthalmics) was presented at the virtual meeting of ASCRS this year. The iTear device is a noninvasive tool that stimulates the trigeminal nerve, resulting in activation of the parasympathetic nerve pathway that controls tear-film homeostasis.

Avoiding Preservatives

"Preservatives are very pro-inflammatory and can, in and of themselves, cause ocular surface disease," Dr. Weikert notes. He says that moving patients off preserved tear formulations can be key for seeing clinical improvement in their dry eye.

"We see this often in our glaucoma patients," he says. "These patients are usually on multiple drops for years at a time, so their ocular surface is constantly exposed to preservatives, depending on the type of glaucoma drop they're on. Using multiple drops over the years can change the chemistry of the tear film on the ocular surface, so it's not unusual to see significant ocular surface disease in these patients. This type of dry eye can be very difficult to manage because the patient may not be able to switch their glaucoma drops to a preservative-free formula."

Oftentimes, insurance companies push for generic eye drops. Dr. Weikert notes, however, that most generic drops aren't typically available in preservative-free formulations and often have harsh preservatives such as benzalkonium chloride, which has consistently demonstrated toxic effects in clinical studies. These effects range from tear-film instability and loss of goblet cells to conjunctival squamous metaplasia and apoptosis.[2]

Autologous Tears

If artificial tears, steroids and medications aren't working for a patient, autologous serum tears are another option. "It's their own immune system working for them," Dr. Grayson says. "Serum tears can be a pain to get, but they work."

At the Cullen Eye Institute at Baylor College of Medicine, plasma-based tears are frequently used for patients with severe dry eye. "Serum tears are made from plasma, but it's plasma without clotting factors," explains Dr. Weikert. "We're formulating platelet-rich plasma, which has a higher concentration of platelet factors compared to serum tears, so they have some advantages and carry some additional anti-inflammatory components that can help relieve dry eye.

"There aren't really any side effects to plasma tears," he continues. "Cost is an issue because they're typically not covered by insurance. Sometimes the preparations are off-label, and plasma-based tears require a blood draw, so that's another cost." Physicians say the process of making the tears is also time-consuming and complex compared to other dry-eye therapies.

Amnion-derived Drops

Another new type of therapeutic eyedrop in the works is derived from amniotic membrane. "Ocular Science has started making amniotic cytokine extract," Dr. Weikert says. "Amniotic cytokine extract is another tear form that has components from amniotic membrane, which is pro-anti-inflammatory. The drop form helps replace tears."

There are currently no FDA-regulated amnion-derived drops available in the United States. Noveome Biotherapeutics (formerly Stemnion;

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Critical **first steps** to treating dry eye symptoms include ocular lubricants, lid hygiene and dietary modifications such as oral fatty acid supplementation.[2]
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Pittsburgh, Pennsylvania) has an amnion-derived cellular cytokine solution for wound healing and dry eye currently in FDA clinical trials. Barcelona Tissue Bank (Catalonia, Spain) has an internationally available amniotic membrane extract for use in dry eye, and Next Biosciences (Johannesburg, South Africa) has an umbilical cord-derived blood serum for severe dry eye.

Protecting the Surface

For severe cases of dry eye, sometimes a bandage lens is necessary to protect the ocular surface. "We're proponents of contact lenses," says Dr. Weikert. "Some scleral lenses also work for keeping a constant layer of fluid against the cornea."

PROSE (BostonSight) is an ocular prosthesis commonly used for treating severe dry eye. "It's expensive," Dr. Weikert cautions, "but it's been life-changing for certain patients, such as those who are dry from graft-versus-host disease. Those who've had leukemia and received bone marrow transplants can sometimes contract this disease. The immune cells from the bone marrow transplant trigger the immune system, which can attack the surface of eye, resulting in significant dry eye."

Dr. Tyson says he rarely uses scleral lenses for treating dry eye. However, he adds, "I find it's helpful for conditions like filamentary keratitis, where the cornea needs protection from the eyelid. You can use a bandage lens for that as well as amniotic membrane if it's severe enough."

Dr. Weikert adds that amniotic membrane is well-suited to a short treatment to get someone over a significant problem, but in terms of dry eye, he says, "I haven't come across any literature that demonstrates the efficacy of it in a good clinical trial for prolonged relief of dry eye."

To Keep in Mind ...

Contracting coronavirus through the ocular surface is a concern. "If you have dry eye, the barrier function of the ocular surface can be decreased," Dr. Weikert says. "We can't draw any direct conclusions, but we know dry-eye patients are more susceptible. They may want to consider wearing eye protection in addition to a mask." REVIEW

Drs. Tyson and Grayson have no financial disclosures related to any of the products mentioned. Dr. Weikert has been a diagnostic equipment consultant for Alcon.

1. Teo CHY, Ong HS, Liu Y, et al. Meibomian gland dysfunction is the primary determinant of dry eye symptoms: Analysis of 2,346 patients. The Ocular Surface 2020;18:4:604-612. [Epub ahead of print].
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Debating Anti-VEGF Injections

Sean McKinney, Senior Editor

Here's why comprehensive ophthalmologists shouldn't inject—or why they should.

Some ophthalmologists are divided over who should administer intravitreal injections to prevent blindness—retinal specialists only or retinal specialists *and* comprehensive ophthalmologists. "It's critical to have the ability to confirm the correct diagnosis before injection, and that has been a problem in some instances involving comprehensive ophthalmologists," says Timothy G. Murray, MD, MBA, president of the American Society of Retina Specialists, which he says officially opposes injections by non-retina specialists. "The diagnosis has been incorrect in these cases. The injection, many of us feel, is the easiest part of the procedure. The hardest part is the diagnosis, comparative monitoring of each injection with OCT and confirming that the patient is clinically sound. To me, it's very clear that the best practice for intravitreal injections for retinal diseases is treatment by a retina specialist."

However, comprehensive ophthalmologists who inject anti-VEGF agents believe advanced residency training in retina care has sufficiently prepared them to provide anti-VEGF therapy, which they say is needed in remote places where retinal specialists can be hours away from needy patients. Rising demand for treatments could also soon be a concern.

Where do you fit in between the two sides of this debate? It depends on your practice orientation, location, training and interests. Read on to find out how this issue could shape the future of the retinal care your patients need.

More Retina Training

Ophthalmology residency programs have focused more on retina training in recent years, some more intensively than others. The Accreditation Council for Graduate Medical Education mandates that each resident perform at least 10 intravitreal injections and 10 panretinal photocoagulation procedures before graduation.[1] Michael Patterson, DO, a comprehensive ophthalmologist who performs thousands of intravitreal injections in Crossville and Cookeville, Tennessee, says he trained extensively on retinal care as a resident at the University of South Carolina, performing "hundreds and hundreds" of intravitreal injections under the direction of John "Jack" Wells, MD, a high-profile retina specialist who served as the program director. "We did more retina injections than any other procedure during my residency," he adds. "There wasn't even a close second."

Besides Dr. Wells, retinal specialist

Philip J. Rosenfeld, MD, PhD, professor of ophthalmology at Bascom Palmer Eye Institute in Miami, also provides residents with heavy doses of training in retina. "Our residents get extensive training in intravitreal retinal injections, the indications for their use, when to retreat, and how to deal with complications," he says. "I'm totally comfortable with any of them giving intravitreal injections after they complete their residency. If an ophthalmologist is adequately trained and has appropriate support from a retina specialist if complications arise, then intravitreal injections don't have to be given by a retinal specialist. But injections have to be given by a trained ophthalmologist who really understands the disease being treated; when it's necessary to inject; how to administer the injection; and what to look for after the injection regarding the potential complications."

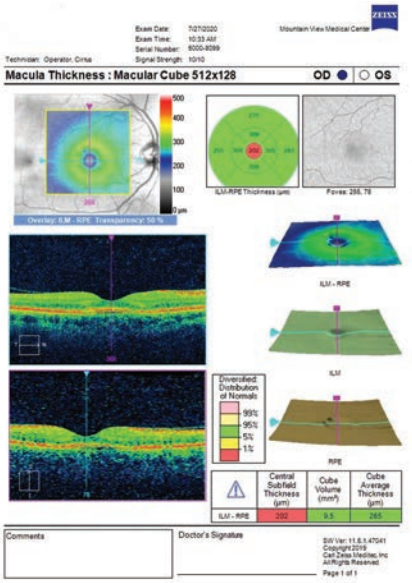
Dr. Rosenfeld expects more comprehensive ophthalmologists coming out of training will need to provide this care when intravitreal therapy for dry AMD is mainstreamed and the number of injections skyrockets in the years ahead. "We'll need to meet the demand," he says.

(See "Why Injections May Spike," below.)

Talen Curry

Comprehensive ophthalmologist Katherine E. Johnson, MD, FACS, of Fairbanks, Alaska, used a trial injection of Eylea for a patient referred to her with possible serous chorioretinopathy. Suspecting masked AMD, she confirmed the diagnosis when the patient responded to the injection. After diagnosis, a sample of Eylea was injected for immediate treatment and her staff completed authorizations and enrolled the patient in the Eylea financial assistance program.

Katherine E. Johnson, MD, FACS



This OCT scan showed resolution of a PED and subretinal fluid, demonstrating improvement after Dr. Johnson's anti-VEGF injection confirmed AMD. Subsequent follow-ups found a return of the PED and subretinal fluid, which was treated successfully with Eylea every four weeks.

Injection Challenges

Dr. Murray of ASRS acknowledges that more ophthalmology residents are now learning to perform intravitreal injections. "But training ophthalmology residents to provide these procedures doesn't make them capable of properly managing intravitreal injections and the variety of complex retinal diseases encountered in clinical practice," he says. "The challenges

Why Injections May Spike

Philip J. Rosenfeld, MD, PhD, professor of ophthalmology at the Bascom Palmer Eye Institute in Miami, sees a "tsunami" of injections brewing on the horizon, adding substantially to today's 3.1 million-plus injections per year. The development of new treatments will increase the durability of the injections for exudative and neovascular macular and retinal diseases, decreasing the current need for those treatments, he acknowledges. "But exciting new therapies for the treatment of geographic atrophy could potentially increase the number of patients needing injections more than tenfold," he says.

Two injectables in clinical trials are positioned to have an impact, demonstrating the possibility of reducing the rate of GA growth:

- Pegcetacoplan (APL-2, Apellis Pharmaceuticals), is a complement C3 inhibitor.
- Avacincaptad pegol (Zimura, Iveric bio), is a novel complement C5 inhibitor.

"Unlike wet AMD, in which we can monitor the patient with OCT to determine the need for injection, in dry AMD, there will be no easy way to determine whether we need to continue injecting or whether we can stop or delay the injections," Dr. Rosenfeld says. "Most likely, once we start injections for dry AMD, we won't stop until the patient's vision has been lost or future studies show that we can increase the treatment interval."

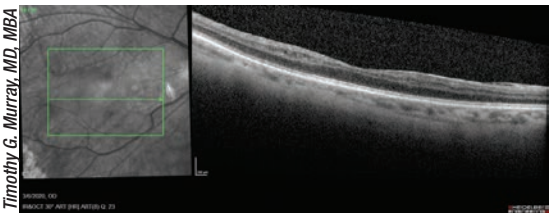
Eventually, he says, doctors will need to treat patients earlier for smaller areas of geographic atrophy, as continuing studies confirm efficacy. "We're most likely going to want to use the treatments to even prevent geographic atrophy from forming," he notes. "So not only will the treatment apply to late dry AMD, but also what we call intermediate AMD. That will encompass a huge number of patients. Remember that only 10 to 15 percent of dry AMD patients progress to wet. So, we're talking about 85 to 90 percent of these patients who are dry potentially benefiting from these injections."

we've been trained to deal with include all retinal diseases, plus unexpected and potentially serious complications."

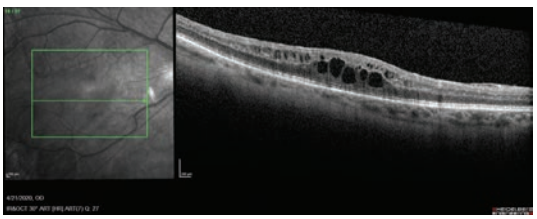
Carl C. Awh, MD, the president-elect of ASRS, agrees that a retina specialist should treat these patients. "These drugs work so well that you don't necessarily have to be an expert to get a very good result for most patients," he admits. "Giving the injection is technically within the skill set of any ophthalmic surgeon. But a lot of cases aren't typical. Even in clinical trials, some well-meaning doctors haven't necessarily recognized when their patients weren't doing as well as they could've been doing. So for those of us who started in practice prior to this age of miraculous anti-VEGF drugs, when we watched our patients almost inexorably lose their central vision over the years, anything that prevents this outcome can seem like a success. But we've learned that optimal treatment with anti-VEGF therapy can mean the difference between vision that's good enough to drive a car and just functional central vision. No matter who's treating them, very few patients will become legally blind. But there's a huge difference between having 20/60 vision and 20/25 vision.

"Because of our extensive training and exclusive focus on the retina, it would be very hard for any general ophthalmologist to show in any objective way that he or she would be better than a retinal specialist at managing a patient with a chronic, potentially blinding retinal condition," continues Dr. Awh, who practices at Tennessee Retina, the largest retina group in central Tennessee. "I don't think there are many areas in this country where care by a retina specialist is not available. However, above all, it's essential that patients who need treatment have access to treatment. So if there were a scenario in which the only way for the patient to get treatment was through a comprehensive ophthalmologist, and not a fellowship-trained retinal specialist, I would be all in favor of that."

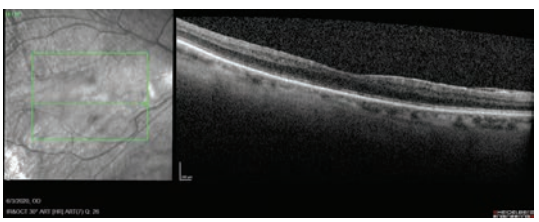
Timothy G. Murray, MD, MBA



This 56-year-old female, with a history of Type-2 diabetes mellitus, initially poorly controlled with hemoglobin A1C (HgA1C) of 11.2%, presented at 20/50 OD. She was injected with bevacizumab (Avastin) every three weeks (note minimal macular edema with anomalous vasculature in the SD-OCT scan) and returned to the care of a comprehensive ophthalmologist at 20/25.



The patient experienced decreased central vision and returned to the retinal specialist at 20/100, reporting that she was told by the comprehensive ophthalmologist that she didn't need another injection and could be seen in three months.



The patient was treated with intravitreal bevacizumab at three-week intervals, while macular edema was monitored via SD-OCT. At her last visit, the patient, at 20/30, reported vision that was improved but still "foggy" and not as good as it had been. SD-OCT revealed decreased macular edema but persistent fluid. Short-interval, ongoing follow-up with consistent anti-VEGF treatment was recommended.

Caring for the Underserved

Katherine E. Johnson, MD, FACS, who trained under Dr. Rosenfeld at Bascom Palmer, is just the type of comprehensive ophthalmologist Dr. Awh has in mind. Dr. Johnson, who has cared for patients in Mexico and Nepal and has founded two international programs aimed at preventing blindness, owns a private practice that serves a population of 100,000 residents in Fairbanks, Alaska, and surrounding areas. "When I showed up here 12 years ago, nobody was doing intravitreal injections," she says. "Patients were sent to Anchorage for injections, requiring a six-hour drive or one-hour flight. The impact of those trips financially—plus the burden the trips put on the schedules of patients and their families—was very significant. It makes you wonder how many times patients just went without treatment instead of taking those long journeys every month. If the 'standard of care' is making patients and their escorts travel over six hours each way for a monthly injection, then I would say that's a terrible standard of care. It's hard for me to believe that doctors would want this for patients when the alternative I offer is available."

Dr. Johnson agrees that a doctor injecting anti-VEGF drugs should be capable of managing the complications of any procedure he or she performs. "Of course, the most concerning complication would be endophthalmitis, and I'm very capable of doing a vitreous tap and antibiotic injection, if needed," she says. "In fact, when I arrived in Fairbanks 12 years ago, I designed the protocol for this procedure at my local hospital, based on the Bascom Palmer protocols. Luckily, the need is rare, but the ability to perform this now exists locally."

Dr. Johnson administers 10 to 12

intravitreal injections per day; medical retina constitutes about half of her practice. She notes that the only procedure she wouldn't perform is a vitrectomy. "But statistically, the risk of endophthalmitis is exceptionally rare and a vitreous tap-and-inject can postpone a needed vitrectomy to allow for travel time to Anchorage," she says. "In fact, the last infection I treated this way was a postoperative infection from retinal surgery performed elsewhere, demonstrating the importance of having this skill set in remote areas."

In the event of a complication, she adds, "I'm able to do an anterior parenthesis without any hesitation." Because Dr. Johnson is a comprehensive ophthalmologist, she points out that she can monitor both the patient's glaucoma and AMD. "Because I have a unique understanding of the status of a patient's glaucoma progression, I can factor glaucoma-related information into my decision-making," she says. "We have patients who have advanced-stage glaucoma. And with macular degeneration, we need to decide if we should still chase the macular degeneration in eyes that are 20/800. We might hold off on an injection if a patient's glaucoma is more threatening to the patient's vision than the macular degeneration."

Dr. Johnson also sends out images to five or six retinal specialists for second opinions when necessary.

Similarly, Dr. Patterson, the comprehensive ophthalmologist in Tennessee, says anti-VEGF treatments add another dimension to his relationship with local retinal specialists. "The retinal specialists help us and we help them," says Dr. Patterson. "The retinal specialists may experience a complication from an IOP rise or acute glaucoma from putting in a dexamethasone implant [Ozurdex, Allergan]. They can't fix this because they don't do tubes, and I can use tubes to help. They aren't equipped with an SLT device, which I can use to help with their ocular hypertension patients. Meanwhile, if we do cataract surgery that results in a dropped nucleus and endophthalmitis, they can fix that for me. I'm not worried because I love our retinal specialists. We do a ton of work together."

Deep Misgivings

Despite these positive experiences, Dr. Murray, speaking on behalf of many of his colleagues in retinal care, firmly believes that patients face unnecessary risks when receiving anti-VEGF injections from a non-retinal specialist. He notes that no case of neovascular AMD, retinal vein occlusion or diabetic retinopathy is the same.

"Deciding on what to treat and when to treat and whether to discontinue treatment can have major implications for your patient's vision," he says. "Determining when an eye has transitioned from dry to wet AMD can be daunting. Some eyes may have indolent, occult neovascular AMD

Which Doctors Inject Anti-VEGF Drugs?

A total of 3,102,033 intravitreal injections were performed in 2017, including aflibercept (40 percent), bevacizumab (26 percent), ranibizumab (21 percent), triamcinolone (4 percent) and dexamethasone (1 percent), according to an abstract based on 2017 Medicare claims that was presented at the ASRS 2020 Virtual Annual Meeting on July 27.[1] The abstract revealed that retina specialists performed 92 percent of anti-VEGF injections and that non-retina specialists in ophthalmology performed 4 percent of the injections.

The numbers of retina specialists and non-retina specialists performing these procedures are apparently not nearly as uneven as the numbers of procedures they perform. A report in the April issue of Ophthalmology, using 2016 Medicare claims, showed 3,637 providers performed anti-VEGF injections in 2016, including:

- Seventy-one percent (2,591), classified as retina specialists, who provided anti-VEGF therapy, retinal laser treatments or retinal surgery; and
- Forty percent (1,046)—including 136 ASRS members—who were hybrid providers, offering cataract surgery in addition to the retinal services provided by retina specialists.[2]

1. Emerson GG, Lapakkos Z, Leder HA, Mason RWH, VanderBeek BL. Medicare 2012-2017 Invitreal Injections: Certification and Credentials of Providers. July 26, 2020. ASCRS 2020 Virtual Annual Meeting. Online.
2. Pandit RR, Wibbelsman TD, Considine SP, et al. Distribution and practice patterns of retina providers in the United States. Ophthalmology 2020 20:S0161-6420:20:30367-5.

that remains stable for a prolonged period without intervention. Previous experience and close monitoring of these eyes is imperative for deciding when treatment is indicated."

Other important challenges to be mindful of include:

- determining if a PED is associated with choroidal neovascularization and requires treatment;
- responding to a retinal pigment epithelial detachment;
- having to determine when an eye with neovascular AMD has type 1, 2 or 4 CNV, retinal angiomatous proliferation and/or polypoidal choroidal vasculopathy. Each of these subcategories of wet AMD may respond differently to anti-VEGF agents. Some are better treated with a thermal laser or photodynamic therapy, rather than with anti-VEGF agents.
- determining if fibrosis in a lesion indicates stability; and
- responding to recurrent CNV.

"You need to be prepared for the unexpected," Dr. Murray says. Macular edema from retinal vascular occlusion or diabetic retinopathy may not compromise vision in some cases or, when it does, may not respond well to anti-VEGF agents, he points out. "A strong background in retina care is required to determine when a combination of intravitreal steroids and continuing anti-VEGF therapy is needed," he says. Another example: Lack of capillary perfusion can be found in retinal vascular occlusions and diabetic retinopathy, affecting long-term treatment. "The physician needs to know when to use the laser. Laser treatment and anti-VEGF may be best for some patients. Knowing when and how to incorporate PRP into the long-term care of proliferative retinopathy is critical."

Too Many Challenges?

Is it impossible to meet all of these challenges in a comprehensive ophthalmology practice? Dr. Johnson says the answer is no. "I do PRPs and retinal tear demarcations all the time," she says, noting that she combs the literature and attends Hawaiian Eye and the Retina Subspecialty Day at the American Academy of Ophthalmology meeting to keep up to date. "I don't laser the entire retina at one time because I have the luxury of bringing patients back multiple times to decrease the inflammatory response to the laser, just as I was trained to do at Bascom Palmer. I certainly have enough volume to maintain a high-level skill set in medical retina. There are several other fields that I don't practice in because of limited volume to maintain a level of excellence, such as pediatrics or corneal-transplant. I'm only going to practice exceptional quality medicine."

She recalls when a stray vitreous strand kept one of her injection sites open for three days. Because she uses a post-injection Betadine drop as a "Seidel test," she avoided a disastrous outcome by bringing the patient back several times over three days and treating the area with antibiotics. Another time, a patient visited with what appeared to be central serous chorioretinopathy. She suspected masked wet AMD and confirmed the diagnosis when the patient responded to a trial injection of Eylea. (*See page 49.*)

"What I do takes longer, but I don't need to meet the demands of a 60-patient injection clinic," she says. "I dedicate time to a quality injection. I perform all needed risk mitigation—and more, in some cases—and I exceed standards of clinical care."

Continuing to Evolve

Ronald Frenkel, MD, a retinal and glaucoma specialist in Stuart, Florida, believes changes in anti-VEGF therapy will continue to evolve, especially as efforts to address care disparities and disease burden progress. "This will be an individualized issue," he says. "The comprehensive ophthalmologist will need the right training in retina. Rural areas may have slightly—or vastly different—needs and availability of retinal doctors, so the patient might be treated by a comprehensive ophthalmologist in those areas more so than in other areas, where retinal specialists may be available. I'm hesitant to draw firm lines in the sand." REVIEW

1. Accreditation Council for Graduate Medical Education. Ophthalmology. https://www.acgme.org/Specialties/Documents-and-Resources/pfcatid/13/Ophthalmology. Accessed 8.12.20.

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How to Manage Ocular Herpes

Michelle Stephenson, Contributing Editor

A review of how to decide which oral and topical agents to use, based on the presentation.

Herpes simplex and herpes zoster viruses can have many ocular manifestations, some of which are serious and vision-threatening. Both conditions have the potential to be chronic and recurrent, as well. Here, experts share the protocols they use when dealing with these sometimes challenging cases.

Herpes Simplex

Cornea specialist Francis Mah, in practice in La Jolla, California, notes that the live virus can cause epithelial keratitis and other ocular manifestations. The classic herpes simplex presentation is a dendrite that can form on the surface of the cornea. The treatment for this is epithelial scraping with an instrument such as a Kimura spatula, along with trifluridine drops—which was a huge advance at the time they were introduced—and oral antivirals, such as acyclovir, valacyclovir and famciclovir, the most commonly used treatments among cornea specialists. A newer agent, ganciclovir gel, is also an option. "Typically, people will develop a dendrite when they're run down, when they've traveled, and when they are stressed or sick," he says. "Sunlight can also stimulate it. Dendrites don't cause much pain. The main symptom will be a change in the patient's vision."

Bennie Jeng, MD, who is in practice in Baltimore, prefers to treat herpes simplex keratitis with oral acyclovir or oral valacyclovir, rather than topical ganciclovir or trifluridine. "Ganciclovir is very expensive, and trifluridine is very toxic to the surface of the eye," he says. "In addition to oral treatment, the cornea can be gently debrided by rolling a cotton tip over the dendrite. That can debulk some of the active viral replicating bodies within the cells. They usually heal after the treatments discussed above, and they may or may not come back. But, once the virus is in you, it can always return."

According to Chesterfield, Missouri, ophthalmologist Jay Pepose, patients who present with pure epithelial keratitis don't typically suffer permanent vision loss. "In fact, it's sometimes self-limiting even without treatment," he says. "Before antivirals, many ophthalmologists just did debridement. In general, dendritic or geographic keratitis without stromal involvement are conditions where a topical antiviral is an appropriate therapy. In the United States, we have ganciclovir and trifluridine. Most people feel that ganciclovir is less toxic and more effective, so we usually start with topical ganciclovir five times a day, and then maybe we taper down to three times a day until

This article has no commercial sponsorship.

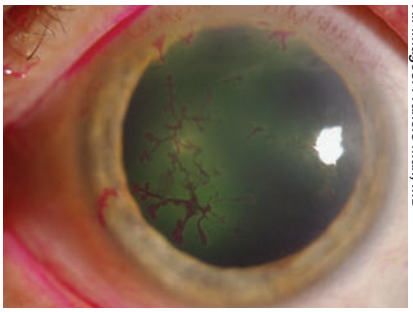
the lesions resolve."

Dr. Pepose believes that, even for patients with pure epithelial disease, it's best to prescribe an oral antiviral. "If you see a lesion on the cornea, where is it coming from? It's coming from the trigeminal ganglion," he says. "If they recurrently reactivate, some of those cells are going to go lytic, and some of the ganglion cells will further establish a latent infection. Over time, the patient could lose enough of those sensory neurons that the eye would become desensitized, and he or she could wind up with a neurotrophic keratopathy. So, I think it's important to shut down the infection at the source, and the only way to do that is with an oral antiviral. I usually use valacyclovir because it's generic, it's inexpensive and it's effective."

Another presentation of herpes simplex is dead viral particles on the cornea that elicit an immune response. "Our body finds them and starts reacting to them. So, it's our own body that's causing edema and opacity in the cornea," Dr. Mah says. "The treatment for this is steroids, but steroids can reactivate epithelial disease, so you can actually get the epithelial disease by treating the stromal disease.[1] We use a steroid with an antiviral, and the antiviral is for prophylaxis."

The Herpetic Eye Disease Study II showed that the live virus and epithelial disease can be suppressed with oral acyclovir.[2] "For people who have recurrent issues of live virus, we recommend oral antivirals indefinitely," says Dr. Mah. "For people who have recurrent stromal keratitis, we recommend long-term steroid drops with either oral or topical antivirals to prophylax that."

Dr. Jeng says stromal keratitis comes in two varieties: necrotizing; and immune-mediated non-necrotizing. "Necrotizing is where active virus is actually eating away at the cornea," Dr. Jeng says. "Obviously, that would require high-dose treatment with oral acyclovir or valacyclovir. But, if it's the more common immune-mediated herpes simplex stromal keratitis, where it's mostly an inflammatory process, then the treatment is topical corticosteroids. I prefer to add oral antivirals, as there could be some viral activity stimulating the immune response, but the role of oral antivirals in these cases is really prophylaxis against having recurrences. Many years ago, HEDS demonstrated that, if you treat patients with a history of stromal keratitis with a low prophylactic dose of oral acyclovir (400 mg twice daily), their chance of experiencing a recurrence decreased by around 40 percent. Generally, I start these patients on antivirals, as well as topical steroids for stromal keratitis. After the inflammatory process is managed, I keep them on a prophylactic dose, because, when this heals, you can end up with some scarring that can decrease vision. Every time you experience a recurrence, there is a possibility for more scarring and decreased vision."



All images: Francis Mah, MD

The classic herpes simplex virus appearance: An epithelial dendritic keratitis.

Dr. Pepose agrees that herpes stromal keratitis can have visual consequences. "When HEDS was initiated in 1989, there was a lot of controversy about using steroids in patients with herpes," he says. "Many people felt that corticosteroids could enhance the replication of the virus and cause more problems. So, HEDS decided to look at the role of steroids in patients with stromal keratitis. It really was a groundbreaking study in many ways. They came to the conclusion that patients who were given steroids did better. Seventy-three percent of the placebo arm failed, compared with 26 percent in the prednisone arm. This showed that there was a role for steroids. In fact, those patients were on steroids for 10 weeks and then they stopped. After 10 weeks, a lot of them lost the clinical gain. This showed us that you have to taper the steroid very gradually. Patients might need to be on low-dose steroids for a significant period of time, possibly months."

Patients with ocular herpes can also develop endotheliitis. "This causes corneal swelling because endothelial cells become stunned and don't work anymore," Dr. Jeng notes. "It's generally treated with both oral acyclovir as well as topical steroids for the inflammation."

A rarer form of herpetic eye disease is disciform keratitis. These patients experience round, demarcated stromal and epithelial edema, and the formation of granulomatous keratic precipitates. "In the past, there was some debate about whether this condition is more of an anterior chamber inflammation or direct infection of endothelial cells," says Dr. Pepose. "Many people feel that there's probably some direct infection of corneal endothelium because the amount of inflammation is usually pretty sparse, and yet the amount of edema is pretty profound. These patients respond nicely to a tapered course of topical steroids. Then, there's necrotizing keratitis, which means that there's stromal involvement with ulcerations. These patients must be followed carefully because they can melt and perforate. It's really important to try to get them to re-epithelialize as quickly as possible."

Other rare presentations are herpetic retinitis, which is sometimes accompanied by herpes encephalitis, and there is acute retinal necrosis syndrome. "There are a variety of viral etiologies to that, including herpes zos-

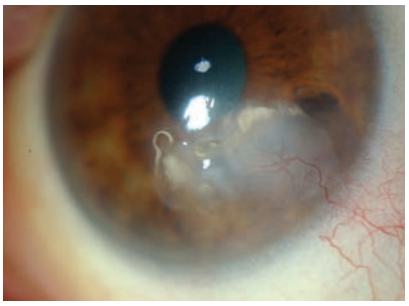
ter and herpes simplex," Dr. Pepose adds. "All of those patients are treated systemically with oral or intravenous antivirals, and in some cases with adjunctive intravitreal injection of antiviral agents."

Herpes Zoster

With varicella zoster virus, the shingles manifestation is most concerning, according to Dr. Mah. "People who get chicken pox are at risk for shingles. Shingles is the reactivation manifestation of the zoster virus," he says. "Actually, the chicken pox vaccine that came out a couple of decades ago has caused a bit of an epidemic of shingles. The vaccine seems to offer protection against chicken pox in the young, but there seems to be an unintended increased risk of shingles in these folks. With the vaccine, people are also at risk for shingles at a younger age. When it affects the eye, patients can get issues ranging from glaucoma to neurotrophic keratitis to iritis. It's very important to diagnose it early and start the patient on significant doses of oral antivirals. Antivirals should be prescribed for at least a week to try to prevent some of the long-term manifestations of the ocular issues of shingles."

Dr. Mah explains the mechanism behind the post-shingles eye problems. "This virus can cause nerve damage and an immune reaction," he says. "Very simplistically, the dead viral antigens are in the eye, and the immune system finds them and causes a reaction. It's actually our own bodies causing the majority of the common issues post-shingles. [Management is typically steroids.] In this case, live virus usually does not come back unless there's an issue with the immune system. Most people believe there is a benefit to long-term prophylaxis with zoster as well as simplex, but we don't have that study yet.

"More questions surround zoster than simplex," Dr. Mah continues.



Experts warn that you can reactivate the epithelial disease with the treatment for the stromal disease, shown here.

"Part of the reason is that we can't grow the virus well, and we don't have many animal models of the zoster virus. We have many animal models of the simplex virus, and we can grow it more easily, so it's easier to study."

Dr. Jeng agrees that herpes zoster is far more complicated than herpes simplex. Epithelial keratitis caused by herpes zoster manifests in two ways. "Sometimes, it's just a mucous plaque, which doesn't necessarily need to be treated with anything beyond lubrication," Dr. Jeng explains. "If a patient gets a pseudo-dendrite, which has been shown to have active viral replication, then treatment is warranted. It can be treated either orally, which is my preference, or topically with ganciclovir. Trifluridine doesn't work for zoster."

Patients can also develop immune-mediated stromal keratitis. "Again, topicals don't work, so it's treated with oral acyclovir or valacyclovir," Dr. Jeng says. "It's important to note that zoster doses for treatment with these oral medications are double what they are for simplex. You can develop an endotheliitis and iritis with zoster, as well, and treatment is similar with steroids and acyclovir or valacyclovir."

The question is whether there's a rationale for using prophylactic treatment to prevent recurrences of zoster, as is done with herpes simplex. "Many people are doing this, but there's no scientific evidence because the simplex and the zoster viruses are actually very different," Dr. Jeng adds.

Dr. Jeng is the chair of the Zoster Eye Disease Study (ZEDS), a large study evaluating whether long-term prophylaxis with oral valacyclovir will decrease some of the corneal manifestations of zoster post-shingles.[3]

This double-masked, placebo-controlled, multicenter randomized clinical trial will test the hypothesis that suppressive antiviral treatment for 12 months with 1,000 mg daily of oral valacyclovir reduces the rate of new or worsening dendriform epithelial keratitis, stromal keratitis, endothelial keratitis, or iritis compared to placebo in patients with herpes zoster ophthalmicus who have had an episode of one of these disease manifestations during the year prior to enrollment. It'll also evaluate whether suppressive treatment reduces the severity and duration of postherpetic neuralgia. Patients in the study will be evaluated every three months for 18 months.

According to Dr. Jeng, vaccination is the best way to prevent herpes zoster. "The new vaccine is more than 90-percent effective, so if everyone were vaccinated, the number of cases would decrease," he says "That would be first-line. But, short of everyone getting vaccinated—which we know isn't going to happen—we hope that ZEDS will give us insights into how best to treat and prevent the anterior segment complications of HZO." REVIEW

Dr. Pepose is a consultant to Glaxo Smith Kline. Dr. Mah is a consultant to Bausch + Lomb, Novartis, Allergan, and Kala. Dr. Jeng has no financial interest in any of the products mentioned.

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2. Wilhelmus KR, Gee L, Hauck WW, et al, for the Herpetic Eye Disease Study Group. Herpetic eye disease study: A controlled trial of topical corticosteroids for herpes simplex stromal keratitis. Ophthalmology 1994;101:12:1883-1896.
3. Zoster Eye Disease Study. https://clinicaltrials.gov/ct2/show/NCT03134196

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After reviewing the material, it is our hope that you will select and encourage your 2nd Year residents to attend one of these educational activities, which are CME accredited to ensure fair balance.

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Managing Glaucoma in A KPro Patient

The Boston keratoprosthesis (Type 1) can preserve vision in many patients, but it's highly associated with glaucoma. Here's help.

Joanne C. Wen, MD, Durham, North Carolina

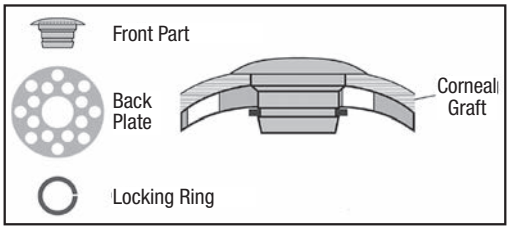
The Type 1 Boston keratoprosthesis, better known as a KPro, is a unique device indicated for severe ocular pathology. Though it's a boon for many patients, the KPro can make dealing with co-existing glaucoma more challenging. How often you'll encounter a patient with a KPro may depend on the nature and location of your practice: If you have a solo practice somewhere remote, you may not see many of these patients, but if you work at an academic center where your cornea colleagues are regularly performing these surgeries, you're likely to see a number of them.

Here, I'll discuss the issues you need to be prepared to deal with when you encounter a KPro patient—especially issues relating to glaucoma.

The KPro's Design

The device itself consists of a plastic front plate with a stem that passes through a corneal tissue graft, with a back plate and a locking ring that holds the device together. *(See illustration.)* The assembled device is sutured in place much as you would normally suture the donor graft during a penetrating keratoplasty.

A KPro implant is generally considered a last-resort option for patients with corneal opacification associated with a number of indications, such as repeated corneal graft failure, ocular trauma, herpetic keratitis, limbal stem cell deficiency, aniridia, Stevens-Johnson Syndrome and congenital opacification;[1] fortunately, it successfully rehabilitates vision in many of these cases. One paper reported that as of the summer of 2014, more than 9,000 KPros had been implanted throughout the world. That was up from 1,161 in 2009, so the number is clearly increasing.[1]



The Glaucoma Factor

Glaucoma is often an issue with these eyes, both before a KPro is implanted and after. Glaucoma is already prevalent in up to 73 percent of these patients before receiving a KPro. This is often related to underlying ocular pathology (herpetic keratitis, aniridia, ocular trauma, etc.).[2]

Even if they don't have glaucoma when they receive the KPro, up to 64 percent of these patients will develop glaucoma afterward.[3] This may be partly a result of being at high risk for glaucoma prior to the implant, but it can also be triggered by the presence of the device. One possible reason for this may be that there can be progressive narrowing of the angle after these implants go in.[4] That, in turn, may lead to the development of synechiae, further closing off the angle. In any case, these patients' glaucoma tends to be pretty aggressive; up to 23 percent will experience glaucoma progression.[5] In fact, it's a leading cause of vision loss in these patients.[6]

Prior to KPro implantation, evaluating the patient for existing glaucoma is helpful. Unfortunately, this can be challenging to do; sometimes the

This article has no commercial sponsorship.

Comparative Safety of KPro Surgery, With or Without a Glaucoma Drainage Device

Outcome	Boston Type 1 keratoprosthesis without glaucoma drainage device n=91 eyes [n(%)]	Boston Type 1 keratoprosthesis with glaucoma drainage device n=46 eyes [n(%)]	p-value (log-rank test)
Any serious vision-threatening postop complication	32 (35.2)	16 (34.8)	0.60
Sterile vitritis	10 (11.0)	4 (8.7)	
Endophthalmitis	1 (1.1)	1 (2.2)	
Hypotony	2 (2.2)	2 (4.4)	
Suprachoroidal hemorrhage	2 (2.2)	1 (2.2)	
Retinal detachment	11 (12.1)	3 (6.5)	
Retinal detachment repaired	9 (81.8)	3 (100)	
Stromal necrosis	12 (13.2)	8 (17.4)	
Infectious keratitis	14 (15.4)	3 (6.5)	

cornea is opaque. But to whatever extent you can, you should try to get a picture of the optic nerve, try to assess the visual field and get an OCT. Any kind of baseline evaluation you can obtain will help you know where you're starting.

Some research suggests that if there's any evidence of glaucoma before the KPro surgery, you should strongly consider a combined KPro and glaucoma surgery, because we know the glaucoma-related risks are so high after the prosthesis goes in and we know our methods of monitoring glaucoma may be limited afterwards. Addressing glaucoma in this situation usually means implanting a glaucoma drainage device; the effectiveness of this approach was first demonstrated by Peter Netland, MD, and Claes Dohlman, MD, PhD, back in 1998.[7] These can be fairly extensive surgeries, and if you proceed with a combined surgical approach, you may need to coordinate with your cornea or retinal colleagues to create the surgical plan.

Of course, a valid concern is whether combining these surgeries is safe for the patient. A 2017 retrospective study from the Jules Stein Eye Institute at UCLA compared KPro surgery alone to KPro surgery combined with glaucoma surgery; no significant differences in the number of vision-threatening complications were found.[4]

Tube Shunt Strategies

If you do find yourself implanting a tube shunt in a KPro patient, these strategies will help you achieve a successful outcome:

- ***Consider putting the tube in the sulcus or the pars plana.*** The anterior chamber in these eyes tends to shallow or collapse, leading to a lot of angle closure and synechiae. For that reason you may want to consider putting the tube in the sulcus or even the pars plana to minimize the risk of it becoming occluded.
- ***Make sure the tube is long and radially positioned.*** This can help you visualize the tip of the tube in the postoperative period more easily.
- ***Consider inserting the tube as posteriorly as you can, possibly with a long scleral tunnel, to minimize the erosion risk.*** Some of these patients chronically wear bandage contact lenses, and having a contact lens riding right over the tube insertion site may facilitate erosion. Also, the tube has to be inserted into the eye more posteriorly because of the back plate on the keratoprosthesis.
- ***Consider using a scleral or corneal patch graft rather than pericardium***. Some authors have hypothesized that using pericardium may be associated with higher rates of erosions with these patients.[8]

If the patient already has a tube shunt, but the pressure-lowering has been inadequate, you may decide to implant a second tube shunt or perform cyclophotocoagulation. (Of course, this still requires going through the steps of assessing how stable and well-controlled the glaucoma is.) The presence of the previous shunt shouldn't impact your surgery, unless the original tube was placed very anteriorly. In that situation, you might need to reposition the tube so it's more posterior to try to minimize the risk of erosion.

Evaluating a KPro Eye

Because the risk of glaucoma is so great after a KPro, it's essential to monitor these patients. However, this may not be easy. One of the biggest challenges is figuring out how to measure the IOP, because you can't applanate plastic. Traditionally we've relied on digital palpation, where you gently bounce the globe between your two fingers under the closed eyelid, to estimate the IOP. But the accuracy of this approach varies based on examiner experience; studies have shown that 31 percent of measurements may be off by as much as 30 percent.[9,10]

Some studies have looked at other, possibly more reliable ways

of measuring the pressure. These include:

• ***Scleral Schiotz tonometry.*** This was one of the first ways ophthalmologists measured intraocular pressure; it's been around for more than 100 years. A lot of third-world countries that don't have access to more modern equipment still use it. In fact, one study concluded that scleral Schiotz tonometry has the highest accuracy when measuring IOP in patients with a keratoprosthesis, compared to the Tono-pen and gold-standard digital manometry.[11]

Another study conducted last year looked at scleral Schiotz tonometry vs. Goldmann applanation. The study authors developed a formula to convert the scleral Schiotz pressure to an equivalent Goldmann pressure and then tested the formula on a series of patients in their clinic. They found that the agreement between the measurements was fairly good; the mean bias was less than -1 and the limits of agreement were pretty reasonable—about -3.7 to 1.8, which is quite good when comparing two IOP devices.[12]

Of course, some clinics may not have this equipment any longer. However, the device is inexpensive—you can still purchase them, typically for less than $100.

• ***Scleral pneumatonometry.*** This is probably more commonly used in this situation than scleral Schiotz tonometry. Two studies, out of UCSF and UCLA, measured the temporal sclera using the pneumatonometer probe and compared it to the corneal pressure measurement. Both of these studies came up with formulas to convert the scleral IOP measurement to a corneal IOP.[13,14] This approach is pretty helpful in the clinic; sometimes I'll use it and do a rough conversion just to get an idea how the patient is doing.

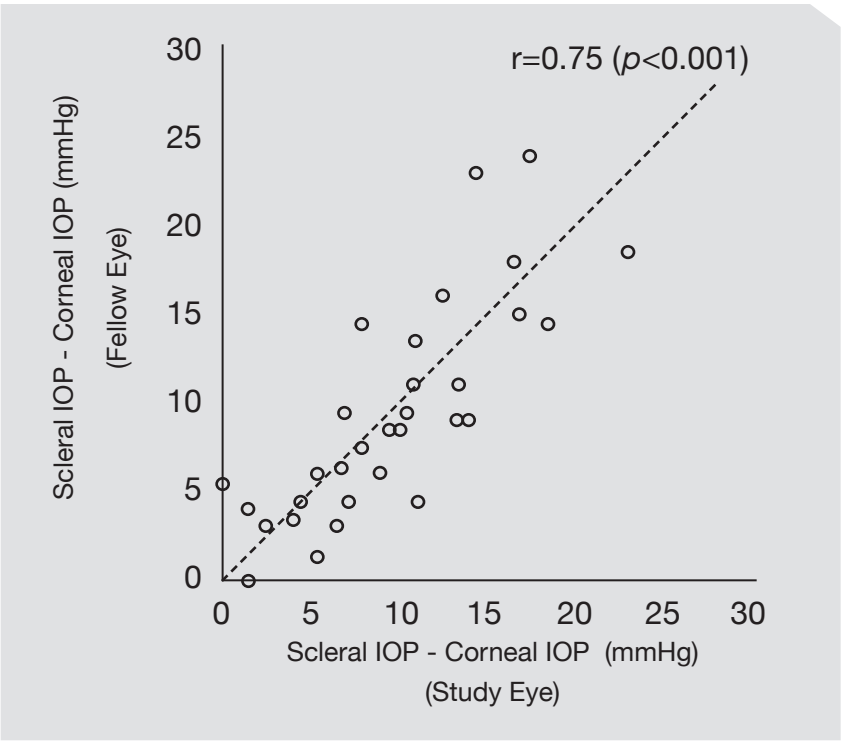
One thing I like about the study out of UCSF[13] is that they did a comparison between the corneal and scleral IOP measurements of paired eyes on the same patient. *(See graph, above.)* The differences were highly correlated. That means that in practice, you can estimate the corneal pressure in the KPro eye based on the scleral measurement, using the difference in the measurements you find in the healthier eye.

The other nice thing they did in this study was to monitor the pressure in patients who had just gotten intravitreal anti-VEGF injections, which are known to cause transient eye pressure elevations. They measured both the cornea and sclera of each eye as the pressure was returning to normal, collecting serial pressure measurements. The differences between scleral and corneal measurements tended to remain constant, even as the pressures were changing. This suggests that you can use the scleral IOP measurement to monitor the eye with a KPro over time, and that scleral IOP changes are representative of corneal IOP changes.

• ***Implantable sensors.*** As technology advances, implantable sensors are becoming more sophisticated. Last year researchers reported placing the Eyemate-IO sensor in KPro eyes; they found that there was a good correlation between the telemetric IOP and tactile palpation.[15,16]

To monitor a KPro patient's eye for glaucoma or glaucoma progression, you also have to assess optic nerve function and structure. Getting a visual field can be challenging, because the KPro optic limits your visual field to about 90 or 95 degrees. You can

Using Scleral Pneumatonometry to Gauge Corneal IOP



A 2015 study found a strong correlation between corneal and scleral IOP measurements made when using scleral pneumatonometry. This suggests that the ratio of cornea to scleral IOP in a healthy fellow eye can be used to estimate the true corneal IOP in the KPro eye, based on the measured scleral IOP in the KPro eye. (Kuo DS, et al)[13]



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still do a Humphrey visual field, but sometimes the testing is unreliable in these patients. For that reason you may want to consider monitoring with Goldmann visual field testing. Studies have demonstrated that this can be effective for monitoring glaucoma progression in these patients.[17]

In terms of assessing structure, again, the 3-mm optic can make things difficult to visualize. If you're trying to get a photo of the disc, a nonmydriatic camera can be helpful. If you're using OCT, the KPro can cause segmentation errors, which you need to be aware of when interpreting the result. Meanwhile, new approaches continue to evolve. At the Massachusetts Eye and Ear Infirmary they've developed a 3-D OCT volumetric scan protocol that seems to be effective for monitoring structural changes in these patients.

If You Add CPC …

So what do you do if you need additional IOP control after the KPro is in place? If the patient already has a drainage tube, you could certainly consider a second tube, but many surgeons will try cyclophotocoagulation.

A few studies have looked at cyclophotocoagulation in KPro eyes. They found a fairly good rate of success controlling glaucoma following CPC —61 to 67 percent—and a relatively low complication rate.[18,19] What's really interesting is that both studies reported cases of endophthalmitis, which we don't normally associate with cyclophotocoagulation since it's not an incisional procedure. A possible explanation for this is that the junction between the optic and the corneal graft never fully integrates—after all, it's a junction of plastic and biological material. If that's the case, organisms could theoretically enter the eye at that interface if something causes the interface to gape.

Since this is a potential problem, some specific techniques should be followed:

- ***Treat this as an intraocular surgery.*** Consider using aseptic technique, including betadine prep.
- ***Transilluminate the eye.*** The anatomy in these eyes can be a little distorted; you can get disoriented during surgery because the landmarks are often difficult to visualize. Transilluminating the eye can help you identify the ciliary body bands, so you can make sure you're treating the right area.
- ***Avoid pushing on the eye.*** Pushing on the eye can cause the

(Continued on page 68)

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Best regards,
Kendall Donaldson, MD, Yousuf Khalifa, MD, Mitchell Weikert, MD, MS

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January 15–16, 2021	January 29–30, 2021	March 5–6, 2021
(Friday - Saturday)	(Friday - Saturday)	(Friday - Saturday)
Course Director:	Course Director:	Course Director:
Yousuf Khalifa, MD	**Kendall Donaldson, MD**	**Mitchell Weikert, MD, MS**

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An Update on Medical Training in Retina

The authors break down the current approach to training in ophthalmology in general—and retina in particular.

Hong-Uyen Hua, MD, Los Angeles, and Jayanth Sridhar, MD, Miami

Vitreoretinal surgical fellowship and ophthalmology residency education have deep roots in the apprenticeship Halsted model of surgical training, i.e., "see one, do one, teach one." In the early days of surgical retinal fellowships, one-on-one apprenticeship was the modus operandi of training, such as Dr. Jose Berrocal under Dr. Charles Schepens or Dr. Thomas Aaberg under Dr. Robert Machemer. We still see elements of the apprenticeship model incorporated into contemporary post-graduate education: Residents and fellows serve under the guidance of faculty mentors for a set number of years and achieve a set number of surgical and procedural requirements. More recently, external stakeholders (e.g., the government, the public, third-party payers, etc.) have placed increasing pressure on educators to provide proof of quality and competency in education. As a result, medical education has transitioned to a core competency-based curriculum, per the Accreditation Council for Graduate Medical Education.

Ophthalmology residency programs currently adhere to the ACGME six core competencies: patient care; medical knowledge; practice-based learning and improvement; interpersonal and communication skills; professionalism; and systems-based learning.[1] Other than ophthalmic plastic and reconstructive surgery, ophthalmology fellowships (including vitreoretinal surgery) are not ACGME accredited. However, the Association of University Professors of Ophthalmology (AUPO) Fellowship Compliance Committee has outlined fellowship program requirements, most of which dovetail with these ACGME core competencies.[2] Challenges in modern vitreoretinal surgical education include standardizing the assessment of medical knowledge and surgical competency. On the other hand, technological advances, such as virtual simulations and video technology, have revolutionized ophthalmic and vitreoretinal education; they've facilitated development of examination and surgery skills while simultaneously improving trainee competency and patient safety.

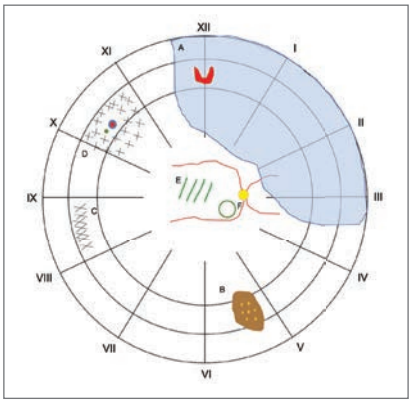

Figure 1. Example of a traditional retinal drawing. (A) Macula-on retinal detachment from 12:00 to 3:00 with a horseshoe tear at 12:00. (B) Choroidal nevus with overlying drusen. (C) Lattice degeneration. (D) Operculated retinal hole with subretinal fluid surrounded by laser scars. (E) Epiretinal membrane. (F) Weiss ring.

Here, we review medical training in ophthalmology, with a focus on vitreoretinal surgery, through the lens of established ACGME core competencies. We also briefly review the recent challenges, opportunities, and creative solutions in ophthalmic education amid the COVID-19 pandemic.

Medical Knowledge and Care

Medical knowledge and patient care encompass two of the six ACGME core competencies, and education in these disciplines can be enhanced both

in the clinic and operating room setting through various methods:

• ***Education in the clinic.*** In the ophthalmology clinic setting, examination and imaging interpretation are critical diagnostic skills. Examination techniques for the retina and vitreous can be particularly challenging, since faculty educators frequently can't verify what trainees are seeing. Appropriate scleral depression to identify retinal pathology can be difficult to learn for many reasons, including patient discomfort, examiner positioning and technique. Furthermore, a retrospective study suggests that trainees' peripheral indirect ophthalmoscopy and laser retinopexy skills have become increasingly inadequate.[3]

There are multiple potential strategies to combat the decline in retinal examination skills. For one, faculty could require residents and fellows to still use "old school" tools, such as retinal drawings, which are a dying art in the age of electronic health records and ubiquitous ultra-widefield fundus photography. Being forced to put pen to paper (or mouse to screen, in the case of an EHR drawing) further motivates the trainee to develop good habits *(Figure 1)*. These drawings also encourage novices to actively recall their exam and provide an opportunity for faculty and mentees to review missed or omitted examination findings.

Technological aids may also be useful in building fundus examination skills. Video indirect ophthalmoscopy consists of a traditional indirect ophthalmoscope attached to an external display, allowing for real-time observation of the same image viewed by the examiner *(Figure 2)*. The screen image can also be recorded for later review. In a prospective, randomized study from our group, VIO proved to be a useful tool for increasing resident efficiency and confidence with the peripheral fundus exam.[4] VIO trainees in the study group were able to receive real-time feedback and instruction from faculty to improve their indirect ophthalmoscopy and scleral depression examination skills.

Figure 2. Photograph showing a teaching session performed using the Heine Video Omega 2C video indirect ophthalmoscope, with faculty supervision.

In addition to emphasizing exam technique, reviewing imaging in the clinic should be an essential practice in ophthalmic and vitreoretinal education. Specifically, the AUPO Fellowship Compliance Committee recommends that vitreoretinal fellows develop a thorough understanding of fluorescein angiography, electrophysiology, optical coherence tomography, ultrasound and radiology.[2] Given the pace of many vitreoretinal clinics, it may be more efficient for faculty and trainees to "round" on interesting and educational fundus photos, OCT scans and FA images after all patients have been seen. Outside of clinic, many institutions host regularly scheduled retinal imaging rounds as part of their resident and fellow educational curriculum; for example, Wills Eye Hospital offers Retina Imaging Rounds for free every other week via livestream.[5]

• ***Education in the OR.*** Molding trainees into skilled and competent surgeons is critical in ophthalmology and vitreoretinal surgery education. As such, it's housed as a distinct competency within the ACGME core-competency of patient care.[6] Many vitreoretinal surgical fellowships still rely heavily on the Halsted apprenticeship approach to surgical training. Watching and learning from an expert, skilled faculty mentor is invaluable. Meanwhile, trainees gradually develop autonomy from abundant opportunities to care for surgical patients.

Today, technology supplements the apprenticeship model. Technological advances now allow vitreoretinal fellows and trainees to build baseline knowledge, experience and competency while optimizing patient safety.

The modern approach to surgical training includes online surgical videos and structured curricula, wet lab teaching courses and virtual simulation. YouTube, the American Academy of Ophthalmology Ophthalmic News and Education Network (https://www.aao.org/clinical-education), and other online video databases provide thousands of videos to observe and learn surgical steps. For retinal surgery specifically, the Vit-Buckle Academy (VBA, https://vitbucklesociety.org/vit-buckle-academy) is the first step-by-step video-based curriculum available online. In addition, industry representatives provide annual surgical wet lab courses, offering opportunities to practice and develop surgical skill in an intimate setting, with several companies dedicating events specifically to residents and fellows.

Virtual simulations of cataract surgery have been extensively studied; however, only four reports to date have evaluated the vitreoretinal modules of the EyeSi Surgical Simulator (VRmagic, Mannheim, Germany).[7] While the studies suggest that the EyeSi can distinguish between experienced and inexperienced vitreoretinal surgeons, there is not yet published data supporting the transfer of skills to the operating room.[7] More studies validating simulation training need to be done before drawing further conclusions on its efficacy as a teaching model, but its potential certainly suggests an increasing importance in the future.

In the OR, there are a number of innovations that can supplement vitreoretinal surgical education due to improved visualization. With the abil-

ity to provide better real-time visual feedback, the chandelier-assisted scleral buckle allows an assistant to observe examination and treatment of the peripheral retina with either cryotherapy or laser.[8] Newer heads-up 3-D visualization systems are competing with traditional microscopes and allow all OR observers access to the primary surgeon's view *(Figure 3)*. There will be a learning curve with this technology; a prospective study suggested that macular peel time was significantly longer in the 3-D display group, compared to a microscope.[9] Still, if these systems become more common, the advantages should easily exceed the disadvantages for surgical education.

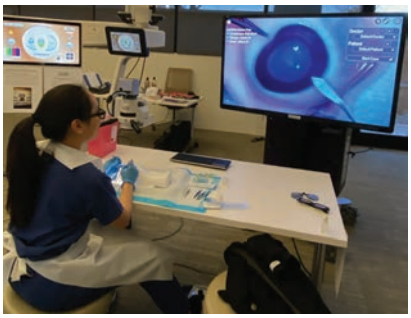

Figure 3. Photo showing Ngenuity 3D Visualization System (Alcon, Vernier-Geneva, Switzerland) for heads-up surgical display.

Approaches to Learning

Next, we review two more ACGME core competencies: practice-based learning (PBL) and systems-based learning (SBL). We discuss how to further PBL and SBL through the lens of new media and amidst the pandemic.

• ***Education in 2020 with new media.*** PBL includes processes and behaviors that foster improvement and continual education in best practices, frequently through review of current literature.[1] In the core competency-based curriculum, PBL is traditionally executed through journal clubs, which are required on a quarterly basis by the AUPO Fellowship Compliance Committee.[2] Outside of traditional journal clubs, new media such as podcasts, webinars, online continuing medical education courses and virtual conferences provide abundant opportunities for practice-based learning. The AAO also provides several online sources for education, including the ONE Network, which provides summaries of recent high-yield ophthalmology publications. Further informal opportunities for PBL include non-peer-reviewed sources like Facebook groups, Twitter, WhatsApp and Telegram text groups, and YouTube. For example, the American Retina Forum is available to vitreoretinal trainees and attendings on Facebook and Telegram as an informal venue for sharing interesting cases and asking clinical questions in a HIPAA-compliant fashion.

Straight From the Cutter's Mouth: A Retina Podcast (SFTCM) was created by our group to provide educational content curated for vitreoretinal specialists, as well as CME credits via the AAO. Episode topics include journal clubs, medical and surgical management techniques, and fundamentals of practice management. Reflecting the increasing demand for new media, the listener base of SFTCM grew quickly, from 684 downloads in the first quarter of 2017 to 16,016 downloads in the third-quarter of 2018.[10] Demographic data from a voluntary survey of all SFTCM podcast listeners at one year showed that 65.7 percent of listeners are between the ages of 25 and 34.[10] This suggests that the primary consumers are either still in training or recently out of training, indicating that podcasts and other new educational media will likely see continued rapid growth as a younger, more tech-friendly generation grows up over the next decade. In a separate survey sent to retinal society members, generally an older cohort, survey respondents stated that national conferences were still their most preferred educational medium, and reading journal articles and listening to grand rounds were rated as significantly more likely to change clinical practice than podcasts.[11] Still, podcasts have a strong standing in the retina community, with 41.1 percent of survey respondents listening to at least one medical podcast a week.[11]

In complement to problem-based learning, SBL refers to the "ability to work within the system and to call on resources within the system to provide optimal care to the patient."[12]

SBL modalities may include traditional morbidity and mortality conferences or opportunities to perform a root-cause analysis of a significant clinical event. Quality improvement projects are also opportunities to implement SBL. While currently there aren't publicly available digital SBL opportunities for vitreoretinal surgeons, one would expect that this space will be filled given recent events.

• ***Medical training and COVID-19.*** The pandemic has introduced new challenges to ophthalmology education, including disruptions in medical and surgical institutional didactics, elimination of traditional in-person conferences, and drastically decreased clinical volumes. This challenge has birthed a revolutionary movement that has fostered creativity and broadened inclusivity through virtual education and conferences. Major domestic organizations such as the AAO, the American Society of Retinal Specialists, Retina Society, Retina World Congress, and The Vit-Buckle Society have either hosted online webinars or transitioned their annual in-person meeting into a digital interactive format. These meetings provide opportunities to discuss difficult surgical cases with a problem-based and video-based learning approach in mind. For example, VBS converted its annual spring meeting into a four-part series of online meetings using the Zoom platform, with audience members able to participate in discussions and post questions for panelists in real time. More than 900 partici-

pants registered for the first part of the series, more than double the typical in-person attendance. The numbers demonstrate the potential for greater inclusivity from virtual educational conferences, as concerns over physical meeting space are eliminated and replaced with an easily solved problem of digital bandwidth.

In addition, with drastically decreased clinical and surgical volumes, the COVID-19 pandemic has given rise to an explosion in telemedicine. Prior to the pandemic, ophthalmology's use of telehealth was primarily geared towards store-and-forward mechanisms for screening for diseases like diabetic retinopathy.[13] Due to COVID-19 restrictions and fears, real-time telemedicine visits and/or hybrid real-time visits with separate office testing have increased out of necessity.[13] With telemedicine on the rise, it's important to include and expose trainees to telemedicine tools, such as educating patients about at-home visual acuity and Amsler grid testing.

In New York City, an epicenter of COVID-19 cases, the pandemic had a dramatic impact on ophthalmic education. In the wake of tthe ragedy, the NYC ophthalmology residency programs banded together, giving rise to multi-institutional didactic series.[14] Residents had access to 45 lectures across different ophthalmology program sites. This inter-institutional didactic curriculum was so successful that it'll remain in place post-COVID.[14] The adaptability of the NYC programs exemplifies the collegial spirit of academic cooperation in education, despite discouraging circumstances.

"Soft" Skills Can Be Hard

The "soft" talents of interpersonal and communication skills, as well as professionalism, are difficult core competency skills to measure. As ophthalmologists, we sometimes have to break the bad news of permanent visual impairment to our patients. Although it's a critical skill, discussing poor outcomes with patients is rarely taught as a communication skill in residency or fellowship training. One online survey found that 88 percent of participants stated that formal training in communication skills for breaking bad news would be beneficial.[15] Sarah Hilkert Rodriguez, MD, while a resident at the Havener Eye Institute at Ohio State University, suggested a formal curriculum for breaking bad news in six steps, through the mnemonic SPIKES, which is composed of the following:

- Setting: Arrange for privacy and avoid interruptions;
- Perception: Inquire about how much the patient already knows;
- Invitation: Discuss how much the patient wants to know;
- Knowledge: Avoid jargon, allow moments of silence;

• Empathy: Acknowledge and validate patient emotions;
• Summary: Confirm understanding, address patient-specific goals.[16]

In Dr. Hilkert's study, all 11 resident study participants stated that they would use the SPIKES approach for breaking bad news in their clinical practice.[16]

In summary, ophthalmology and retinal surgical education has evolved drastically from its origins in individual apprenticeship to today's more broad, inclusive, core-competency-based model. Technological advancements in surgical training tools and online content sharing have led to exceptional innovation in medical training in ophthalmology in general, and vitreoretinal surgery in particular, and the recent challenges brought about by the pandemic have further accelerated the shift towards digital education.

If we've learned anything from the last few months, it's to expect the unexpected. With that in mind, we look forward to seeing more ingenious and creative educational solutions in ophthalmology beyond what we've reviewed here. REVIEW

Dr. Hua is chief resident at the Roski Eye Institute, Department of Ophthalmology, University of Southern California in Los Angeles. Dr. Sridhar is an associate professor of clinical ophthalmology and vitreoretinal surgery at the Bascom Palmer Eye Institute in Miami. Neither author has any financial interest in any of the products discussed.

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(Continued from page 62)

interface to gape, increasing the risk of endophthalmitis.

• ***Monitor for hypotony afterwards.*** Hypotony could also theoretically cause the interface to gape and increase the patient's infection risk.

A Battle Worth Winning

If you're performing the KPro surgery yourself, remember that glaucoma is very common in these eyes, and consider implanting a tube shunt before or at the time of KPro surgery. If you're managing a patient with a KPro implant, you may find that monitoring glaucoma remains challenging, but it's not impossible. Meanwhile, newer technology on the horizon will eventually improve our ability to help this challenging population.

Some of these patients are extremely complex, but they can also be some of your most satisfying cases. REVIEW

Dr. Wen is a glaucoma specialist at the Duke Eye Center and an associate professor of ophthalmology at Duke University School of Medicine. She reports no financial interest in any products discussed in this article.

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A night of substance abuse leaves a 35-year-old man blind in one eye and seeking the emergency room.

Matthew N. Pieters, MD, Bruce J. Markovitz, MD

Presentation

A 35-year-old Hispanic male with a history of polysubstance abuse presented to an outside emergency room with right eye pain, redness, swelling and vision loss after a presumed alkali chemical exposure the day before. The patient reported that someone accidentally sprayed him from several feet away with a mixture of "cocaine, heroin, fentanyl, meth and dirty water" from a syringe. He then injected these same substances intravenously. His recollection of subsequent events was admittedly suboptimal, stating that he "passed out for multiple hours" shortly after the alleged exposure. He awoke the following morning with the above presenting symptoms, leading him to seek care later that day at an emergency room.

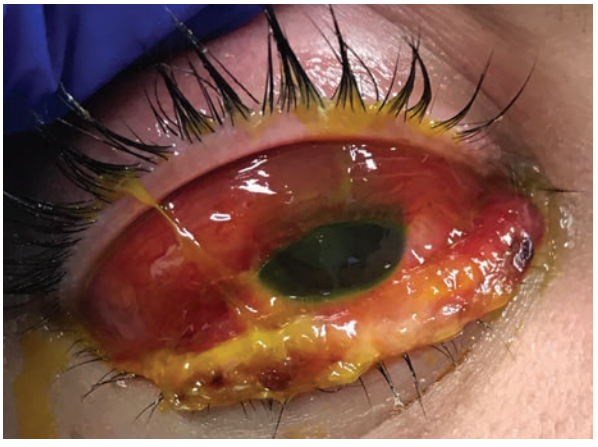

Figure 1: External photograph of the right eye on presentation to an emergency room demonstrating extensive conjunctival injection, subconjunctival hemorrhage and chemosis.

At the ER, the pH of the patient's right eye was 9 but improved to 7 after irrigation with 10 L of normal saline. In the right eye, vision was hand motion, intraocular pressure was 23 mmHg, and motility was globally limited in all gazes. The right pupil was minimally reactive and miotic, and the ER physicians were unsure of the presence of a relative afferent pupillary defect. Examination of the left eye was within normal limits.

Bedside examination of the right eye with a 20-D lens revealed extensive 3+ conjunctival injection, subconjunctival hemorrhage and chemosis with mild edema and erythema of the upper and lower lids *(Figure 1)*. The cornea demonstrated mild, diffuse haze without epithelial defects, symblepharon or limbal whitening. The lens appeared clear, and the view to the posterior segment was limited secondary to cooperation and miosis. Examination of the left eye was normal.

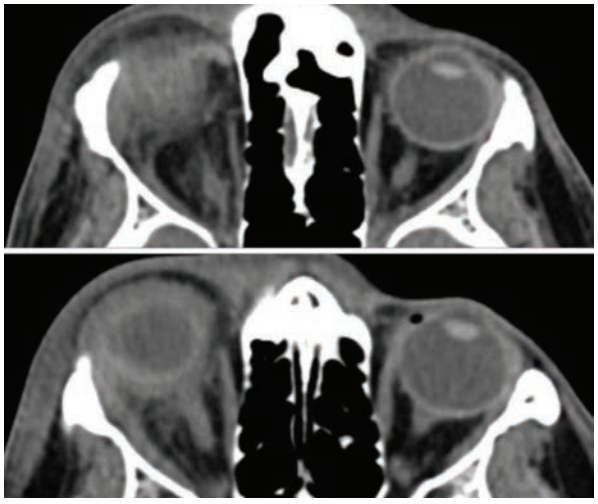

Figure 2: CT scan of the orbits (axial view) demonstrating significant retrobulbar edema and fat stranding of the right orbit with mild proptosis without evidence of globe injury.

CT scan of the orbits demonstrated significant retrobulbar edema, fat stranding and mild proptosis without evidence of globe injury *(Figure 2)*. Bedside ultrasound revealed choroidal thickening with a positive T-sign and mild vitritis. No retinal detachment or obvious penetrating globe injury was noted. CT angiogram of the head and neck, and transthoracic echocardiogram were unremarkable. Laboratory investigation was within normal limits and included a complete blood count, complete metabolic panel, angiotensin-converting enzyme, rapid plasma reagin, anti-neutrophil cytoplasmic antibody, rheumatoid factor, quantiferon-TB gold and Lyme titers.

The patient was admitted for inpatient observation and initiated on aggressive lubrication with preservative free artificial tears and erythromycin ointment, as well as topical

"I was only seeing light flashes early on, but light FLASHES when you've not seen anything for so many years—it was wonderful"

—Keith H, retinal prosthesis recipient

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ofloxacin, prednisolone acetate, cyclopentolate drops, oral vitamin C and intravenous vancomycin, piperacillin/tazobactam and methylprednisolone. Over the next four days, his vision decreased to light perception in the right eye despite improving chemosis and a grossly clear cornea. At this time, the providers were concerned for etiologies separate from chemical exposure causing vision loss, and he was transferred to Wills Eye Hospital for further evaluation.

Medical History

Past history: polysubstance abuse of alcohol, marijuana, cocaine, opiates and amphetamines; and a history of intravenous drug use. No prior ocular history. No systemic or ocular medications at presentation.

Examination

Ocular examination at Wills demonstrated visual acuity of bare light perception in the right eye and 20/20 in the left. The right pupil was pharmacologically dilated with a 3+ RAPD by reverse; the left pupil was round and briskly reactive. IOP was 7 mmHg in the right eye and 13 mmHg in the left. There was improved, but still limited, motility in all gazes on the right with full motility on the left.

Anterior slit lamp examination of the right eye revealed improving 1-2+ injection and trace chemosis without any limbal whitening or symblepharon. The cornea had dense superficial punctate keratitis, mild edema and a few Descemet's folds. There was a white cataract with pigment on the anterior lens capsule in an annular distribution and scattered broken posterior synechiae *(Figure 3)*. There was no view to the posterior segment. Anterior and posterior segment exam of the left eye was within normal limits. B-scan ultrasound of the right eye revealed vitritis, a shallow serous choroidal detachment, choroidal thickening and a positive T-sign without retinal detachment.

Based on this information, what's your diagnosis? The diagnosis appears below.

Workup, Diagnosis and Treatment

Shortly after the patient's arrival at Wills, the differential diagnosis was broadened from chemical exposure, especially given the benign corneal exam with improving conjunctival injection and chemosis. Given the presence of vitritis and the initial concern for a possible infection, a vitreous sample was obtained, followed by intravitreal injection of vancomycin, ceftazidime and voriconazole. Vitreous cultures, blood cultures and HIV testing were all unremarkable. Careful B-scan ultrasound by a retina specialist didn't reveal any evidence of rupture, and exploration was deferred.

Despite the initial concern for infectious etiologies, including endogenous sources as well as penetrating inoculation, the onset and course of the patient's vision loss wasn't consistent with these entities. The presence of acute unilateral vision loss, a large RAPD, initial retrobulbar edema, proptosis and ophthalmoplegia pointed toward a diagnosis of "Saturday night retinopathy" with additional elements of orbital infarction, especially given the onset of symptoms following a prolonged state of unconsciousness. This diagnosis was also muddled by the presence of an acute onset cataract. Although no evidence of penetrating injury was discovered, the presence of pigment on the anterior lens capsule was suggestive of a Vossius ring. This was hypothesized to be due to blunt trauma to the right eye, likely occurring while intoxicated.

The patient was treated with topical steroids, cycloplegics, and lubrication. Repeat B-scan five days later showed resolved vitritis and a flat retina with improved choroidal thickening and resolved choroidal detachment. Topical ste-

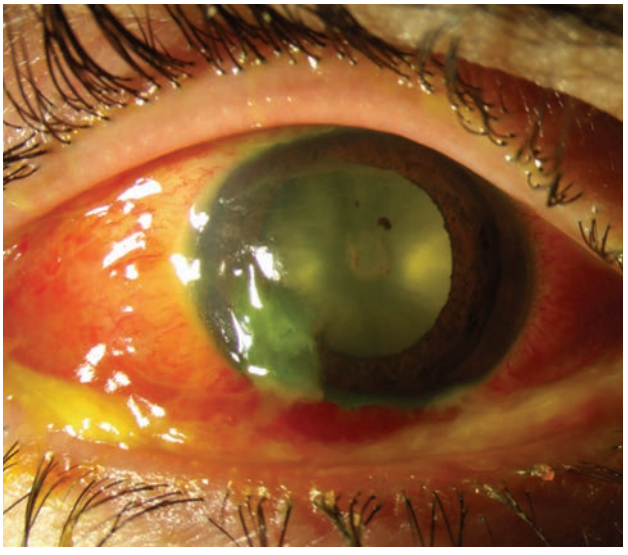

Figure 3: External photograph of the right eye on presentation to Wills Eye Hospital demonstrating improved conjunctival surface, a grossly clear cornea and a dense cataract with broken posterior synechiae and pigment on the anterior lens capsule in an annular distribution.

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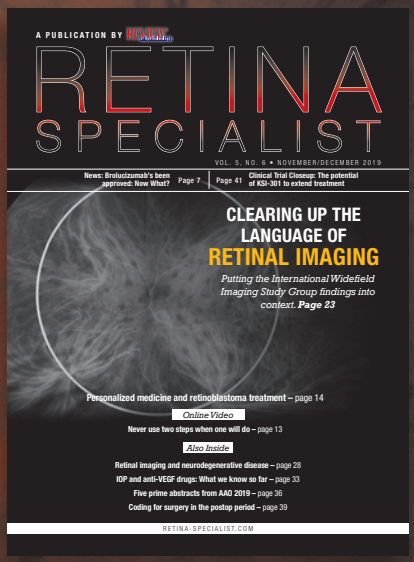

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roids were slowly tapered. The patient was counseled on his poor visual prognosis. He was recommended to seek close follow-up with a local ophthalmologist to discuss possible cataract extraction after a period of sustained quiescence, but he was unfortunately lost to follow-up.

Discussion

Saturday night retinopathy is a rare, unilateral blinding condition, first described in 1974,[1] that's characterized by permanent vision loss in the setting of continuous external orbital pressure following substance-induced stupor and unconsciousness. Similar iatrogenic etiologies are well-documented in cases of unilateral vision loss following surgeries that require prolonged prone positioning against a headrest.[2] The hypothesized mechanism involves the collapse of orbital vessels secondary to the external pressure on the orbit, in addition to a sedative-induced dampened response to painful stimuli that would otherwise act to alleviate the insult. Vision loss specifically is thought to be due to lack of blood flow through either the central retinal or ophthalmic artery with resultant ischemia, while other orbital signs like proptosis and ophthalmoplegia may be due to temporary obstruction and subsequent reperfusion of multiple small orbital vessels.[2] One report documenting the fluorescein angiography and optical coherence tomography findings in a patient with Saturday night retinopathy noted delayed choroidal filling, delayed retinal filling and severe full thickness disorganization of retinal architecture with subretinal and subretinal pigment epithelium fluid, further supporting the hypothesis that ophthalmic artery occlusion plays an important role in the pathophysiology of this rare entity.[3]

Despite several confounding factors, including a traumatic cataract and chemical conjunctivitis, our patient demonstrated many classic features of SNR. One study cataloging three cases of SNR noted poor visual acuity ranging from no light perception to hand motion with large RAPDs in all subjects, similar to our patient's examination findings.[4] Additionally, two of the three patients in this study presented with periorbital swelling, proptosis and ophthalmoplegia, which improved to varying degrees over subsequent visits despite persistent visual loss, as was also observed in our subject. Further, our patient concurrently used cocaine in addition to opiates. Other studies have hypothesized that the powerful sympathomimetic and vasoactive properties of cocaine may exacerbate the ischemic insults of SNR.[5]

In summary, Saturday night retinopathy is a rare, blinding condition characterized by vascular obstruction from prolonged orbital compression during a substance-induced state of unconsciousness. Given that patients wake with severe ischemic vision loss in a scenario occurring outside of the hospital, no productive preventative measures or treatments are available. Knowledge of this entity is important for both ophthalmologists and emergency medicine providers, as the patients are often unable to give a detailed history of events due to their intoxication. As was seen in our case, our patient's convoluted history and initial findings made diagnosis particularly challenging. REVIEW

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REVIEW Advertising Index

oxervate™
(cenegermin-bkbj ophthalmic solution) 0.002% (20 mcg/mL)

Brief Summary of Safety

Consult the full Prescribing Information for complete product information.

INDICATIONS AND USAGE

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% is indicated for the treatment of neurotrophic keratitis.

DOSAGE AND ADMINISTRATION

Contact lenses should be removed before applying OXERVATE and may be reinserted 15 minutes after administration.

If a dose is missed, treatment should be continued as normal, at the next scheduled administration.

If more than one topical ophthalmic product is being used, administer the eye drops at least 15 minutes apart to avoid diluting products. Administer OXERVATE 15 minutes prior to using any eye ointment, gel or other viscous eye drops.

Recommended Dosage and Dose Administration

Instill one drop of OXERVATE in the affected eye(s), 6 times a day at 2-hour intervals for eight weeks.

ADVERSE REACTIONS

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

In two clinical trials of patients with neurotrophic keratitis, a total of 101 patients received cenegermin-bkbj eye drops at 20 mcg/mL at a frequency of 6 times daily in the affected eye(s) for a duration of 8 weeks. The mean age of the population was 61 to 65 years of age (18 to 95). The majority of the treated patients were female (61%). The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1-10% of OXERVATE patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary There are no data from the use of OXERVATE in pregnant women to inform any drug associated risks.

Administration of cenegermin-bkbj to pregnant rats or rabbits during the period of organogenesis did not produce adverse fetal effects at clinically relevant doses. In a pre- and postnatal development study, administration of cenegermin-bkbj to pregnant rats throughout gestation and lactation did not produce adverse effects in offspring at clinically relevant doses.

Animal Data

In embryofetal development studies, daily subcutaneous administration of cenegermin-bkbj to pregnant rats and rabbits throughout the period of organogenesis produced a slight increase in post-implantation loss at doses greater than or equal to 42 mcg/kg/day (267 times the MRHOD). A no observed adverse effect level (NOAEL) was not established for post-implantation loss in either species. In rats, hydrocephaly and ureter anomalies were each observed in one fetus at 267 mcg/kg/day (1709 times the MRHOD). In rabbits, cardiovascular malformations, including ventricular and atrial septal defects, enlarged heart and aortic arch dilation were each observed in one fetus at 83 mcg/kg/day (534 times the MRHOD). No fetal malformations were observed in rats and rabbits at doses of 133 mcg/kg/day and 42 mcg/kg/day, respectively. In a pre- and postnatal development study, daily subcutaneous administration of cenegermin-bkbj to pregnant rats during the period of organogenesis and lactation did not affect parturition and was not associated with adverse toxicity in offspring at doses up to 267 mcg/kg/day. In parental rats and rabbits, an immunogenic response to cenegermin-bkbj was observed. Given that cenegermin-bkbj is a heterologous protein in animals, this response may not be relevant to humans.

Lactation

There are no data on the presence of OXERVATE in human milk, the effects on breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for OXERVATE, and any potential adverse effects on the breastfed infant from OXERVATE.

Pediatric Use

The safety and effectiveness of OXERVATE have been established in the pediatric population. Use of OXERVATE in this population is supported by evidence from adequate and well-controlled trials of OXERVATE in adults with additional safety data in pediatric patients from 2 years of age and older [*see Clinical Studies (14)*].

Geriatric Use

Of the total number of subjects in clinical studies of OXERVATE, 43.5 % were 65 years old and over. No overall differences in safety or effectiveness were observed between elderly and younger adult patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis and Mutagenesis Animal studies have not been conducted to determine the carcinogenic and mutagenic potential of cenegermin-bkbj.

Impairment of fertility Daily subcutaneous administration of cenegermin-bkbj to male and female rats for at least 14 days prior to mating, and at least 18 days post-coitum had no effect on fertility parameters in male or female rats at doses up to 267 mcg/kg/day (1709 times the MRHOD). In general toxicology studies, subcutaneous and ocular administration of cenegermin-bkbj in females was associated with ovarian findings including persistent estrus, ovarian follicular cysts, atrophy/reduction of corpora lutea, and changes in ovarian weight at doses greater than or equal to 19 mcg/kg/day (119 times the MRHOD).

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Important Safety Information

WARNINGS AND PRECAUTIONS

Patients should remove contact lenses before applying OXERVATE and wait 15 minutes after instillation of the dose before reinsertion.

ADVERSE REACTIONS

The most common adverse reaction in clinical trials that occurred more frequently with OXERVATE was eye pain (16% of patients). Other adverse reactions included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation, and increase in tears (1%-10% of patients).

For additional safety information, see accompanying Brief Summary of Safety Information on the adjacent page and full Prescribing Information on Oxervate.com/HCP.

*Complete corneal healing was defined as the absence of staining of the corneal lesion and no persistent staining in the rest of the cornea after 8 weeks of treatment. Based on results from the REPARO trial (Europe, NGF0212; N=156) and the US trial (NGF0214; N=48).[7,8]

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