Wills Eye Resident Series: A 78-year-old man complains of strobe lights and blurred vision, *p. 69*

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Surgeons reveal how they encountered unexpected difficulties—and overcame them. **P. 47**

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VOLUME XXXI • NO. 9
SEPTEMBER 2024

Diabetes May Lessen the Effect Of Anti-VEGF Therapy in AMD

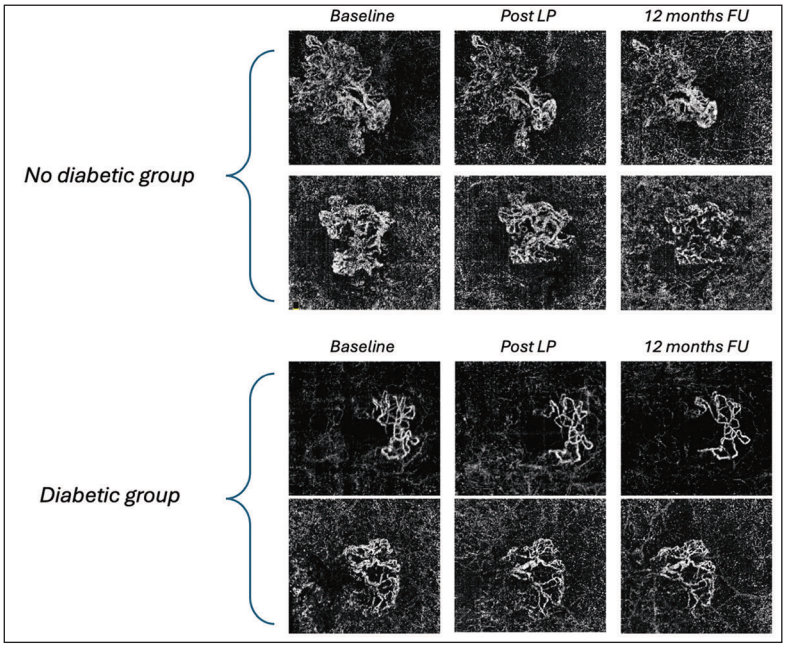
Several environmental and genetic factors contribute to the pathogenesis of age-related macular degeneration, but many in the scientific community debate the role of diabetes mellitus in the more advanced neovascular age-related macular degeneration (nAMD), questioning whether it contributes to or protects against the disease progression. Using OCT-A to observe the morphological changes in type 1 exudative macular neovascularization (MNV) following one year of anti-VEGF therapy, researchers found patients with mild diabetic retinopathy had a divergent response in type 1 MNV lesion area.

According to their findings, recently published in the journal *Investigative Ophthalmology & Visual Science*,[1] although there was a significant reduction in lesion size between the baseline visit and the post-loading phase, there was no noticeable further reduction in lesion area at the 12-month follow-up visit. Alternatively, nAMD patients with no history of DM had a continuous reduction in MNV size. Researchers say this highlights the significance of DR as a potential modifier of treatment outcomes in nAMD management, with DM considered a risk factor during anti-angiogenic treatment.

The retrospective study included 45 eyes with exudative nAMD with type 1 MNV, all of whom were enrolled at the Medical Retina Service at the University of Bari Aldo Moro in Italy. Patients were divided into the Diabetic group, which included 21 eyes of 21 patients with mild DR; and Not Diabetic Group, which consisted of 24 eyes of 24 patients with no history of DM. The outcome measures included best corrected visual acuity changes, central macular thickness, MNV lesion area, and MNV flow area. All of these parameters showed significant improvement after the loading phase, according to the study.

"The most interesting finding pertained to the behavior of the neovascular lesion after one year of treatment initiation," they wrote in the study. "Specifically, the Diabetic group did not exhibit a reduction in MNV after 12 months; instead, there was a lack of significant reduction of the area of the MNV. In contrast, the Not Diabetic group showed a continuous reduction in the size of the MNV. This last result appears to be highly significant, especially considering that the size of MNV evaluated with OCT-A serves as a valuable biomarker in assessing the response or lack of response to treatment."

They speculated about the mechanisms that could be contribut-



Researchers report that during anti-VEGF therapy, macular neovascularization lesion size continued to decrease in the non-diabetic group over the course of 12 months, but had a smaller decrease in the diabetic group, suggesting the disease may be a risk factor to consider during anti-angiogenic treatment. *Photo: Boscia G, et al. Invest Ophthalmol Vis Sci. August 2, 2024*

ing to this result, including the possibility that the presence of DR alters the angiogenic pathways involved in MNV. "DR is associated with dysregulated VEGF signaling and increased levels of inflammatory cytokines, which could potentially lead to a different response to anti-VEGF therapy," they said. "These altered pathways may result in a reduced responsiveness to anti-VEGF therapy, leading to a less pronounced reduction of neovascularization over time. Another possibility is that the microvascular changes associated with DR, such as capillary dropout and basement membrane thickening, create a less conducive environment for the resolution of neovascular complexes. The compromised vascular structure and function in diabetic eyes may impede the ability of anti-VEGF therapy to induce significant regression of the MNV, resulting in a lesser degree of reduction compared to non-diabetic eyes."

The sample size was relatively small, noted the authors, which could have potentially limited the generalizability of their results. The lack of control group also means observed differences during the follow-up period could have occurred even without anti-angiogenic therapy. "Furthermore, the use of spectral-domain OCT-A, which utilizes shorter wavelength light compared to swept-source OCTA, may result in reduced signal penetration through the RPE, potentially affecting the accuracy of our imaging data," they added.

Despite these factors, the authors say they felt confident in the strengths of their study, and say it's the first comprehensive investigation of the impact of DR on longitudinal morphological and functional changes in type 1 MNV associated with AMD in patients undergoing anti-VEGF therapy for 1 year. The divergent response they discovered in this study highlights the role DR plays in treatment outcomes, and they concluded saying, "Future larger studies utilizing swept-source OCT-A and longer follow-up durations are necessary to validate our preliminary findings."

1. Boscia G, Bacherini D, Vujosevic S, Grassi MO, Borrelli E, Giancipoli E, Landini L, Pignataro M, Alessio G, Boscia F, Viggiano P. Long-term impact of diabetic retinopathy on response to anti-VEGF treatment in neovascular AMD. Invest Ophthalmol Vis Sci. August 2, 2024. [Epub ahead of print.]

New Aflibercept Biosimilar Approved

Sandoz recently received FDA approval for the company's aflibercept biosimilar, Enzeevu (aflibercept-abzv) 2 mg vial kit and pre-filled syringe for intravitreal injection. The new drug is indicated to improve and maintain visual acuity in patients with wet age-related macular degeneration. Also, the company says the FDA provisionally determined Enzeevu would be interchangeable with the reference drug as it's "currently subject to an unexpired exclusivity for the first interchangeable biosimilar products."

The approval was based on the company's Mylight study.[1] Mylight was a prospective, double-masked, two-arm, parallel Phase III study. Participants with wet AMD were randomized 1:1 to receive eight injections of the biosimilar (n=244) or reference aflibercept (n=240) over 48 weeks. The primary endpoint was mean change in best-corrected visual acuity score from baseline to week eight.

The researchers found similarity in mean change in BCVA score between the biosimilar (n=235) and reference aflibercept (n=226) at week eight, and out to Week 52. They reported no clinically meaningful differences between groups in terms of anatomical outcomes. The drugs' safety profiles were similar, with comparable incidences of treatment-related adverse events (Enzeevu: 2.5 percent; reference aflibercept: 2.9 percent).

1. Bordon AF, Kaiser PK, Wolf A, et al. Efficacy and safety of the proposed biosimilar aflibercept, SDZ-AFL, in patients with neovascular age-related macular degeneration: 52-week results from the Phase 3 Mylight study. Retina 2024;10.1097/IAE.0000000000004174.

CORRECTION

In the August article, "Treating Wet AMD Patients Who Also Have GA," a physician is quoted as saying both pegcetacoplan and avacincaptad pegol have been rejected by the EMA for the treatment of GA secondary to AMD. However, only the former has been rejected so far. The marketing authorization application for avacincaptad pegol for that indication is still being reviewed by the EMA.
Review regrets the error.

New Metamorphopsia Tool Studied

It's tough to know exactly what a patient sees, particularly if they have a visual disorder such as metamorphopsia. The symptom, often arising from displaced photoreceptors at the macula, is commonly present in AMD and vitreoretinal conditions; understanding the patient's experience of it can be valuable to disease management. The tried-and-true Amsler grid isn't able to map the exact image distortion experience in any way that a clinician can experience firsthand. Recently, however, researchers from London published a novel method of assessing this visual phenomenon called the Image Warping Test (IWT).[1] Their paper, published in *Retina*, found that this test compared favorably to established measurement tools.

The IWT is a uniocular test in which the patient is presented with a grid of black lines on a white background

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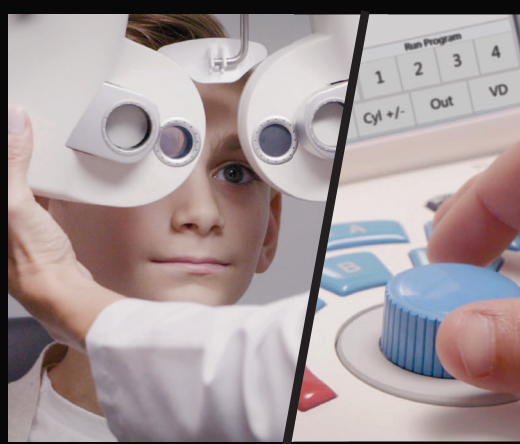

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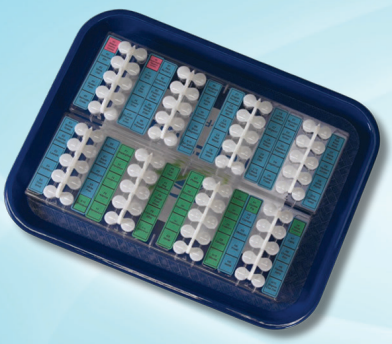

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DEPARTMENTS

September 2024

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44% and 55% of patients taking XDEMVY in SATURN-1 (N=209) and SATURN-2 (N=193), respectively, achieved a significant improvement in their eyelids (reduction of collarettes to no more than 2 collarettes per upper lid) at Day 43 vs 7% (N=204) and 12% (N=200) of patients taking vehicle ($P<0.01$ in each trial).*

INDICATIONS AND USAGE

XDEMVY (lotilaner ophthalmic solution) 0.25% is indicated for the treatment of *Demodex* blepharitis.

IMPORTANT SAFETY INFORMATION:

WARNINGS AND PRECAUTIONS

Risk of Contamination: Do not allow the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to minimize contamination of the solution. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Use with Contact Lenses: XDEMVY contains potassium sorbate, which may discolor soft contact lenses. Contact lenses should be removed prior to instillation of XDEMVY and may be reinserted 15 minutes following its administration.

ADVERSE REACTIONS: The most common adverse reaction with XDEMVY was instillation site stinging and burning which was reported in 10% of patients. Other ocular adverse reactions reported in less than 2% of patients were chalazion/hordeolum and punctate keratitis.

Please see next page for a Brief Summary of the full Prescribing Information.

*The safety and efficacy of XDEMVY for the treatment of DB were evaluated in a total of 833 patients (415 of whom received XDEMVY) in two 6-week, randomized, multicenter, double-masked, vehicle-controlled studies (SATURN-1 and SATURN-2). Patients were randomized to either XDEMVY or vehicle at a 1:1 ratio, dosed twice daily in each eye for 6 weeks. All patients enrolled were diagnosed with DB. The primary efficacy endpoint was defined as the proportion of patients with collarette reduction to no more than 2 collarettes per upper eyelid at Day 43.

Reference: XDEMVY [prescribing information]. Tarsus Pharmaceuticals, Inc; 2023.

tarsus

REVIEW NEWS

displayed on a computer monitor. This background is dynamically warped by an operator until the grid lines appear straight to the patient and the metamorphopsia is canceled out. "The reversal of this correction generates a grid which represents the pattern of the participant's metamorphopsia," the researchers explained in their paper.

They analyzed metamorphopsia measurements of 25 volunteer subjects who had metamorphopsia secondary to vitreoretinal pathology. Tests included standard Amsler grid, a modified Amsler grid called Morphision (in which the central area is presented in a warped pattern), the M-Charts collection of grids and the IWT.

They reported no correlation between best-corrected distance visual acuity and IWT score or between M-Charts score and IWT score, but they did find several significant associations between subjective estimation of severity and IWT score; between Morphison result and IWT score; and between vitreoretinal pathology and IWT score.

The researchers wrote in their *Retina* paper that the value of the IWT over other established measures "is its ability to create a digital map of the metamorphopsia experienced. Such mapping opens the possibility of non-invasive treatment through inversely mapping the distortion onto images or video, providing personalized correction of distorted vision. Combined with a 'see-through' head mounted display with forward facing video cameras, live video feed and gaze tracking, there is the real potential to dynamically correct metamorphopsia in [the] future and improve quality of life as a result." ◀

1. Suárez CV, Than J, Ling Y, et al. The image warping test: A novel method to quantify and quality metamorphopsia. Retina 2024. [Epub ahead of print].

INDUSTRY NEWS

Atsena Receives Rare Disease Designation
Atsena Therapeutics announced the FDA granted Rare Pediatric Disease designation for gene-therapy product ATSN-201 for the treatment of X-linked retinoschisis.

New Executive Director of ASOA
The American Society of Ophthalmic Administrators appointed Abigail Markward, MBA, as executive director of ASOA. Markward will continue her role as executive director of the ASCRS Foundation, a position she has held since November 2023.

New CPT Code for LumiThera Treatment
LumiThera, a medical device company commercializing a photobiomodulation (PBM) treatment for ocular damage and disease, announced a new Category III CPT code effective January 1, 2025.

Orbis Mounts Mission To Mongolia
Orbis International is conducting a three-week training project on board the Orbis Flying Eye Hospital in Mongolia to "build the skills of local eye-care teams, strengthen the ability of partner hospitals to deliver care and raise awareness about eye health."

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REVIEW of OPHTHALMOLOGY

WALTER C. BETHKE, EDITOR IN CHIEF
EDITOR'S PAGE

Unfair Surprise

Regular readers of this column might recall that one of my daughters has a talent for graphic design and illustration, and we were recently engaging in the time-honored process of college tours, hoping to winnow the options down to the best one for her.

I'm happy to report that, after traveling up and down the Eastern Seaboard visiting various schools, and digging into all of their facets—tuition cost, the degree program, tuition cost, student life, location, tuition cost, etc.—she committed to a university in the spring. There was much rejoicing and sighs of relief.

Then we went to "Accepted Student Weekend."

It's at this point it's worth mentioning a cool term I just learned: "unfair surprise." It's from the world of law. It can also be found on Accepted Students Weekend.

It has a broad meaning, but it essentially means what it says: One party in a contract or legal proceeding is blindsided by something that they had no previous knowledge of, and may have changed the outcome of the situation had they known.

Our surprise came in a session for parents of accepted students. During his presentation, one of the college's student life directors informed us that, due to our daughter's incoming class being so large, they were going to have to take rooms that were normally sized for two students and instead stuff three kids in there.

The parents came at the guy with torches and pitchforks. Backing up against the wall, his eyes darting around at the exits, he assured us that it wasn't all the students, just some. But, as lawmaker Mr. Murphy would have predicted, my daughter was one of the victims, er, beneficiaries, of the new policy.

This idea of an unfair surprise (a term that's really growing on me and that I plan to use a lot from now on; I'm toying with the idea of a tattoo) sounds like something to keep in mind when you think about switching your electronic health records system, the topic of one of our feature articles this month (pg. 40).

Such a transition is rife with potential for unfair surprises, such as the potential inability of the practice management systems in the EHR to communicate with each other (billing and optical for example), expecting an EHR vendor to be in it for the long run, as your partner, but instead you find out they're actually not; or when you expect it to interface with your diagnostic equipment but instead it falls short.

Fortunately, the physicians and practice management experts we spoke to cover a lot of these unfair surprises, and share advice on how to avoid them if and when you make the switch. Hopefully you can profit from their adventures (and misadventures).

Until we visit again next month, may your EHR system run smoothly, and may the only surprise you experience be finding $20 in your jeans.

— Walter Bethke
Editor in Chief

For the treatment of all stages of neurotrophic keratitis (NK)

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- **Up to 72% of patients** achieved complete corneal healing in clinical trials*†[1-3]
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*Resolution was evaluated in clinical trials as complete corneal healing, defined as the absence of staining in the lesion area and no persistent staining in the rest of the cornea after 8 weeks of treatment and as <0.5-mm lesion staining at 48-week follow-up.[1-3]

†Key study findings were after 8 weeks of treatment, 6 times daily. REPARO (Study NGF0212): 52 patients with Stage 2 or 3 neurotrophic keratitis (NK) in 1 eye per group; 72% (36/50) of patients completely healed; vehicle response rate 33.3% (17/51). Study NGF0214: 24 patients with Stage 2 or 3 NK in 1 or both eyes per group; 65.2% (15/23) completely healed; vehicle response rate 16.7% (4/24). Last post-baseline observation carried forward; chi-squared test. Patients without any post-baseline measurements were excluded from the analysis.[1-3]

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

Important Safety Information

WARNINGS AND PRECAUTIONS

Use with Contact Lens

Contact lenses should be removed before applying OXERVATE because the presence of a contact lens (either therapeutic or corrective) could theoretically limit the distribution of cenegermin-bkbj onto the area of the corneal lesion. Lenses may be reinserted 15 minutes after administration.

Eye Discomfort

OXERVATE may cause mild to moderate eye discomfort such as eye pain during treatment. The patient should be advised to contact their doctor if a more serious eye reaction occurs.

ADVERSE REACTIONS

In clinical trials, the most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Eye pain may arise as corneal healing occurs. Other adverse reactions occurring in 1% to 10% of OXERVATE patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation, photophobia, tearing, and headache.

USE IN SPECIFIC POPULATIONS

Pregnancy

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

Lactation

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 pediatric patients 2 years of age and older is supported by evidence from adequate and well-controlled trials of OXERVATE in adults with additional safety data in children.

INDICATION

OXERVATE® (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL) is indicated for the treatment of neurotrophic keratitis.

DOSAGE AND ADMINISTRATION

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

To report ADVERSE REACTIONS, contact Dompé U.S. Inc. at 1-833-366-7387 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

References: 1. OXERVATE® (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL) [US package insert]. Boston, MA; Dompé U.S. Inc.; 2023. **2.** Bonini S, et al. *Ophthalmology*. 2018;125:1332-1343. **3.** Pflugfelder SC, et al. *Ophthalmology*. 2020;127:14-26. **4.** Data on File. Clinical Study Report (NGF0212). Dompé U.S. Inc., 2016.

See more clinical data
OXERVATE.com/hcp

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Brief Summary of full Prescribing Information

Consult the full Prescribing Information for complete product information, available at www.oxervate.com/prescribing-information.

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

General Dosing Information

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.

WARNINGS AND PRECAUTIONS

Use with Contact Lens

Contact lenses should be removed before applying OXERVATE because the presence of a contact lens (either therapeutic or corrective) could theoretically limit the distribution of cenegermin-bkbj onto the area of the corneal lesion. Lenses may be reinserted 15 minutes after administration.

Eye Discomfort

OXERVATE may cause mild to moderate eye discomfort such as eye pain during treatment. The patient should be advised to contact their doctor if a more serious eye reaction occurs.

ADVERSE REACTIONS

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.

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. Eye pain may arise as corneal healing occurs.

Other adverse reactions occurring in 1% to 10% of OXERVATE patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation, photophobia, tearing, and headache.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of OXERVATE. 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.

Eye disorders: eye irritation, blepharitis (including eyelid margin crusting and eyelid edema) and corneal neovascularization.

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.

Lactation

Risk Summary

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.

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, Mutagenesis, Impairment of Fertility

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).

Dompé

The End of History

Musings on life, medicine and the practice of ophthalmology.

MARK H. BLECHER, MD
CHIEF MEDICAL EDITOR

A few decades ago, philosopher and political commentator Francis Fukujama wrote a book with this title and posited that the socio-economic progression of humankind had reached an endpoint.

He argued that we had evolved to the most optimal and ideal geopolitical and economic structure. Western liberal democracy with the fall of the Soviet Union, had proved itself ascendent and there was no need to look further for a more perfect state. Even at the time, it was a highly suspect point of view and clearly, we're not in a state of nirvana. But it did stimulate a discussion of whether we could ever get somewhere so good we didn't need to or couldn't improve on the status quo.

Humans have this hardwired need to do better, to improve. We must hone the world around us, ourselves, our WiFi reception. The status quo is never a desirable state of being, and that's one of the nicest things I could say about our species. I suppose this doesn't apply to everyone, though at some level it should. Not everyone wants to save the world, cure cancer, wipe out hunger, etc. But in our own little ways, in our own small existences, we should never be completely satisfied with our situation. Appreciate what we have, sure. Rest on our laurels, not so much.

So, it occurred to me recently while teaching new senior residents cataract surgery, that we've reached a status quo, "the end of the internet," so to speak, as in what was previously felt to be limitless does indeed have an endpoint—at least at this moment.

I remember vividly the onslaught of new phaco technology, and of new nucleo-fractis techniques. Divide and conquer, stop and chop, vertical, horizontal, phaco flip. New instruments every week named for all our favorite surgeons as a legacy to the profession. And there were new courses to teach all these techniques, filling the schedules of conferences.

As I walked my residents through the progression of current phaco techniques I realized I had nothing new to teach them—nothing new to me, anyway. Innovations in intraocular lenses, sure, but removing the lens, no. And while it's possible I've missed some exciting and innovative milestone, I'm pretty sure I haven't. So, the question popped up, have we reached the best we can do? Has innovation stopped? For cataracts anyway, potential new technology is prevention, not extraction. And while topical medications to prevent or reverse lenticular oxidation may be on the horizon, there will still be cataracts to be done for decades to come.

I suppose I should be glad that I don't have to learn a new surgical technique and that perhaps what we have is indeed ideal. But I find that thought unsettling. Or perhaps, it's that we have settled—maybe for good enough, because what we have is pretty good. However, my DNA isn't letting me accept this. I still hope someone will share a better way to remove the nucleus: Less invasive, less variable, more reproducible and more efficient. We've learned that even small tweaks can make a huge difference over a large number of surgeries. And it would be nice to achieve these advancements, not only through the use of new high-tech and high-expense innovations, but with surgeon-driven technique changes. We've already made many attempts to bankrupt the healthcare system with interesting and often impressive industry-generated technologies. That said, I welcome all efforts to move my favorite procedure forward.

In 1889, Charles Duell, the head of the U.S. Patent Office declared that everything that could be invented had been and he was going to close the office. There had been an era of great advancements that was followed by a period of relative quiet. He couldn't see what lay ahead. And at the moment, for cataract extraction anyway, neither can I. But that doesn't mean it won't occur. It doesn't mean it shouldn't occur. At least for now I suppose I can glide a bit and bask in the thought that what I'll teach this year's seniors will be useful to them for perhaps a little bit longer than my training was with a cryo probe. ◀

This article has no commercial sponsorship. **Dr. Blecher** is an attending surgeon at Wills Eye Hospital.

An Update on Dead Bag Syndrome

The cause of this rare presentation is still a mystery, but many are dedicated to its continued research.

LIZ HUNTER
SENIOR EDITOR

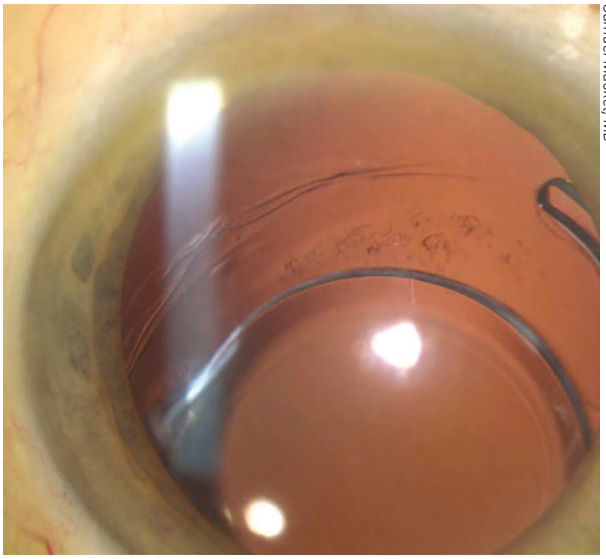
Intraocular lens dislocation may be rare, but it's a scenario every cataract surgeon prepares for. Late in-the-bag dislocation has been linked to pseudoexfoliation syndrome, uveitis, myopia and other diseases, and surgeons are trained in management strategies that include IOL exchange or suturing techniques.[1] Not all cases are so easily explained, however. What if a patient presents with a late dislocated IOL and none of the typical conditions appear to be a contributing factor?

This could be "dead bag syndrome." Coined over 25 years ago by Sam Masket, MD, this term refers to a capsular bag that appeared pristine and clear, with no posterior capsule opacification or fibrosis of the anterior capsulotomy. Despite its clean appearance, when it occurs late, this phenomenon often indicates a degenerating capsule bag.

Since its initial identification, reports of DBS are becoming more common, but its cause remains a mystery. We spoke with some of the surgeons who are at the forefront of the research and education around this syndrome to find out what progress has been made and what more needs to be done. Here's what they said.

What the Research Says

Dr. Masket, clinical professor at UCLA's Stein Eye Institute, was the first to sound the alarm on DBS after witnessing it in a couple of patients. He recalls attending meetings in the late '90s and asking peers if they had observed this. It wasn't until he got the attention of Liliana Werner, MD, PhD, and Nick Mamalis, MD, co-directors of the Intermountain Ocular Research Center at the Moran Eye Center in Utah, that real progress started happening on the pathology of these capsule bags.



Samuel Masket, MD

An in-the-bag decentration of this one-piece acrylic IOL is noted. Superior zonulysis is evident and the capsule is noted to be thin and clear with no fibrotic change; very minor PCO is noted.

Drs. Werner, Mamalis and Masket were co-authors, along with others, of a landmark study published in the *Journal of Cataract & Refractive Surgery* in 2022.[2] It included 10 suspected DBS cases, each of which had no signs of zonular instability during the cataract removal. Of those 10, researchers removed eight IOLs and seven capsular bags because of subluxation or dislocation. Histopathologic examination of the seven capsular bags showed capsular thinning and/or splitting. Two specimens were completely absent of lens epithelial cells, and five had rare LECs on the capsule's inner surface.

"Their research revealed that lens epithelial cells in these bags had undergone degeneration and loss," says Dr. Masket. "This raised the question of whether these cells were already deficient immediately following surgery, or if they had initially developed normally but then degenerated slowly over time."

Dr. Werner explains, "Lens epithelial cells are important to the capsule as they continue to deposit extracellular matrix and lens capsule components at their basal ends, which contributes to the thickening of the capsule throughout life, as well as maintaining its integrity.

"On the other hand, the capsule is also important to the lens epithelial cells," she continues. "It represents an anchor point for the basal surfaces of the cells, also pro-

This article has no commercial sponsorship.

Dr. Chayet is considered a pioneer in refractive and cataract surgery, and is the medical director of the Codet Vision Institute in Tijuana, Mexico. He is a clinical investigator for RxSight, LensGen and ForSight Vision6.

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REFERENCES:
1. Data on File. 2024DOF4002 **2.** Data on File. DOF2023CT4052 **3.** Data on File. 2024DOF4005 **4.** Data on File. DOF2023CT4023 **5.** Data on File. DOF2023CT4007 **6.** Data on File. DOF2019OTH4002

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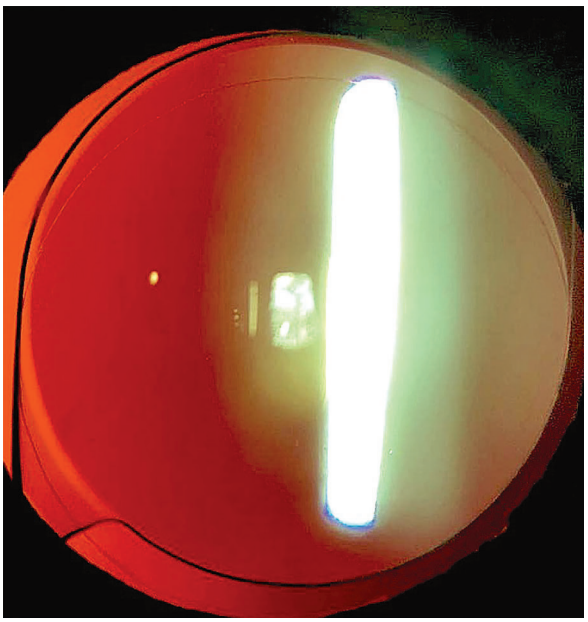
Samuel Masket, MD



A perfectly clear capsule bag is noted in this eye now 11 years post routine cataract surgery. The anterior capsule rim shows no fibrosis and the posterior capsule is intact and clear. In this case there is no zonulopathy and the single-piece acrylic IOL is well centered.

viding necessary signals for proper lens cell proliferation, migration and differentiation. Therefore, in the dead bag syndrome there may be a problem in the cells, which degenerate, affecting the capsule, or a problem in the capsule itself, initiating a cycle of damage to the cells with further damages the capsule. The exact etiology is still unknown."

In the cases included in the original *JCRS* paper, Dr. Werner says there were no fibrotic changes or proliferative material within the capsular bags. "The main histopathological findings were capsular splitting/delamination, and rare or absent lens epithelial cells attached to the capsule," she says. "It's possible that our cases represent the severe end of a spectrum, as informal online discussions describe cases where the capsule was floppy and delicate, but still exhibited a certain amount of proliferative material within it, including abnormal gel-like Soemmering's ring formation."

Research hasn't slowed down. Just last month, Dr. Werner published another study, co-authored by Shizuya Saika, MD, and members of the Department of Ophthalmology at Japan's Wakayama Medical University School of Medicine. This one focused on the immunohistochemical findings of DBS capsules.[3]

"Nine capsular bag specimens from dead bag syndrome cases, as well as two control specimens from late-postoperative in-the-bag IOL dislocation cases related to previous vitrectomy, pseudoexfoliation, and blunt trauma were included," explains Dr. Werner. They were processed for histopathology; unstained sections were obtained from each one, and analyzed by immunohistochemistry targeting collagen type IV and laminin (components of basement membrane, i.e., lens capsule), vimentin (cytoskeletal components of lens epithelial cells), collagen type I and fibronectin (extracellular matrix components of fibrotic posterior capsule opacification).

"Immunohistochemistry confirmed that scarce or no lens epithelial cells were present in the capsular bags from dead bag syndrome cases, but suggested that cells were present after surgery, secreted components of fibrotic posterior capsule opacification, but something happened later and the cells died/detached," she says.

This research highlights the importance of distinguishing between different types of collagen laid down by lens epithelial cells post-surgery. "Dr. Werner determined that there was more fibrotic material present at one time, but that the type of collagen wasn't characteristic of the normal postoperative capsule bag; it was a softer type," Dr. Masket says. "There was also no evidence of vimentin. That would only be present if the LECs were viable. This indicates that the degeneration process doesn't start immediately after surgery but occurs over time."

Dr. Masket continues, "Histologically, the capsular bag is essentially the basement membrane of the lens epithelial cells, and as these cells degenerate, so does the capsular bag in some cases. This degeneration often affects the periphery of the capsule and the zonular fibers, which can lead to a decentered bag. In some cases, the entire capsular bag may become decentered, or the lens may decenter within the bag if it's not fixated in a fibrotic fashion as it normally does postoperatively. If the capsule degenerates significantly, it can become thin and split, allowing the IOL to actually pop through the bag. Consequently, the lens may end up decentered within a decentered bag or even outside the bag.

"The variety of ways in which an IOL can become decentered from this condition is extensive, and we currently have more questions than answers," he continues.

Thoughts on the Theories

Increased awareness of DBS has inevitably led to speculation on its causes within the cataract surgery space. Some can be debunked, while others need a closer look.

The first theory questions if DBS is related to capsular polishing during phacoemulsification. "When looking at the results of our original study, especially regarding the scarcity of lens epithelial cells in the capsules, surgeons are naturally asking the question about a possible relationship with capsular polishing," Dr. Werner says. "There has been a lot of emphasis on polishing techniques to prevent capsular bag opacification, especially in association with premium lenses. However, even extensive polishing can't completely remove all lens epithelial cells, and polishing is usually not done at the capsular bag equator, as this region isn't readily visible. Therefore, to date there is no established association between capsular

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1. VEVYE® (cyclosporine ophthalmic solution) 0.1% [package insert], Harrow IP, LLC; 2024. **2.** Restasis® (cyclosporine ophthalmic emulsion) 0.05% [package insert]. Allergan, LLC; 2024. **3.** Cequa® (cyclosporine ophthalmic solution) 0.09% [package insert]. Sun Ophthalmics, LLC; 2024. **4.** Sheppard et al., Water-free 0.1% Cyclosporine A Solution for Treatment of Dry Eye Disease: Results of the Randomized Phase 2B/3 ESSENCE Study. Cornea 2021;00:1–8. **5.** Akpek et al., Efficacy and Safety of a Water-Free Topical Cyclosporine, 0.1%, Solution for the Treatment of Moderate to Severe Dry Eye Disease The ESSENCE-2 Randomized Clinical Trial. *JAMA Ophthalmol*. doi:10.1001/jamaophthalmol.2023.0709. April 6, 2023. **6.** Data on file.

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Data

Animal Data: Oral administration of cyclosporine oral solution to pregnant rats or rabbits was teratogenic at maternally toxic doses of 30 mg/kg/day in rats and 100 mg/kg/day in rabbits, as indicated by increased pre- and postnatal mortality, reduced fetal weight and skeletal retardations. These doses (normalized to body weight) were approximately 7,250 and 48,000 times higher than the daily maximum recommended human ophthalmic dose (MRHOD) of 0.67 mcg/kg/day, respectively.

No adverse embryofetal effects were observed in rats or rabbits receiving cyclosporine during organogenesis at oral doses up to 17 mg/kg/day or 30 mg/kg/day, respectively (approximately 4,100 and 14,500 times higher than the MRHOD, respectively).

An oral dose of 45 mg/kg/day cyclosporine (approximately 10,900 times higher than MRHOD) administered to rats from Day 15 of pregnancy until Day 21 postpartum produced maternal toxicity and an increase in postnatal mortality in offspring. No adverse effects in mothers or offspring were observed at oral doses of up to 15 mg/kg/day (3600 times greater than MRHOD).

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Risk Summary

Cyclosporine is known to be excreted in human milk following systemic administration but excretion in human milk after topical treatment has not been investigated. VEVYE® doses are approximately 4,700 times lower than recommended oral doses of cyclosporine, with blood concentrations being undetectable after topical administration. However, caution should be exercised when VEVYE® is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

GERIATRIC USE

No overall difference in safety or effectiveness has been observed between elderly and younger patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Evaluation of the potential carcinogenicity of cyclosporine was conducted in male and female mice and rats. In a 78-week oral (diet) mouse study, at doses of 1, 4, and 16 mg/kg/day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value.

In a 24-month oral (diet) rat study, conducted at 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate in the low dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related. The low doses in mice and rats were approximately 120 times higher than the maximum recommended human ophthalmic dose (0.67 mcg/kg/day), normalized to body surface area.

Mutagenesis

In genetic toxicity tests, cyclosporine has not been found to be mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone-marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. Cyclosporine was positive in an in vitro sister chromatid exchange (SCE) assay using human lymphocytes.

Impairment of Fertility

Oral administration of cyclosporine to rats for 12 weeks (male) and 2 weeks (female) prior to mating produced no adverse effects on fertility at doses up to 15 mg/kg/day (approximately 3,600 times higher than the maximum recommended human ophthalmic dose).

PATIENT COUNSELING INFORMATION

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polishing and this condition."

Dr. Masket also rules this out. "My first observed case of DBS didn't involve phacoemulsification or capsule polishing," he says. "This early case involved a white mature cataract treated with extracapsular cataract extraction, and yet the dead bag phenomenon still occurred over many years."

Others wonder if the use of intracameral medications may be a cause. Again, Dr. Masket says this is unlikely. "Another case I performed in 1993, involving phacoemulsification under local block with no intracameral medications, also developed bilateral dead bag syndrome, eventually leading to a lens decentering and even UGH syndrome in one eye where one loop of the lens poked through the capsule," he says.

Self-induced trauma or eye rubbing is another theory. "There's currently no pathological evidence linking eye rubbing to the changes seen in dead bag syndrome," Dr. Masket says. "Eye rubbers are more prone to both cataract formation as well as zonulopathy, which is understandable from chronic trauma, but the evidence isn't clear because most patients reported with dead bag syndrome have been monocular, which is inconsistent with the behavior of eye rubbers who typically rub both eyes."

One link that is worth more investigation is that of atopic dermatitis. "An interesting development this year in the *Journal of Cataract & Refractive Surgery* explored the capsular bag in patients with atopic dermatitis," notes Dr. Masket. "The findings in these patients were quite similar to those observed in dead bag syndrome. This raises the question of whether there's a link between atopic dermatitis and dead bag syndrome, a connection that has yet to be thoroughly investigated. The study distinguished capsular bag changes in atopic patients from those in patients with decentered or dislocated capsular bags due to other causes, such as pseudoexfoliation."[4]

Finally, IOL type can be ruled out as a contributor, as DBS has been associated with all varieties of IOLs, including silicone, acrylic and PMMA lenses, and has been reported in both hydrophobic and hydrophilic acrylic lenses, says Dr. Masket.

Raising Awareness

There are many unanswered questions not only about the etiology of this syndrome, but also in its manifestations. Surgeons should be careful not to immediately presume any late, in-the-bag IOL dislocation is DBS. The condition itself remains rare, but those who are frequently referred to for dislocated IOLs may encounter a higher number, approximately one per month.

"The rate of late postoperative in-the-bag IOL dislocation has been reportedly increasing, and among the known predisposing conditions are pseudoexfoliation and other conditions associated with progressive zonular weakening," says Dr. Werner. "However, in the dead bag syndrome, signs of zonular weakness are usually absent in the original IOL implantation procedure, and we hypothesize that late postoperative zonular failure is related to capsule splitting/delamination occurring at the level of zonular attachments. It's therefore fitting that management is advised on a case-by-case basis, depending on presentation, as well as status of the zonular support."

Dr. Masket says, despite the progress made on the topic, DBS is very much in its infancy. "Now that we've called the profession's attention to it, my sense is we're going to hear more from all the corners of the world," he says. "DBS's recent increased recognition parallels historical cases like hemorrhagic occlusive retinal vasculopathy. It was a postoperative complication with horrific retinal changes that turned out to be associated with an unusual immunologic response to intraocular vancomycin. There weren't a large number of cases, but all of a sudden cases started coming out of the woodwork. Many of us had used intraocular vancomycin for years and never saw a case, but awareness eventually led to understanding and resolution.

"I think we're going to see a parallel here with DBS," he concludes. "As the profession becomes more alert to this phenomenon, further reporting and research will be essential to uncovering its causes and improving patient management." ◀

Samuel Masket, MD

Although LEC polishing and intracameral antibiotics have been suggested as possible causes of DBS, researchers haven't found a connection.

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DISCLOSURES

Dr. Masket and **Dr. Werner** have no disclosures to report.

SPRUCE UP YOUR DED ALGORITHM

Several new treatments are available now. Here's how experts are integrating them into their dry-eye management.

CHRISTINE YUE LEONARD
SENIOR ASSOCIATE EDITOR

Innovation in the dry-eye space has taken off over the last few decades, and now ophthalmologists have more options than ever before for treating patients' dry-eye disease. "It's an amazing time to be a specialist in this area because there are so many different therapeutic options available to handle the complexity and variety of the ocular surface issues we encounter on a day-to-day basis in the clinic," says Christopher Starr, MD, FACS, a cornea and cataract/refractive specialist at Weill Cornell Medicine in New York. "As new treatments get FDA approved and become available, I try to incorporate them into my personal algorithm."

While it's an exciting time, the plethora of options might feel overwhelming. What's the best way to incorporate all these into your practice? We spoke with several dry-eye experts to learn about their specific approaches and to find out how they're using the newly approved treatments.

A DED Roadmap

Treating patients' dry eye can be as complex as the disease itself. Many clinicians find dry-eye treatment algorithms—such as DEWS II, CEDARS and the ASCRS Preoperative Ocular Surface Disease algorithm—helpful because they remove some of the mental load when it comes to deciding next steps based on diagnosis or severity.

"It's a balance—that's why it's called the Art of Medicine," says Sabrina Mukhtar, MD, a cornea specialist at the University of Pittsburgh Medical Center. "I use the ASCRS algorithm since I'm in a referral practice and many of my patients are referred to me for procedures. Even if you go through the algorithm and have a list of treatments for the patient, I work with them to address the high-impact things."

"I look at the ASCRS algorithm, but I don't always follow it exactly," says Amy Lin, MD, a cornea specialist at the Moran Eye Center in Salt Lake City. "It's nice to see what all the options are at each step, and it can be good to perform things in a stepwise function. I try to tailor the dry-eye treatment for the patient. For example, ideally, I like to start patients on a long-term topical anti-inflammatory for treatment for dry eye prior to placing punctal plugs. But, if there are insurance or cost issues that prohibit the use of any of the topical anti-inflammatories, then I may go to punctal plugs next. If those fall out but the patient feels relief when they're in, then I may jump to punctal cautery as the next step after plugs.

"If a patient really doesn't like eye drops, if they don't have the means to instill eye drops because of disability or they don't have anyone who can help them put drops in, then the varenicline nasal spray can be a nice alternative," she continues. "I have patients who don't want any prescriptions at all—no drops or any oral medications. They want to keep things natural. For these patients, the nasal spray can be

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Dr. Meghpara is a consultant for Allergan, Sun Pharma, BioTissue and Tarsus. **Dr. Starr** is a consultant for Novartis, Allergan/Abbvie, Trukera, Sun Pharma, Bruder, BlephEx, Kala, Quidel, Dompé, Johnson & Johnson Vision, Sight Sciences, Essiri LLC., Tarsus, Oyster Point, CSI Dry Eye, Aldeyra, Alcon, Versea, Bausch + Lomb, Novaliq, Lumenis, Théa, Glaukos, Amgen, Oculis, Eye Care International, Sofia Biologics, Azura and Allgenesis. **Dr. Behshad**, **Dr. Lin** and **Dr. Mukhtar** have no relevant financial disclosures.

a good option because it stimulates the patient's own tears. That might be something I introduce early on, maybe right after artificial tears for certain patients."

Treat the Underlying Cause

Failing to treat the underlying cause of dry eye is one of the biggest challenges of managing this chronic condition. The bread and butter of dry-eye treatment revolves around the diagnosis, Dr. Starr explains. "When we wrote the ASCRS Preoperative Ocular Surface Disease algorithm, treatment decisions hinged on accurate diagnoses. To this day, many clinicians lump any symptoms of ocular surface disease together and call it 'dry eye' and treat it as if it were simple 'dry eye.' That's what led to a lot of the frustration for both doctors and patients, because without a careful diagnosis, the treatment's not going to be right."

An ocular surface disease diagnosis is often multifactorial. "There are multiple ocular surface disease subtypes, all of which might contribute simultaneously to the constellation of symptoms that a patient might be having. So, it behooves us to spend a little extra time during the exam on symptom identification. This is where questionnaires come in and talking to the patients about exactly what their symptoms are. If you just treat based off a remark like, 'my eyes are irritated,' you're going to mistreat many, many times. These patients are going to take a little bit longer than, say, the average cataract patient, where the presence or absence of a significant cataract isn't much of a diagnostic challenge. That said, in the era of modern medicine, time constraints and reimbursements are a significant challenge, and it's often difficult to secure this additional chair time for complex dry-eye disease/ocular surface disease patients."

Dr. Mukhtar agrees. "We often don't have time in our busy clinics to sit down and truly talk to the patient and understand why they're having their symptoms," she says. "To address this challenge, the University of Pittsburgh Medical Center established a dry eye center of excellence. We see fewer patients each day, but they have a longer visit. They're typically referred to us from our other colleagues in the department.

"Whenever you see a patient, it's a snapshot in time and can be difficult to figure out all the potential factors contributing to their dry-eye disease," she continues. "We have this questionnaire called CSI Dry Eye that uses machine learning to compute reasons why a patient may have dry eye based on lifestyle, diet, treatments, medications, medical problems, and so on. This makes it a lot easier for the eye-care provider because it helps us target our therapy. We can't fix everything at one visit, but we can focus on the top one or two things that bother patients."

When speaking with patients, Dr. Starr and Dr. Mukhtar say a useful questions to ask is, "What is the thing that bothers you most about your eyes?" Dr. Starr says, "Usually, these patients have a long list of complaints, and but usually one symptom is at the top of the list, and this helps me prioritize what symptom I'm going to try to control first, whether that's a vision-related thing or discomfort, itching, crusting or redness, etc."

Most of the dry-eye patients Dr. Starr sees are referred to him after trying multiple medications. "Their frustration levels are pretty high because they're still suffering," he says. "These patients tend to be more challenging and complex and require an upfront discussion to attempt to isolate symptoms and talk about what has worked and what hasn't, or when the symptoms occur. You have to always be thinking about the corneal nerves too. Corneal neuropathic pain and neurotrophic keratitis are often misdiagnosed, diagnosed late or not diagnosed at all."

"Neurotrophic keratitis patients may have decreased corneal sensation," Dr. Lin says. "These are challenging patients to treat because have little to no clinical signs yet have very severe symptoms. Oxervate may be prescribed for even as low as stage one NK, but certainly should be entertained for stages two or three. These patients may actually fall into the neuropathic pain category, which is very difficult to treat."

"If a patient tells me they feel worse at the beginning of the day and wake up with gritty eyes, that tells me they have a little bit of lagophthalmos or possibly floppy eyelid syndrome, where their eyes are drying out overnight," Dr. Mukhtar says. "So, that's what we'll target, whether it's through lubricating ointments or nighttime goggles. If the patient tells me their eyes feel worse as the day goes on, especially while at work, that tells me it might be incomplete blink and likely meibomian gland dysfunction."

Dr. Mukhtar performs a full review of the patient's medical issues and medications. "We want to make sure we have an understanding of what's contributing [to the dry eye]," she says. "It's pretty in-depth. Dry eye is quite medical. Because we're a referral center, we see a lot of autoimmune conditions. In fact, we have a dedicated Sjögren's clinic where a rheumatologist and one of our cornea partners co-manage patients because their systemic treatment is really important. In the dry-eye clinic, we also see a lot of long-term chemotherapy patients, since that can cause dry eye too. I've diagnosed many sleep apnea cases since I examine patients' eyelids. Thyroid disease may also be identified since there's a specific staining, which is important to do."

Unfortunately, reimbursement and coverage for many dry-eye treatments including those newly approved remain persistent challenges for both providers and patients. "The reality of the situation is the accessibility of new treatments is sometimes hindered by insurance coverage," says Beeran Meghpara, MD, a cornea and cataract/refractive specialist at Wills Eye Hospital in Philadelphia. "Often, the paperwork that's required on the part of the practitioner to get these medications to patients is cumbersome, and

despite us doing all the paperwork, copays may be extremely high. This is by far one of the biggest challenges when it comes to getting new treatment options into the hands of patients."

Three Things First

Dr. Mukhtar gives every dry-eye patient a homework sheet with a few things she says every patient should do, regardless of why they have dry eye:

1. A warm compress. "Incomplete blink is one of the most common causes of dry eye that then contributes to meibomian gland dysfunction," she says. "I compare this to brushing your teeth every day. It's important to take care of your eyelids as well.

2. Blinking exercises. "Going off the 20/20/20 rule, I tell patients to blink actively 20 times to stimulate the lacrimal and meibomian glands.

3. Environmental modifications. Some of these include using larger text when working on the computer, using an anti-glare monitor and ensuring active air isn't moving into the eyes."

Quieting Inflammation

One of the major underlying causes of dry eye is inflammation. "Anti-inflammatory medications include steroid eye drops, some of which are specifically indicated for dry eye while others are used off-label, and steroid-sparing agents or immunomodulators," Dr. Meghapra says. "Steroid eye drops are a short-term treatment since the long-term side effects may include high pressures and cataract formation. Immunomodulators, on the other hand, are a long-term treatment. There are a handful of these drops available, including Restasis, Cequa and now Vevye, which are all cyclosporine, and Xiidra, which is lifitegrast.

"If a patient isn't doing well on Restasis, I'll often switch to Cequa because it has a higher concentration of cyclosporine and a newer vehicle," he continues. "However, if a patient still isn't doing well on Cequa or they're not happy with their symptom control, then I'll usually switch them to a different class of medication, such as serum tears."

"Vevye has been a great option for patients with both aqueous deficient and inflammatory dry eye mixed in with evaporative dry eye," says Soroosh Behshad, MD, MPH, a cornea and cataract/refractive specialist at Emory University School of Medicine. "I find that patients who haven't tolerated previous options such as Restasis, Cequa or Xiidra, due to symptoms of burning or irritation, do better with Vevye and demonstrate clinical improvement in about two to four weeks." He adds that his patients have had difficulty with the bottle and report wasting drops.

"I've used Vevye for patients who [couldn't tolerate] the burning and stinging of other cyclosporine drops," Dr. Mukhtar says. "The limitation, unfortunately, is the cost. It's just a limitation for a lot of these dry-eye medications. It's really hard to get them covered for our patients, espe-

TABLE 1. SOME TEAR REPLACEMENT THERAPIES

Product	Company	Notes
iVizia	Thea	A preservative-free artificial tear with sodium hyaluronate, povidone and trehalose. Available in multidose bottles. Lubricant eye gel available in single-dose vials.
Clear Eyes Pure Relief	Prestige Consumer Healthcare	A preservative-free artificial tear formulated with glycerin and sodium hyaluronate. Available in multidose bottles.
Optase Dry Eye Intense	Scope	A preservative-free artificial tear with hyaluronic acid. The MGD Advanced lipid-based drop is also preservative-free. Both are available in multidose bottles.
Biotrue	Bausch + Lomb	A preservative-free artificial tear with hyaluronic acid. Available in single-dose vials and multidose bottles. Safe to use with contact lenses.
Blink Triple Care	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 Hydration	Alcon	A preservative-free artificial tear formulated for sensitive eyes with HydroBoost. Available in multidose bottles.
Soothe XP Emollient	Bausch + Lomb	Restores the lipid layers with mineral oils to seal in moisture and protect against 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%.
Refresh Relieva PF Xtra	Allergan	Preservative-free artificial tear in a multidose bottle with the company's HydroCell technology, a NaCl-free glycerin-based solution.
TheraTears	TheraTears	A hypotonic, electrolyte-balanced formula that replicates healthy tears.

cially the older patients, who seem to need it the most. If you have commercial insurance, it's pretty easy to get these medications through specialty pharmacies at a reasonable cost, but the reason I don't use Vevye much is because my older patients have trouble getting it."

For patients suffering from this condition, Dr. Mukhtar says that in addition to warm compresses, "I try to get them on some anti-inflammatory medication such as cyclosporine or lifitegrast in addition to a steroid taper to calm things down, since these anti-inflammatories take almost two months to work.

"The procedure I most commonly do for ocular rosacea patients is intense pulsed light therapy," she continues. "It has been FDA approved for meibomian gland dysfunction as well. It's very good at controlling these vicious inflammatory cycles—what happens in ocular rosacea is that the dilated blood vessels bring inflammatory mediators to the surface of the eye, which creates the vicious cycle. If I start patients on a topical anti-inflammatory, that's not really treating the underlying cause. In order to achieve success with IPL, choose the right patient to do it on. It won't treat dry eye caused by Sjögren's disease because that's a different pathophysiology."

She notes that there are several key limitations for IPL. "If a patient has active herpetic keratitis or any herpetic disease in the eye, I wouldn't do IPL then," she says. "Any active uveitis is also a contraindication. IPL is also suitable only for certain Fitzpatrick skin types. Patients with darker skin or more melanin in their skin aren't good candidates. Radiofrequency treatments, which use a different method to heat up the oil glands to improve function and treat inflammation, is another option, but I don't use that in my practice yet."

For persistent, severe dry eye, amniotic membrane can help stave off some symptoms with the growth factors and stem cells they contain as well as their anti-inflammatory properties. "I've used [amniotic membrane] extensively in patients with non-healing corneal epithelial defects, Stevens Johnson Syndrome or burns, but recently I've started using it for some patients with dry-eye disease," Dr. Lin says. "I probably wouldn't bring up the option until a patient has failed multiple treatments. It's important to tell patients it can be a bit uncomfortable for a few days and will blur vision significantly while it's in. However, for the right patient, it can be a very effective treatment for decreasing dry-eye symptoms for several months."

Making and Keeping Tears

For patients with evaporative dry eye, production of additional tears that remain on the ocular surface can help soothe symptoms. Tyrvaya activates the trigeminal parasympathetic pathway to stimulate basal tear production.

"I see many patients who'd rather not take drops or who have a hard time placing them," Dr. Starr says.

TABLE 2. SOME OPTIONS FOR TREATING INFLAMMATION, PROMOTING TEAR PRODUCTION AND/OR RESTORING THE OCULAR SURFACE

Product	Company	Notes
Tyrvaya	Oyster Point & Viatris	A prescription varenicline solution nasal spray that stimulates the trigeminal nerve to naturally increase tear production.
Vevye	Novaliq	A cyclosporine ophthalmic solution 0.1% indicated for the treatment of inflammation and other symptoms of dry-eye disease.
Restasis	Allergan	A prescription ophthalmic emulsion (cyclosporine 0.05%) that increases the eye's natural ability to produce tears and reduces inflammation.
Generic cyclosporine ophthalmic emulsion 0.05%	Mylan Pharmaceuticals	A Restasis generic (cyclosporine ophthalmic emulsion 0.05%), available in single-use vials.
Cequa	Sun Ophthalmics	A cyclosporine ophthalmic solution 0.09%; this prescription drop increases tear production using nanomicellar technology.
Xiidra	Novartis	A prescription drop (lifitegrast ophthalmic solution 5%) that targets the source of dry-eye inflammation.
Lotemax	Bausch + Lomb	A loteprednol etabonate ophthalmic suspension 0.5% often used off-label for treating dry eye.
Inveltys	Kala Pharmaceuticals	A loteprednol etabonate ophthalmic suspension 1% with mucus-barrier penetration technology, often used off-label for treating dry eye.
Eysuvis	Kala Pharmaceuticals	A loteprednol etabonate ophthalmic suspension 0.25% with mucus-barrier penetration technology for dry eye.
Klarity-L Drops	ImprimixRx	A preservative-free loteprednol-chondroitin 0.5% ophthalmic suspension for controlling acute inflammation.
Klarity-C Drops	ImprimisRx	A preservative-free cyclosporine ophthalmic emulsion 0.1%.
Oxervate	Dompé	A cenegermin-bkbj ophthalmic solution 0.02% (recombinant human nerve growth factor) for treating neurotrophic keratitis.
iTear100	Olympic Ophthalmics	A handheld, noninvasive neurostimulator that stimulates the trigeminal nerve to increase tear production.
Blink NutriTears	Baush + Lomb	A daily oral supplement of curcumin, lutein, zeaxanthin and vitamin D to promote tear production.
Verkazia	Harrow	A cyclosporine 0.1% emulsion approved for treating vernal keratoconjunctivitis in adults and children.

TABLE 3. A SAMPLE OF TREATMENTS FOR BLEPHARITIS & MEIBOMIAN GLAND DYSFUNCTION

Product	Company	Notes
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.
NuLids	NuSight Medical	An at-home treatment for dry eye and lid hygiene. An oscillating tip stimulates the meibomian glands and cleans away debris.
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.
Avenova	NovaBay Pharmaceuticals	A hypochlorous acid wash 0.01% for long-term hygiene management of blepharitis. Kills a broad spectrum of bacteria.
Cliradex	BioTissue	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.
Xdemvy	Tarsus	A lotilaner ophthalmic solution 0.25% that targets and kills *Demodex* mites via GABA-Cl channels.
TheraPearl Eye Mask	Bausch + Lomb	A hot-and-cold therapy that helps to alleviate dry eye.
Biune Spray	Primera	Azithromycin 1% with Ocusoft Lid Scrub Plus lid cleanser.
For Meibomian Gland Dysfunction		
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.
Systane iLux2	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 the lid structure.
Miboflo	MiBo Medical Group	Treats dry eye by delivering consistent, emissive heat and ocular massage to the meibomian glands.
eyeXpress	Holbar Medical Products	An eye hydration system for in-office therapy. A goggle system delivers uniform, regulated heat to the lid structure.
OptiLight	Lumenis	An intense pulsed light system for MGD indicated for professional use in patients 22 or older with moderate to severe DED and with Fitzpatrick skin types I-IV.
OptiPLUS	Lumenis	A radio frequency treatment for MGD.
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.
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.
Thermal 1-Touch	Ocusoft	A localized heat therapy that applies heat and gentle pressure to the lids to release meibum.
Miebo	Bausch + Lomb; Novaliq	A perfluorohexyloctane ophthalmic solution that mimics key functions of natural meibum to inhibit tear evaporation and promote ocular surface healing.

"Tyrvaya nasal spray is a much easier and preferred route of administration for these patients. It not only increases aqueous volume but also stimulates meibum and mucin secretions, making it a great first-line treatment for dry-eye disease, especially in those with an aversion to eyedrops."

"I like using the nasal spray in a lot of different patient populations," says Dr. Meghpara. "It's great for patients who don't have the manual dexterity to put drops in or for contact lens users who may not be able to use certain medications while their contact lenses are in their eyes. Glaucoma patients also like Tyrvaya because it's not another drop."

Dr. Behshad says he doesn't use Tyrvaya often because it's difficult for patients to get coverage and is cost-prohibitive.

Punctal occlusion is a common approach to reducing tear outflow, often started after patients try artificial tears but need additional measures to combat dry eye. In addition to punctal plugs, clinicians can now use a cross-linked hyaluronic acid derivative canalicular gel called Lacrifill. Lacri-

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fill molds to the patient's canalicular system to create punctal occlusion and reduce tear outflow. Experts say it doesn't seem to elicit as much of an inflammatory response as silicone plugs since nothing rubs on the conjunctiva or can get stuck in the ducts.

"I haven't tried [Lacrifill] yet, but I think it could be an exciting alternative to plugs," Dr. Lin says. "Lacrifill may be more cost-effective if used in all four puncta, because once you open it you can't reuse it again. So, it may be best for patients who need all four puncta occluded."

Scleral lenses are another option that can help soothe the ocular surface. "Scleral lenses can be very effective for symptoms because they are a fluid-filled reservoir that bathes the cornea constantly while the contact lens is in," Dr. Lin says.

Might vs. Mite

Blepharitis is an umbrella term encompassing anterior and posterior subtypes and their respective signs and symptoms. For anterior blepharitis, warm compresses, daily lid scrubs and topical antibiotics can help relieve symptoms, expert say.

"Much of the time, when patients come in with a prior diagnosis of 'blepharitis' but are still suffering despite lid hygiene and warm compresses, *Demodex* blepharitis is the undiagnosed and untreated culprit," Dr. Starr says. "The best way to identify that is to have the patient look down at the slit lamp and look for collarettes, cylindrical buildup of material at the base of the lashes, which is pathognomonic for *Demodex* blepharitis. Xdemvy, which is administered twice a day for six weeks, is a highly effective FDA-approved antiparasitic treatment for *Demodex*.

"Unlike some ocular surface treatments we start, such as artificial tears and immunomodulators, there's a finite endpoint with Xdemvy for *Demodex* blepharitis," he continues. "That's new. When we put patients on cyclosporine or other immunomodulators, there's no predefined endpoint—they'll often need to use the medication indefinitely—but with Xdemvy, we are able to stop it at six weeks."

Along with Xdemvy, adjunctive use of microblepharoexfoliation with the BlephEx device to mechanically remove collarettes and biofilms at the lid margin is complementary and helps resolve the signs and symptoms of *Demodex* blepharitis faster, Dr. Starr says. "Many patients with *Demodex folliculorum* will also have *Demodex brevis* in the meibomian glands and significant MGD. Anything we can do to treat those simultaneously is an advantage. Thermal pulsation procedures like LipiFlow and light-based procedures like intense pulsed light therapy can also be effective and adjunctive to Xdemvy when *Demodex* is present. We know that a lot of *Demodex* comes from the cheeks and facial skin of patients with rosacea, and IPL can help to reduce the mite load on the skin."

Dr. Mukhtar approaches *Demodex* in two ways, with a supportive approach and with Xdemvy. "The supportive way includes tea tree oil lid wipes, which are important because they sterilize the mites," she explains. "I then ask patients to use a thick lubricating ointment such as Refresh nighttime ointment or Systane nighttime ointment on the base of their eyelashes. This suffocates the mites. They like to come out overnight. In the morning, I have patients use the lid wipes. The ointment application has two purposes: one is to suffocate the mites and the other is to ensure the patient uses the wipes in the morning, because now they have the ointment all over their eyes."

Dr. Mukhtar points out to patients

TABLE 4. SOME PUNCTAL OCCLUSION & SCLERAL LENS OPTIONS

Product	Company	Notes
Punctal Plugs for Aqueous Deficiency		
Lacrifill	Nordic Pharma	A canalicular gel made of a crosslinked hyaluronic acid derivative that temporarily blocks tear drainage.
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 for Severe Dry Eye		
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, the company says, increases surface water retention and lubricity and minimizes deposits on the lens.

that the more conservative therapy is lifelong. "As soon as they stop, the mites will come back," she says. "But with lotilaner, it's basically one drop twice a day for six weeks, and studies show that the mite load is significantly decreased in all populations no matter the pre-treatment mite load. And if the mites come back, they come back at a lesser load than before treatment. Unfortunately, as a newly approved drug, cost is a huge issue for many of our patients. Secondly, we don't yet know what the long-term side effects are."

"Xdemvy is something that I go to as a first-line treatment for *Demodex*," Dr. Meghpara says. "I don't do blepharoexfoliation treatments like BlephEx in the office, but others do. Xdemvy by itself has shown impressive results in terms of collarette reduction. In the office, we're seeing similar results. Patients respond really well."

"This has been a game changer for patients with *Demodex* blepharitis," says Dr. Behshad. "Prior to this we really didn't have a great treatment option. The majority of my patients have their *Demodex* cleared by six weeks. I also notice improved MGD as patients continue to use this medication, which may be due to Xdemvy's lipophilic component."

Meibomian Gland Dysfunction

Common treatments for MGD include warm compresses, thermal pulsation treatments, mechanical expression of the glands, IPL therapy and anti-inflammatory medications. "If a patient has co-existing severe meibomian gland dysfunction, I might turn to oral doxycycline or a hypochlorous acid spray twice a day to control that," says Dr. Lin.

Miebo (perfluorohexyloctane) was recently approved for meibomian gland disease. Dr. Starr says Miebo is used four times a day and each drop can last for several hours. "When the meibomian glands are obliterated, it's hard to revive them, so you have to replenish the missing lipid layer," he says. "I've found that Miebo is a good way of doing that and is a compelling first-line treatment in these patients."

"Miebo coats and lubricates the ocular surface to try to restore what a normal, healthy tear film would be like," Dr. Meghapra says, adding that this medication doesn't really have a category yet since it's the first of its kind. "I use Miebo for evaporative dry-eye patients who've failed the more common treatments such as warm compresses, or they're on anti-inflammatory medication already and supplementing with regular artificial tears and they're still symptomatic. That's when I reach for Miebo."

Dr. Behshad says that Miebo has been a great first-line agent for his evaporative dry-eye patients and those with screen time-related dry eye. "Patients note the decreased symptoms and often describe how these drops last longer than previous lubricating drops they've tried," he says. "There's a steep learning curve for patients with the bottle and proper use, however. Many comment that they feel they waste a lot and finish their supply before they're able to get a refill."

"I tell my patients that [Miebo] isn't really treating any underlying cause; it's more supportive," Dr. Mukhtar says. "Most of my patients still really love it and continue to use it, especially those who have meibomian gland atrophy. It's a great option."

When to Use Serum Tears

When traditional treatments aren't enough to relieve the signs of dry eye and patients' persistent symptoms, autologous serum tears may hold the answers. "I've tried them in patients with severe symptoms without many signs of dry eye, and I've had variable success," Dr. Lin says. "For severe dry eye, autologous tears are very helpful."

"Patients go to a lab and get their blood drawn," Dr. Meghpara says. "The red blood cells are removed and what you're left with is serum, a straw-colored liquid that has many different components including anti-inflammatory factors, nerve growth factor and epithelial growth factor. The serum is diluted to a certain concentration of these components that mimics the normal composition of a healthy tear film. It's a very effective treatment. The downside is the inconvenience of it, the need for a special compounding pharmacy and the fact that the cost isn't covered by insurance."

Dry eye caused by Sjögren's disease is tricky to address. "Not only are patients not making enough tears, but the tears they are making are very inflammatory," Dr. Mukhtar says. "Even though there are treatments that stimulate tear production, such as varenicline, the tears aren't good-quality tears. Patients end up having to be on a very extensive regimen, and it's challenging to optimize their tear film and ocular surface.

"I love serum tears for these patients," she continues. "In the Cornea Society, opinions on serum tears for Sjögren's are split. Some feel that if a patient has a systemic inflammatory syndrome, you shouldn't be using serum tears. Others feel that if it's Sjögren's type 1, it should be fine, but if it's Sjögren's type 2, you shouldn't use them. My thought process is that we can try it, and if it works, great. I give patients a lot of anticipatory guidance to help them manage expectations."

"The most difficult types of dry eye to treat are usually dry eye secondary to something else," Dr. Meghpara says. "Graft versus host disease is one of the worst. It can lead to rapidly progressive dry eye. We had a patient who came in with a flare of graft versus host disease and they went through a number of treatment options, starting with steroid eye drops to control their inflammation, amniotic membrane placement to help heal the cornea and then an immunomodulator for long-term control. Despite all that, the patient still had a lot of dryness and staining on the cornea. They ended up needing to go on autologous serum tears and have now been stable for years." ◀

ADVANCED RETINAL IMAGING BECOMES PART OF ROUTINE CARE

One retinal practice is using the iCare EIDON Ultra-Widefield Module for every patient workup

By Sharam Danesh, MD

As a specialist in a multi-office retina practice located in the greater Phoenix area, I know that time is an invaluable asset when it comes to providing the highest level of care for our patients. We strive to make sure our patients are well-informed about their conditions, helping to increase the likelihood they will comply with our disease management plans.

Explaining everything thoroughly and answering all of the patients' questions so they leave with a greater understanding of their condition is important and not something that happens in an instant. Technology that gives us back time with our patients is extremely desirable. As it turns out, a family of iCare EIDON imaging systems we purchased two years ago to improve our diagnostic capabilities was so effective at helping us identify and monitor pathology, it ended up giving us more time to spend with our patients. The images we obtain from these imaging devices have become integral to our daily practice and we include them as part of routine patient workups.

INTRODUCING ULTRA-WIDEFIELD IMAGING

In August 2022, we made the decision to install the iCare EIDON Ultra-Widefield (UWF) Module. The technology provided us a much wider field of view of the retina than our previous imaging device and now offers up to 200° of superior image quality. We immediately noticed a difference in our ability to view the periphery of the retina on the crystal clear, high-resolution images delivered by the iCare EIDON UWF's TrueColor Confocal Technology. Two years later, my EIDON devices still yield the best image quality that I have found.

Our offices see a large volume of cases involving macular degeneration and diabetic retinopathy, along with other conditions such as epiretinal membranes, macular holes, and retinal detachments. Without question, the iCare EIDON UWF has made a monumental difference in following these kinds of pathologies involving the peripheral retina. For example, in diabetic retinopathy, we can clearly view pathology in the peripheral retina. We can better detect retinal tears. And we can see changes occurring in the periphery of the retina, even in macular degeneration. This aids in our ability to identify and treat progressive diseases earlier and acute manifestations more expediently.

TECHNOLOGY OFFERS A CLINICAL LEAP FORWARD

I believe the TrueColor Confocal Technology built into iCare EIDON devices provides even better diagnostic capability than a clinical exam. For example, very subtle findings, such as microaneurysms or tiny drusen that are difficult to detect on other images and which could go missed on clinical exams, can be seen with sharp clarity. We are able to document those findings and more optimally monitor patients.

The "flicker" feature, which enables image comparison over time, has helped us analyze especially challenging cases. It's critical to be able to see subtle progression of disease, particularly in geographic atrophy cases, or increasing microaneurysm presentations in diabetic retinopathy. Relying on clinical exams alone or less advanced imaging is not good enough. Using the flicker function to compare high-resolution images can show us the slightest progression of disease.

ADDITIONAL ICARE EIDON SYSTEMS

Another modality we have incorporated and routinely use in prac-

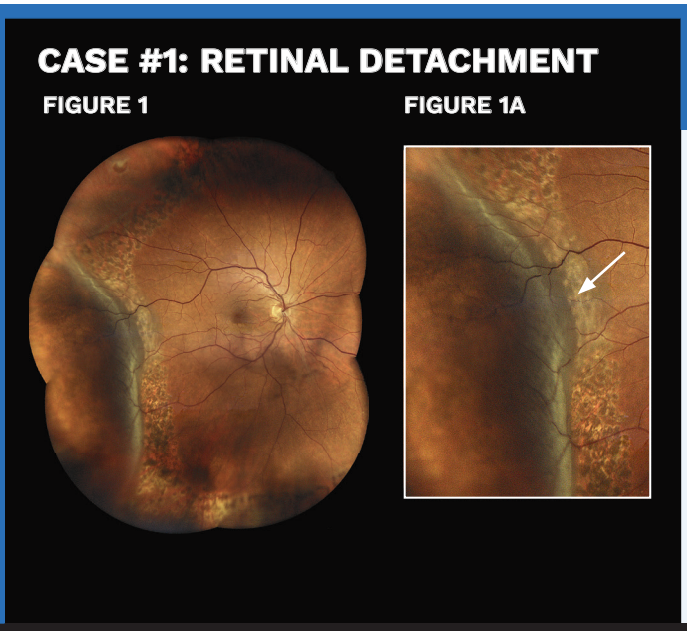


Figure 1. iCare EIDON Ultra-Widefield Module revealed the retinal detachment temporally OD. **Figure 1A.** Shows area where fluid has crossed the laser barrier.

A 54-year-old female patient came to me for a second opinion for a retinal detachment. She had been diagnosed with a peripheral retinal detachment and treated with laser demarcation.

The iCare EIDON UWF Module revealed the retinal detachment along with evidence of the laser procedure. The image further showed that fluid was crossing the laser barrier temporally, indicating the laser was failing and the patient needed surgery.

The patient subsequently underwent a vitrectomy and recovered very well. Imaging using the iCare EIDON UWF Module enabled us to promptly detect the failure of the laser demarcation performed by another physician so we could quickly intervene.

tice is the iCare EIDON FA confocal fundus imaging system. The system provides a dynamic widefield view of retinal vasculature and circulation mechanisms, with video acquisition functionality capable of capturing a clear detailed video to the periphery for an active view of pathology.

In addition, our iCare EIDON AF offers exceptional images in pupils as small as 2.5 mm. Its automation makes it easy for all of my staff to run tests. We use the AF modality to follow geographic atrophy now that some treatments are available to reduce the disease's progression rate.

TECHNOLOGY WITH A POSITIVE ROI

Unquestionably, our iCare EIDON systems have been a worthwhile investment. The images they produce have such high resolution and help us in detecting the smallest pathology that we spend less time on examination and more time speaking to patients. In turn, we have happier patients and can see a larger volume of patients. The wait times have also decreased due to the automated image acquisition and the fact that we can rapidly take images with ease.

Our iCare EIDON imaging system is so fundamental to our daily practice that every patient who comes in for an exam also gets an iCare EIDON UWF photo to help us diagnose and treat patients faster. This has streamlined our workflow and allowed us to see more patients and spend more time with them so we can deliver better patient care. Gaining additional time with our patients is an investment that is hard to quantify but which continues to pay us back daily in our practice.

CASE #2: DIABETIC RETINOPATHY

FIGURE 1

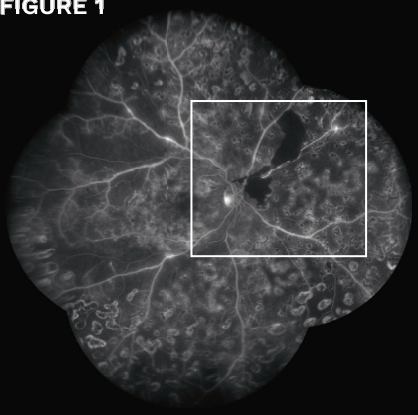


FIGURE 1A

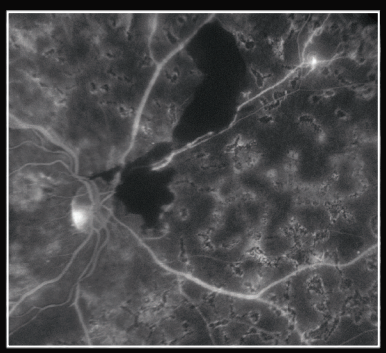


FIGURE 1B

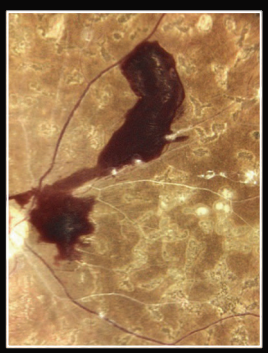


FIGURE 2

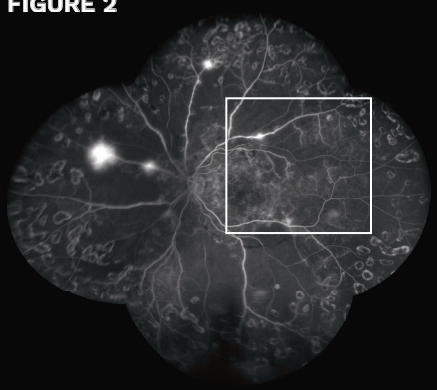


FIGURE 2A

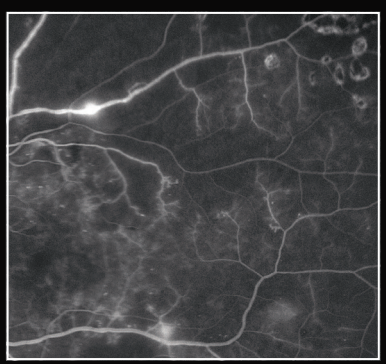


Figure 1. iCare EIDON FA - OD revealed extensive ischemia, evidenced by capillary dropout. **Figure 1A.** iCare EIDON FA shows the same area. **Figure 1B.** iCare EIDON color revealed recurrent pre-retinal hemorrhage nasal. **Figure 2.** iCare EIDON FA - OS revealed extensive ischemia, evidenced by capillary dropout. **Figure 2A**. Enlarged to show extent of ischemia.

This case involved a 31-year-old type 1 diabetic patient with a long history of diabetic retinopathy, who had been treated extensively with PRP laser.

With iCare EIDON confocal color imaging, we could see a recurrent pre-retinal hemorrhage nasal OD extending into the superior and inferior arcades. This suggested recurrent disease activity, increased risk, and the patient may need to be treated.

Findings using iCare EIDON FA uncovered in both eyes extensive ischemia, evidenced by capillary dropout, and areas of neovascularization leaking along major vessels.

It was clear this patient needed treatment so they were treated with injections of Avastin.

MORE THAN MEETS THE DRY EYE

Experts share their examination methods and tools when diagnosing patients with dry-eye disease.

ANDREW BEERS
ASSOCIATE EDITOR

Dry-eye disease is used as an umbrella term to capture the various signs and symptoms of ocular surface disruptions in patients. Not all patients experience the same issues. If there was an examination technique that perfected the diagnosis of all dry-eye patients, then all ophthalmologists would use it. Unfortunately, such a device doesn't exist, and there are many questionnaires, dry-eye tests and tools that are instead employed on a case-by-case basis.

Here, physicians provide the methods they use before deciding how to treat various forms of dry eye.

Diagnostic Methods

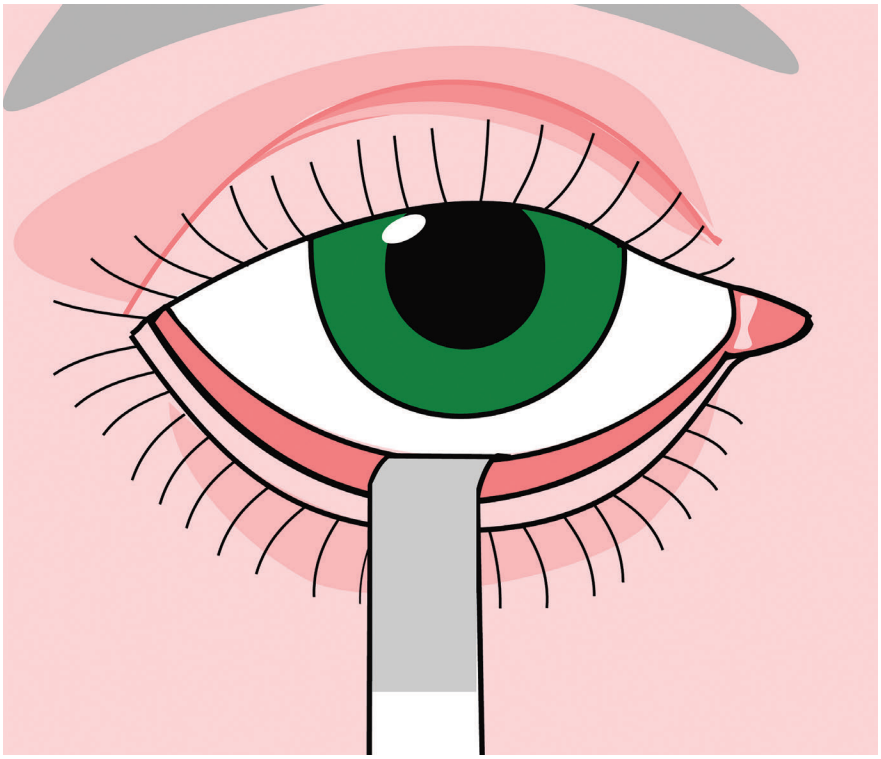
Diagnosing dry eye can be as simple as observing the ocular surface and eyelids under a slit lamp for signs and symptoms. Sometimes, in more severe cases, ophthalmologists turn to other tests to better understand the underlying pathology. In most cases, physicians provide a routine exam for their patients before moving forward with further testing.

"We actually do a quick, but comprehensive exam to try to look at contributors of patient symptoms that fall under the umbrella of dry eye," says Anat Galor, MD, an ophthalmologist from the University of Miami Health System in Florida. "We start with an external exam because conditions of the periocular skin can contribute to dry-eye symptoms, such as rosacea and other types of dermatitis. Then, we look at the eyelids and eyelashes because things like anterior and posterior blepharitis can impact symptoms. Then, we look at tear stability, tear production and epithelial disruption. And at the same time, we're looking for any lumps or bumps, whether it's on the conjunctiva, such as a pinguecula or pterygium on the cornea, like Salzmann's nodular degeneration, because any anatomical issue can lead to symptoms of dryness.

"Overall, we call the contributors above nociceptive contributors," Dr. Galor continues. "What that means is they can trigger corneal (and conjunctival) nerves to fire, and those nerves transmit signals to the brain that lead to a patient feeling dryness, or other unpleasant sensations, in their eyes. But the other situation is that sometimes the nerves themselves become abnormal and contribute to symptoms. And nerve dysfunction can occur in both peripheral and central nerves. If the nerve abnormality is due to a lesion or disease, we call that neuropathic and if we can't identify a definite lesion or disease, we call it nociplastic. But it really comes down to the nerves being too sensitive. There's a flip side though, and sometimes the nerves aren't sensitive enough and don't respond appropriately to signals on the ocular surface. And these patients can end up with low tear production and corneal staining, and look similar to dry eye from other causes but, in this case, the problem is in the nerves, and we call the condition neurotrophic keratitis. And if that's not complicated enough, individuals can have a combination of nociceptive, neurotrophic and neuropathic

This article has no commercial sponsorship.

Dr. Karakus is a consultant for Dompé US. **Dr. Galor** is a consultant for AbbVie, Alcon Vision, Dompé US, and Oyster Point Pharmaceuticals.



Wiki User: Jmarchn

Though not everyone uses Schirmer's testing for ocular surface disease patients, some physicians appreciate its ability to help hone the diagosis. *Creative Commons License: https://creativecommons.org/licenses/by-sa/3.0/deed.en.*

abnormalities happening at the same time. Let's face it, humans are really complex."

Yes, humans are complex and that's a challenge physicians need to face when diagnosing dry-eye cases. So, in order to keep up with the complexity of human biology, it's best to keep an armamentarium of tests and tools for dry-eye diagnosis and staging. In addition to the slit lamp exam, some physicians also still use Schirmer's.

"During my initial exam, I like to do a Schirmer's test," says Sezen Karakus, MD, an assistant professor of ophthalmology at Johns Hopkins School of Medicine in Baltimore. "I know it's traditional and not everyone really thinks that it's necessary, but I still believe that that piece of information is helpful for different reasons. I think it's important to know if there's a really low Schirmer's level and to monitor where we start from and where we move forward. My technician does the Schirmer's testing, and it might not always be perfectly reliable if it isn't done properly and if it shows excessive tearing from reflex tearing, or if it touched the cornea."

In some cases, anesthetic drops are used to help perform the examination. Dr. Karakus finds this useful when conducting a Schirmer's test as it helps her better determine if Sjögren's disease is present. "With an anesthetic eye drop, it's important how you perform the test," she says. "My technicians know that it has to be placed away from the cornea with closed eyes for five minutes. I believe that piece of information is important. It's not like I do it every single time that they come back for follow-ups. But at the initial visit, and maybe once a year or if we have further considerations or further suspicions for Sjögren's or an autoimmune disease, then I'd like to see if it's changing. And it might be affected by other things too."

Dr. Galor also uses anesthetic drops in her armamentarium but checks in on her patients following the examination since pain could persist after eye-drop instillation. This assessment is a part of a nerve function test she conducts. "We check corneal sensitivity to look for increased or decreased sensitivity, we assess for persistent pain after anesthesia, which can indicate a central nerve abnormality, and we overall assess whether symptoms and signs align, whether symptoms are out of proportion to signs or whether signs are out of proportion to symptoms," she says. "And then based on that quick, but comprehensive exam, we tell patients what we think is causing their symptoms and how to best treat it. While all these contributors can fall under the umbrella of dry eye, treatments are different for different contributors."

Tear osmolarity and MMP-9 testing could be used to help make decisions on what treatment options to employ. Dr. Karakus doesn't attempt to take an osmolarity measurement during every patient visit, but she finds the information quite useful in some cases. "Tear osmolarity is something I test sometimes," she says. "Also, though I don't believe that an MMP-9 test has to be part of a dry-eye exam 100 percent of the time, I occasionally like to use it, too. I don't do it routinely at the initial visit. I like to have information about whether or not the MMP-9 was positive. So sometimes that helps me make certain decisions with the treatments available. And I might not do it at the initial visit, but at some point, your decision becomes based on what you see, and your experience leads you towards a certain direction in terms of what might be going on."

Fluorescein and Lissamine

Drs. Galor and Karakus also discussed the staining methods they use and why they use them. Although rose bengal staining is an

option, neither of the physicians use this routinely for dry-eye diagnosis.

"Staining is definitely used every single time," says Dr. Karakus. "So, the slit lamp exam, fluorescein and lissamine green staining are indispensable parts of my exam. Every single patient visit I have to do a full slit lamp exam and full vital dye staining."

"On my first evaluation, I use fluorescein and lissamine in 100 percent of my patients," shares Dr. Galor. "Both right at the same time. Fluorescein helps me see the location and characteristics of corneal epithelial staining, highlights tear stability or instability, allows me to assess for anatomic abnormalities like conjunctivochalasis, and highlights the tear lake. Lissamine green helps me look for conjunctival epithelial abnormalities and highlights lid-margin keratopathy."

Dr. Karakus finds that staining is beneficial for detecting the level of dry-eye severity in patients. Using the SICCA grading scale, she can observe the surface staining to better understand her patient's condition. "There are different staining grading systems you can easily adapt in the clinic," she continues, "Oxford and NEI might be a little complicated for day-to-day clinical exams. In clinical studies we use it. But I like to use SICCA because it's simple, and it gives me enough information when assessing both corneal and conjunctival staining.

"There are different ways to grade using these dyes," continues Dr. Karakus. "With them, we look for punctate epithelial erosion, which you can see with both dyes. I like to use fluorescein to observe the cornea primarily, but lissamine green gives us more than surface staining. That's why it's indispensable for me. So, I use the SICCA grading system to grade the surface staining, which requires both of them, and that's one of the reasons I use both."

Dr. Karakus expands on why she finds lissamine green staining important and finds it to be more useful than fluorescein staining: "With my lissamine green, I go ahead and check how the lid margins are stained by the lissamine green," she explains. "First, that helps me to see Marx's line. I like to see if we have a regular thin staining with lissamine green. You don't see it with fluorescein, but you see it with lissamine green. So, if Marx's line appears regular, large, thickened, and it's dislocated behind the meibomian gland orifices, or in the opposite way, then those are important signs for us to know whether there's cicatrizing scarring, conjunctival diseases, if an inflammatory disease might be developing, or if meibomian gland dysfunction is significantly affected.

> **It's important to focus on the patient as a whole, and how symptoms and signs correlate is an extra piece of information that's very important. It's important to look for the overlapping disease and it's important to align the patient's expectations with yours when you talk to them.**
>
> ***- Sezen Karakus, MD***

"In addition, I like to observe the lid wiper area," Dr. Karakus continues. "I believe sometimes without having significant ocular surface staining, meaning corneal or bulbar conjunctival staining, patients might be very, very symptomatic. And if you didn't use lissamine green, you would miss the lid wiper epitheliopathy, which is very painful, very uncomfortable, and leads to a burning sensation. The other important thing you would miss if you didn't do lissamine green is superior limbic keratoconjunctivitis. You have to ask patients to look down and observe the superior bulbar conjunctival area, which isn't uncommon that you'd see this with lid wiper epitheliopathy in the upper lid, because that's from friction. The upper lid wiper area is touching for different reasons, but in SLK, we see that the superior bulbar conjunctival area is very loose and staining with the lissamine green shows that every time they blink, they feel that pain."

Fluorescein staining can be useful, as well. "I think [lissamine green and fluorescein] are both useful and placing them in the eye at the same time is quick and informative," comments Dr. Galor. "For me, it's a Venn diagram where there is some overlap in the information you get from the tests, but each gives unique information, so I prefer to do both."

Severity of Dry Eye

Trying to understand the severity of a patient's dry eye is difficult, since there are many interpretations on what defines a dry-eye case as mild, moderate or severe. It's important to figure out a patient's disease severity in order to make better judgments when choosing treatment options.

Different organizations have attempted to categorize dry eye. For instance, the TFOS DEWS II report, a comprehensive report on defining and diagnosing dry-eye disease, focused on the underlying pathogenesis of dry eye, while other reports, such as the ADES/JDES, emphasized the importance of physicians' observations when speaking with and assessing their patients.[1]

"I think it's definitely a challenge, first of all," comments Dr. Karakus. "How to categorize dry eye using one single method has been our dream, but it's never come true. For research studies, you have to define it very well, and you have to use certain parameters, but in my clinical practice, judgments are based on

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how much signs and/or symptoms are affecting the patient."

Dr. Karakus shared broad examples of mild, moderate and severe cases of dry eye at her clinic. "If they're not complaining about dry eye, and they're okay with basic treatments like warm compresses and using artificial tears as needed, then that's mild dry eye in my clinic," she says. "If they're still complaining, we've tried different prescription treatments and we can't get anything under control, then they're still suffering, and I ask these questions: 'Do you think about your dry eye every day? Every day do you think that dry eye is interfering with your daily life?' If they answer yes, that's not mild dry eye. That has to be moderate in my case. It could be from the symptoms, it could be from the signs, but it's affecting this person every day. Severe to me means that the patient is miserable in terms of their symptoms, and/or corneal staining is severe, or maybe they're on the brink of developing an epithelial defect."

Dry-eye Comorbidities

Dry eye isn't always alone. There are several comorbidities that can mimic or lead to dry-eye disease. Sjögren's syndrome, for example, has been mentioned before in this article and Dr. Karakus explained how she uses a Schirmer's test to help her diagnose these cases. Dr. Galor takes it a step further and provides her patients with questionnaires.

"In patients with Sjögren's there are some additional questionnaires that we administer, the ESSDAI and ESSPRI, which highlight systemic involvement in Sjögren's," Dr. Galor states. "Not all individuals with Sjögren's look the same and we want to understand how the eye fits in with systemic disease. We work closely with the rheumatologist to deliver multi-specialty care, so understanding the eye/body connection is important."

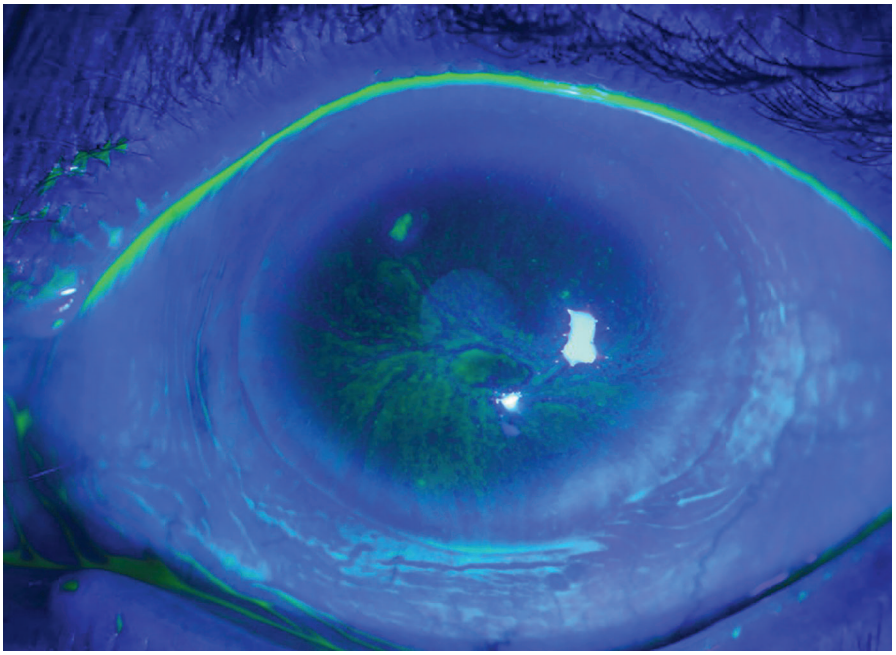
Another important comorbidity is conjunctivochalasis. Dr. Karakus uses her vital dyes to assist with the diagnosis of these cases. "Sometimes it's not easy to understand this condition without using the vital dyes and just looking at the slit lamp," she explains. "You might not notice the folds. Sometimes it's very obvious and you're seeing the folds piling up right in front of the cornea. Those are the easy ones. But with fluorescein or lissamine green, you could actually observe those folds piling up on the lid margin and you could make the connection whether it looks like they're causing some of the symptoms or problems."

Drs. Galor and Karakus shared what other comorbidities to look out for, which include inflammatory skin diseases such as psoriasis, eczema and rosacea. They noted that these diseases could set off a chain reaction that could lead to lid margin disease which would lead to meibomian gland dysfunction. It's best to assess for these skin conditions to avoid future complications with more severe comorbidities.

If a patient were to develop meibomian gland dysfunction, ophthalmologists can inspect this simply by using a slit lamp. But there are other methods that can be used to observe this underlying condition. "Within meibomian gland dysfunction, we have about 10 different metrics that we grade," says Dr. Galor. "We grade the amount of anterior blepharitis and where the blepharitis is located, it could be at the base of the lash suggesting *Demodex* as a culprit or mid-lash, suggesting a concomitant skin condition. We look for telangiectasia as a sign of ocular rosacea. We look for keratinization and plugging of the meibomian gland orifices. We squeeze the meibomian glands and look at the quality of the meibum. And then we try to evaluate gland anatomy.

"Sometimes it's hard to see the gland anatomy with retroillumination," Dr. Galor continues. "So, we have various devices that use infrared technology to image the meibomian gland. When we don't see the glands, we describe it as areas of dropout. But it

Community Eye Health



Cobalt blue light is emitted to excite the fluorescein in order to view dry eye signs and symptoms. Dr. Galor uses this form of staining to locate and characterize corneal epithelial staining, highlight tear stability, assess for anatomic abnormalities and highlight the tear lake. *Creative Commons License: https://creativecommons.org/licenses/by-nc/2.0/.*

doesn't necessarily mean the glands are gone. It could simply mean that they're atrophied, and that is why we don't see them. But certainly, it means the anatomy isn't 100 percent. So, this is where some of the advanced imaging technologies can help us. These devices, like the Keratograph, can also help highlight other aspect of tear help, measuring tear stability non-invasively. And that gives you suggestions of whether or not having normal meibomian glands is impacting ocular surface health as a secondary effect."

"I always pay extra attention to how the lids are closing, because [the action of] lagophthalmos not normally closing well is something you can easily observe without slit lamp examination," shares Dr. Karakus. "But if you pay close attention, sometimes you see there's a little bit of an opening and that's very obvious, so I do like to use fluorescein for that. Sometimes it's helpful to put the fluorescein in and then ask the patient to close their eyes. Then, using blue light, you could see the staining, so that might give me an idea.

"And then we see floppy eyelids," continues Dr. Karakus. "We always ask about obstructive sleep apnea and CPAP mask use. I discuss what type of mask they use because some of them might be blowing air into their eyes. If the eyelids aren't sealing well overnight, then the CPAP exposure is more prominently causing dry-eye symptoms in the morning."

Patient Comfort is Key

"We're here for patients," states Dr. Galor. "So, if a patient tells me, 'Every time you put a Schirmer's strip in, I have pain for weeks.' Then, I just don't put the Schirmer's strip in. There's no reason to cause patients any more discomfort than we absolutely need to. None of these tests beyond the slit lamp are necessary, and we meet patients where they are."

Patient satisfaction tends to be at the forefront of every clinic, and sometimes the lead up to treatment can be as uncomfortable as the treatment itself. There are many examples for why a patient might be uncomfortable with a slit lamp exam, anesthesia eye drops as well as noninvasive imaging tests.

"Let's start with slit lamp exam," begins Dr. Karakus. "With the lights, patients are very light sensitive and it's really hard to avoid this. But with the compassion that you should have as a physician, I think encouraging them to have a complete exam might give them the answers they've been looking for. However, if it's difficult to withstand the light, of course, you can always adjust it. That's something you can do.

"Normally, we try to avoid numbing drops like proparacaine," Dr. Karakus continues. "We try to avoid them because they might make the surface worse, but if they're going to help with the exam, I might use them sometimes. For staining, patients might not really like it, but I explain it to them how important it is using these dyes to examine their ocular surface. I tell them that's how we're going to identify some other things that might have been overlooked.

"Tear osmolarity, for instance, I wouldn't consider it invasive, but again, with very low tear volume, it might not be easy to collect enough tears for that test to work," Dr. Karakus adds. "Patients may decline that and that's okay. Also, imaging tests I wouldn't consider invasive but, for instance, when examining inflammatory responses, you touch the palpebral conjunctiva on the side of the eyelids. Sometimes patients are very sensitive, and their nerves are probably feeling more than they're supposed to, and it might not be comfortable to image them. But again, encouraging them, telling them how beneficial this test might be, taking breaks and talking with compassion is always achievable."

Dry-eye disease is going to continue to affect millions, so the future is going to be focused on improving not only treatment options, but also the examination methods available. This'll be important to ensure that every patient's needs are met. "Everyone has to work together with the goal of delivering better care to patients," comments Dr. Galor. "Drug companies want to sell their product to everyone, of course, but they recognize that their product may not be appropriate for everyone. And it's in everyone's best interest to figure out which drug is best for which patient. This way, patients get the therapy or therapies they need with less chair time, less costs and less frustration. It's a win for everyone."

Physicians can do everything they can to connect with pharmaceutical companies to develop the next best dry-eye testing device or treatment, but success lies with the attention they give to their patients. "It's important to focus on the patient as a whole, and how the symptoms and signs correlate is an extra piece of information that's very important," mentions Dr. Karakus. "It's important to look for the overlapping diseases and it's important to align the patient's expectations with yours when you talk to them.

"Part of the success of treatment is from how we present the disease to our patients, and we shouldn't dismiss how the daily activities of patients are affected by this disease that brought them into our chair," Dr. Karakus continues. "That's very important, because sometimes we don't see many signs or symptoms of dry eye, but patients are miserable. We should keep looking before something more serious develops or presents."◀

1. Shimazaki J. Definition and diagnostic criteria of dry eye disease: Historical overview and future directions. Investigative Ophthalmology and Visual Science 2018;59:14:7-12.

EHR: IS IT TIME TO MAKE THE SWITCH?

Transitioning to a new EHR system can be a time-consuming and challenging process. Here, those with experience offer advice on how to make it go as smoothly as possible.

LIZ HUNTER
SENIOR EDITOR

When health-care practices that provide care under Medicare and Medicaid were first mandated to adopt electronic health records years ago, many would admit it was a headache going from paper to digital. Looking in the rearview mirror, they'd also tell you the experience was worth it for the efficiencies it created across all departments of a practice.

However, those initial efficiencies may be losing their luster after so many years, leading physicians to explore new platforms and features. Embarking on another transition can be a daunting task for practices, and it's not uncommon for them to push this off to avoid the inevitable monopolization of time and energy, not to mention cost. "Many practices choose to stick with their current systems because the process of switching can seem overwhelming and problematic," says Barbra Dey, OD, COE, the CEO of Seattle-based Dey Ophthalmic Consulting, and a member of the American Society of Ophthalmic Administrators' Mentorship Committee. "Effective switching requires meticulous organization and careful planning."

"I'd put us in that category," says Guido Piquet, MBA, COE, the COO at Mann Eye Institute in Houston. "We probably held on to our previous product longer than we should have for that very reason, knowing it was going to be a painful transition. However, we eventually reached a point where the pain of staying with the old system outweighed the pain of making the switch because we didn't feel like we were moving forward."

According to the doctors, practice administrators and consultants we spoke with, there are some unavoidable challenges in the process of switching EHR systems, but they pale in comparison to the long-term benefits. Read on to find out about their experiences, lessons learned and top pearls for making a successful transition.

Considerations for Switching

Whatever the cause, EHR migration can be a labor intensive commitment that's not undertaken lightly.

"There's usually significant factors that make a practice want to switch," says Julia Lee, JD, principal consultant for NorthStar Vision Partners, located in the Philadelphia region, and chair of the American Academy of Ophthalmic Executives. "Probably the most common is if their current platform is just not keeping up with new development, or isn't yet providing the support required, or even just sunsetting."

The ophthalmology specialty has seen considerable consolidation in the EHR market, according to Michael V. Boland, MD, PhD, assistant chief medical information officer at Mass Eye and Ear and associate professor at Harvard Medical School. "Despite this consolidation, many vendors remain, including smaller ones that may struggle to adapt to changes in regulations, clinical practices, and user preferences," he says. "It's understandable that some practices, initially incentivized to adopt EHRs in the mid-2010s, have since decided to transition away from those systems."

Another scenario is more along the lines of want vs. need, especially when it comes to integration.

"Most of the reasons for inefficien-

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Dr. Boland, Ms. Dey, Mr. Kushner, Ms. Lee and **Mr. Piquet** have no disclosures related to this topic.

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cies within the system stem from poor integration between different software systems," says Ms. Dey. "In ophthalmology, practices typically use a practice management system to handle billing, patient outreach, scheduling and other tasks. Additionally, they use an EHR system. If the practice has an optical component, there's yet another optical software system involved. Ideally, these systems should communicate with each other seamlessly, but in reality, they often don't. This is where the biggest frustrations come in."

Infrastructure is another consideration. Practices want to move from managing server-based solutions to cloud-based solutions. "I know a lot of practices that say, 'Wow, keeping up with all of these IT infrastructure requirements is becoming increasingly burdensome and costly. We'd like to go to some type of subscription model,'" says Ms. Lee.

This was a top priority for Tri-Century Eye Care in Southampton, Pennsylvania. The practice had recently merged, with each entity using different EHR and practice management systems. "Part of the reason for migrating to a new system was to unify the entire practice onto a single platform," says Zach Kushner, MBA, MSIT, COE, the CEO of Tri-Century. "We could've simply integrated half of the practice into the system used by the other half. However, each software had its own inherent challenges. For me, the main driver was transitioning to a cloud-based platform. I wanted to move away from the hardware cycle of replacing servers every three to five years. I wanted a system that our doctors could access from anywhere on the web without needing to VPN into our data center."

For Mann Eye Center, it was less about one specific feature and more about finding a vendor who could be viewed as a partner. "One of the biggest reasons we decided to switch to a new product was our need for a solution we could build upon for the next 10, 15, even 20 years," says Mr. Piquet. "We were looking for a company that was making sufficient investments in improving their product. We understood that no one product is perfect, but we wanted to partner with a vendor who was going to be here for the long run and continue to invest in their product and work with us as a partner. We didn't really have that type of relationship with our previous platform, which is why our strategy was more about long-term potential rather than finding an immediate perfect fit."

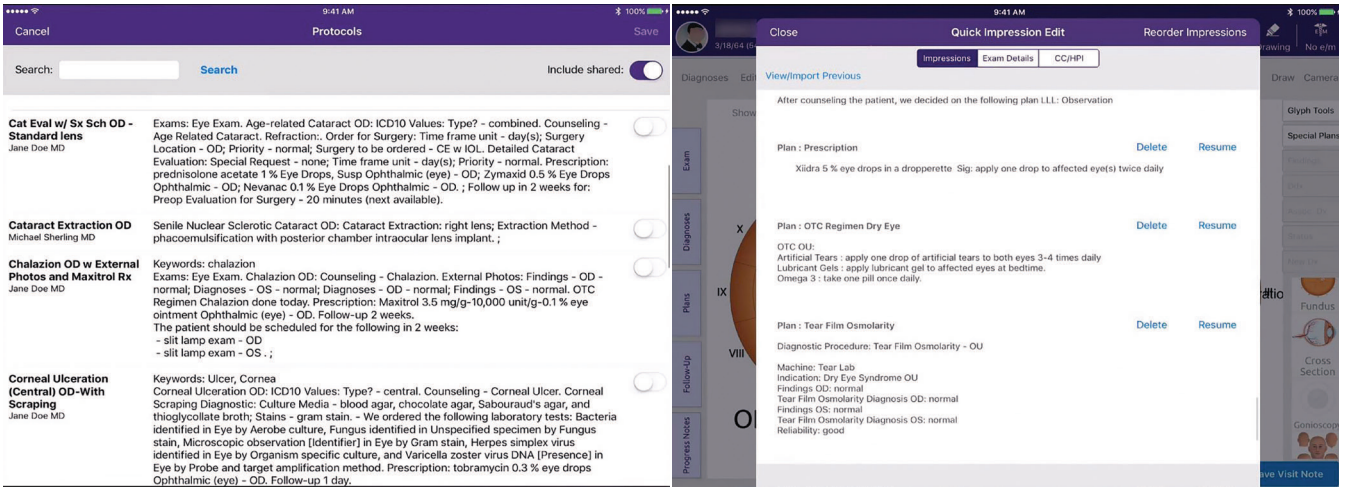
Despite having these concrete goals and wishes, it can take years for practices to commit to the project of switching.

"I think the biggest barriers to switching are probably time and resources, meaning the time and effort required to manage a successful transition, because no matter what resources the vendor will provide, there's always going to be a heavy lift required of the practice," says Ms. Lee. "You really need somebody very strong and on top of it internally who's going to coordinate and make sure that the implementation steps are happening successfully within the practice on the ground."

At Tri-Century, Mr. Kushner says the prospect of merging onto a single system was discussed, but not prioritized, between 2019 and 2020. "It wasn't until 2021 that we seriously considered it," he says. "After six months of due diligence on various platforms and facing staffing difficulties due to the pandemic, the project was put on pause. We revisited the discussion in late 2022 and early 2023. We eventually implemented the new system in August 2023. This lengthy process was due to misalignment among doctors and staffing challenges, leading to a protracted timeline."

Most-requested Features

As practices begin the investigation phase, one of the most important—and sometimes complicated—steps is to get all departments on the same page about their expectations.



In the EHR software system used by Mann Eye Institute there's a feature called "Protocols," which helps physicians create pre-built plans that allow them to chart an entire exam in seconds. Once these protocols are applied, the physician can then make the few changes that apply to that specific patient.

"To ensure a successful transition, a high-functioning team that includes representatives from all relevant departments should be assembled," Ms. Dey says. "This team should develop a comprehensive plan, including must-have and nice-to-have features for the new EHR system."

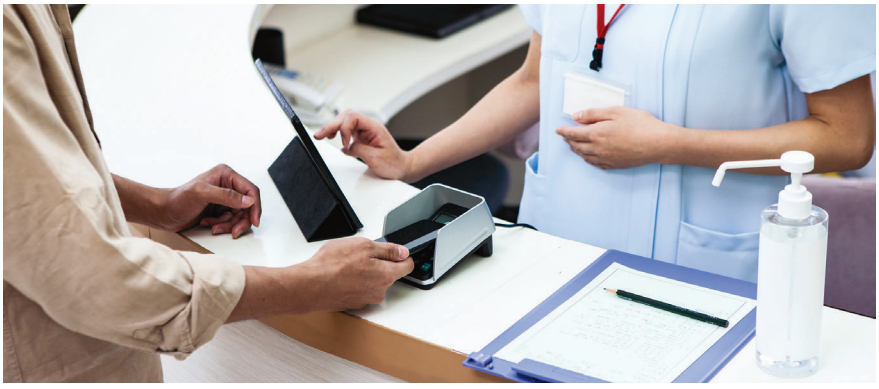
When evaluating EHR systems, practices commonly look for features that enhance efficiency and simplicity. "Questions often center on how well the system interfaces with diagnostic equipment, tracks patient time from check-in to check-out, and integrates with billing and point-of-sale systems," says Ms. Dey.

Some of the most commonly asked questions when researching systems are:

- Does it automatically send out registration paperwork?
- Does it send it by text?
- Do appointment reminders go out by text, robocall and/or email?
- How many minutes is the check-in process?
- Does the system track how many minutes each step in the process takes, total time?
- Does it interface with our other diagnostic equipment? Is that built in or is it an add on?
- How much clicking does the doctor need to do?
- Are diagnoses pre-loaded with coding suggestions?
- How do we submit claims?
- How does it integrate with my POS and is the charge reflected in my PM system? and
- Can patients e-sign to reduce paper?

Provide vendors with these requirements in advance to ensure they can meet them, advises Ms. Dey. "Organize a team call where you talk through each of them and ask the vendor to tell you how it will work in the new system," she suggests. "It's important to have a clear understanding of the vendor's capabilities and limitations to avoid disappointments later."

"In the research phase, I was the primary person responsible for evaluating different options and meeting with vendors," recalls Mr. Piquet. "I had some key criteria in mind for each vendor: efficiency; scalability; and future technological investments, including automation and artificial intelligence. It was important to see which vendors were ahead in these areas and had concrete plans for future advancements."



When upgrading to a new EHR system, hardware is another important component to consider. Pracitces should prepare to invest in technology such as tablets, new credit card machines and reliable internet connectivity.

In addition to wanting a cloud-based system, Mr. Kushner says they also wanted a little bit of simplicity. "It's a tough dynamic, simplicity vs. complexity," he says. "You want a system that's complex enough to handle your workflows and your documentation needs, at the same time you want it simple enough where the software is working for you and you're not working for the software."

One concept that rose to the top of their list was "point of thought" data points, explains Mr. Kushner. "Doctors need intuitive entry points for data as they proceed through their workflow," he says. "Our previous platform had different templates for each thing. Glaucoma had an independent template, retina had an independent template, contact lens had an independent template. If they're in the middle of a complete exam and also doing a contact lens check, doctors have to juggle a couple different templates to document all of the pieces of that exam. On our new system, everything is on a single-scroll page, so all they're doing is hitting their mouse wheel and moving up and down within that same page. It's almost like a long web page, and everything is visually right there."

Financial Considerations

System costs may not vary dramatically in the industry, but practices should be aware of how fees are structured by vendors and how the initial investment might compare to monthly fees and add-ons.

"Vendors should be clear about any future cost increases and the financial implications of system upgrades," says Ms. Dey. "Typically, all of this information is on the cloud now, and that requires a monthly subscription fee. Those fees can change over time. Have the conversation up front with your vendor about how long that monthly fee will last, and what percentage increase you should expect over time. Also, as their product gets upgrades, would those be considered add-ons for a separate fee? What if it's a feature you told them you wanted and they said it's in the works? Will you be charged?"

This was a consideration of Mr. Kushner's. "Older systems had significant upfront costs but lower ongoing maintenance costs, while newer systems operate on a subscription model with higher monthly costs but lower upfront investment," he says.

There was also the matter of hardware, which can't be overlooked even though systems are on the cloud. "Planning for hardware needs, includ-

ing computers and internet connectivity, was also essential," continues Mr. Kushner. "You need to evaluate and make sure that your hardware is up to snuff with the software that you're choosing. Do you have scanners? Do you have credit-card machines? Do you have the appropriate computers around your offices? Is your internet connection strong enough and reliable enough for a web-based platform? Previously, we had our servers in house. If our internet went down, we could still function. With a web-based platform, if our internet goes down, we're dead in the water. The resiliency of backup internet connectivity is important."

Migrating data from the old system to the new one can also be a significant cost, says Ms. Lee. "This is one of the biggest surprises for practices going from one EHR to another," she says. "There are varying philosophies, but typically, data migration is handled by a third-party company. This company should ideally have proficiency working with both systems, because they're going to have to extract from the one and map it over to the other. But that cost is a pretty significant variable, depending on what data you want to migrate over and how much of it."

The discrepancies between vendors adds to confusion. "Each EHR has its own method for storing data, and there's no standardized way to migrate all data seamlessly," says Dr. Boland. "When considering migrating to a new EHR system, it's crucial to ask the current vendor how to handle data extraction. This process will likely involve costs, either for the new vendor's services or for hiring external assistance."

In Mann Eye Center's case, Mr. Piquet says they incorrectly assumed they'd be able to keep their old system as a reference for about a year, once all patients had been seen on the new platform. "We were able to migrate all of the patient demographics and medical data in the form of a PDF chart note, but no discrete data," he says. "A couple of the big things that we weren't able to get were financial data and past appointments. However, we decided to prepare and implement an EHR archive solution, which now gives us the ability to retain all of that important financial information and past appointment data. In hindsight, I would have created a larger team to assist with the data migration component, which could have made each patient appointment a little more efficient."

Training and Going Live

Once practices have committed to the new EHR system, training is the next step and there's more than one way to go about it.

"Depending on the internal team's capabilities, the decision might be to either train a few key individuals who then train the rest of the staff or to bring in trainers from the vendor," says Ms. Dey. "If you choose to train the trainer, this person is now in charge of an EHR transition while also being responsible for their own daily job tasks. Can they give their full attention to this transition?"

There are pros and cons to both, says Mr. Kushner, and he's had experience with both. "For our previous EHR, we did the train the trainer model and we took small groups aside at various points during the day and we also had staff come after hours, so there was a time investment on our core team outside of normal operating hours, but it also gave us the flexibility to juggle things and not have to shut down patient schedules," he says.

For this latest EHR implementation, they chose to have the vendor train everyone. "We shut down the practice for two hours each morning over two weeks," says Mr. Kushner. "Every doctor and every staff member attended every session, whether it pertained to them or not. Doctors learned the PM side, call center and front desk staff learned the EHR—everybody saw the same thing. I wanted them to have that broad brushstroke picture of the way the systems interact. I wanted them to understand what their peers within the practice were dealing with, so that it's not an us vs. them type of mentality."

Training and implementation may take longer than expected, notes Mr. Piquet. "We initially went in with a goal of going live within six months, but it became clear that it was going to take longer than anticipated," he says. "Based on our experience, I now recommend adding three to six months to your initial estimate—this is dependent on the size and scope of an organization. As you start the investigation process, you're going to unearth problems you didn't know you had, and they have to be addressed. For us, the process ultimately took nine months."

Mr. Kushner says his practice had a six-month runway, which allowed them to manage training, go-live dates, and hardware delivery and installation without extreme time pressure. "This time flexibility was a significant advantage, helping us avoid the tight deadlines that vendors often impose," he says.

During the implementation, it's beneficial to have a beta-test environment where departments can test the system with test patients and identify potential issues before going live, says Ms. Dey. "This allows for adjustments and ensures the system is fully integrated and functional."

Mann Eye Center implemented a gradual ramp-up strategy for patient scheduling, according to Mr. Piquet. "We started with 50 percent of our usual patient load and increased to 75 percent over a few weeks, aiming to reach full capacity within three months," he says.

Experts recommend having vendors on site during the initial go-live phase to address immediate issues and support staff. "When the trainers initially told us how long they'd need to stay on site, I was skeptical," says Mr. Piquet. "But they told us to trust their recommendation, so we did. And they were right. Our users were quickly able to get up to speed. Especially when you have employees who all learn at different paces, we were able

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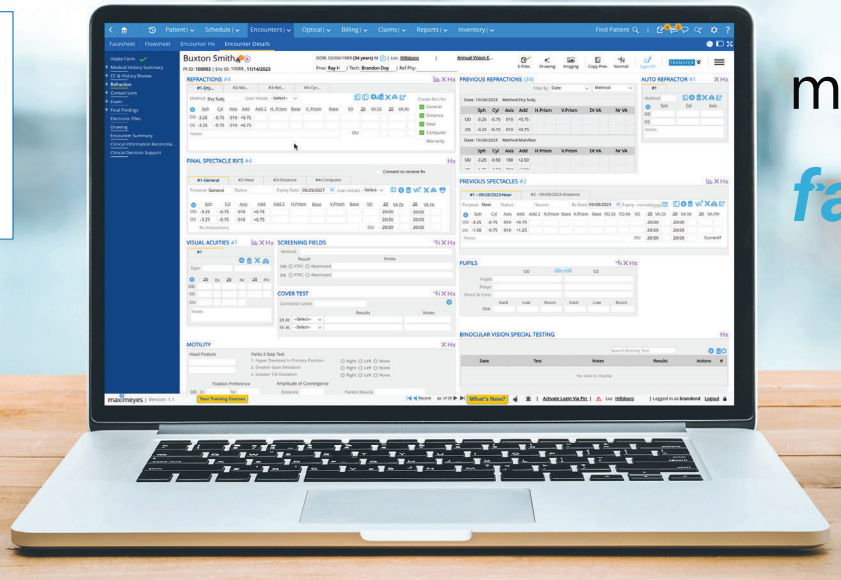

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to focus on those who were struggling and give them additional support."

Training doesn't stop after that initial week or month, continues Mr. Piquet. "We did additional training sessions, followed by an optimization visit at the one-year mark where we brought the trainers back in to retrain people and find even more efficiencies," he says. "At that point we started to get over the hump of the pain of the change and we started to see those efficiencies, with some providers seeing three to five additional patients a day. The staff are more efficient because of the new tools they have but it's an investment in time and patience, and it takes resolve. It's crucial to have people in leadership who are a voice of support and will help people see the end goal."

On the Other Side

From Mr. Piquet's perspective, he says it could take at least a year to realize the efficiencies that are better than what you had before. "Even with a great system, it just takes time for all of those components to flow through the practice from every level and for people to continue learning," he says. "We've been on the system for two years and we finally hit a stride."

No one goes through the process unscathed, says Ms. Lee. "I'd say the majority of practices are excited about the new functionalities they have access to on their latest and greatest system. If you've done your vetting and your selection process, if you've gone through that thoughtfully, then by the time implementation comes around, a lot of it is just frustration in terms of that last-mile differences between how your practice used to do something and what the new platform can accommodate."

"Every administrator wants the system to be perfect before you go live, and we tried, but it's never going to be perfect on day one," Mr. Piquet says. "Whenever I get referral calls from other people looking to make a switch, I tell them that switching to a new EHR is less about finding the perfect software and more about finding a product you can grow with."

Top Pearls for Success

We asked our sources to provide their most important pieces of advice for those who are considering a new EHR platform. Here's what they said:

• ***Lean on peers***. "My initial step was to reach out to industry contacts to gather opinions and then narrow down our choices to two main contenders," says Mr. Piquet. "Getting advice and hearing experiences from peers in the industry was huge in the beginning. Once I had that feedback it helped me go in a certain direction."

Shadowing another practice that uses the same system can be beneficial. "It's advisable to ask for references and visit those practices to get a better sense of the system's effectiveness," recommends Ms. Dey. "However, it's important to remember that each practice's environment is unique, and what works for one may not work for another. Many practices aren't fully satisfied with their EHR systems, and better planning and understanding of limitations can help manage expectations and reduce frustration."

• ***Invest in "super users."*** "One thing that we've implemented within the past six months is the creation of an internal group called 'super users,'" Mr. Piquet says. "This group consists of individuals who receive additional training and are considered the strongest users within our practice. A key strategy was to include physicians on the super-user team. When physicians provide efficiency tips to their peers, the advice is often received better than if it came from an administrator or trainer.

"This group also finds out what areas they'd like to see improved and what's working well," he continues. "This feedback helps us mold the system to better fit their workflows and provides tips for greater efficiency and accuracy to use the system as intended."

Change management happens from the top down, adds Ms. Lee. "You really need physician champions and key users from each group, from front desk to medical records to billing to technicians, and all the providers. Having your 'super users' in place and really using them as internal resources to help reduce staff anxiety and be the go-to folks on the ground during those first weeks and months when everyone's acclimating."

• ***Budget for a slowdown***. 'We started an escrow account early in the due diligence process to accumulate funds for the project," says Mr. Kushner. "This helped cover revenue losses during training and go-live periods. You're going to have a schedule reduction when you go live to allow staff enough bandwidth to get acclimated while they're dealing with live patients. This inevitably leads to a revenue downturn. You need cash on hand, and the longer lead time you give yourself for that buffer to build up, the better off you'll be."

• ***Look at the process holistically***. "We use the term 'EHR migration' almost like shorthand, but it's really more accurately 'system migration' because quite often EHR migration will involve practice management migration," says Ms. Lee. "Maybe there's new payment processing that comes along with it. There's certainly going to be new patient engagement tools that come along with it, and billing, and perhaps even a new clearing house for your claims. If it's the EHR that's driving the migration, obviously that should be front and center, but please don't forget all of these other very, very important practice functions that are going to be impacted."

• ***Don't ignore the human aspect***. "Change is difficult for everyone, and managing the human aspect of the transition is as important as the technical aspects," says Ms. Dey. "Employees go through various stages of adaptation, from denial to acceptance, and eventually excitement. Supporting them through this process and recognizing the different paces at which people adapt can help ensure a successful transition and maintain staff morale." ◀

NAVIGATING CHALLENGING CATARACT CASES

Surgeons reveal how they encountered unexpected difficulties—and overcame them.

SEAN MCKINNEY
CONTRIBUTING EDITOR

Below is a review of cataract surgery challenges that range from the immediately obvious to the seemingly imperceptible. From trauma-induced issues decades in the making to a failure to achieve what seemed like easily attainable postop goals. Plus, a capsule tear in a shallow anterior chamber at the worst possible time. All of these dilemmas were eventually resolved. Here's how.

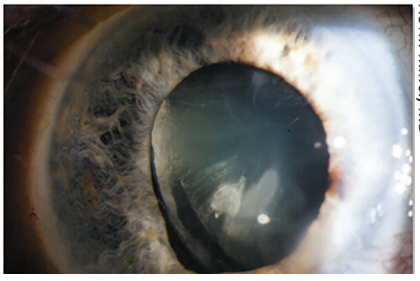
CASE #1:

Trauma-induced Cataract, 50 Years Later

The 69-year-old male suffered a battery explosion in his right eye in the 1970s, receiving only eye drops for treatment. The result: A pupil sphincter tear, zonular dialysis and, eventually, a traumatic cataract *(See Figure 1)*. The patient was counting fingers at three feet by the time he visited Kevin M. Miller, MD, of the Stein Eye Institute at the University of California Los Angeles.

"This case called for a manual approach," explains Dr. Miller. "I used phaco, instead of the femtosecond laser, my usual choice. But first I fashioned an inferotemporal Hoffman pocket where the zonules were missing so I could eventually suture a capsule tension segment to the sclera in the meridian with the greatest zonular loss."

Dr. Miller then performed vitrectomies in the posterior and anterior chambers, first turning to a pars plana approach with the use of a diamond knife to create a sclerotomy. Once he'd amputated the vitreous connection between the front and back of the eye, he removed the vitreous in the anterior chamber, being careful not to capture the iris with the vitrector.



Kevin Miller, MD

Figure 1. A slit lamp view of a patient's eye reveals a dense cataract, zonulopathy and a pupil sphincter tear.

Next, Dr. Miller inserted a capsule retractor in the area of the zonulopathy at 4 o'clock. "I know some surgeons might've inserted up to four capsule retractors and/or iris hooks in a case like this," says Dr. Miller. "But I was able to use a single capsule retractor, knowing that I could use more, if necessary."

Divide and Conquer?

Rather than employing a chop or standard divide-and-conquer approach, Dr. Miller opted for an *in-situ*, divide-and-conquer technique *(See Figure 2)*. "The nucleus wasn't rotating at all, and the capsular bag remained stable," he says. "I removed the nucleus and cortex without needing a capsule tension ring."

Dr. Miller then injected a capsular tension ring and removed the capsule retractor *(See Figure 3)*. "When injecting the ring, you need to make sure you fill the capsular bag with OVD, preferably a highly cohesive type," he notes. "If you're right-handed, you should inject as far to the right as possible, laying it out for 180 degrees and

This article has no commercial sponsorship.

Dr. Miller is a consultant for Alcon, BVI Medical, and Johnson & Johnson Vision. **Dr. Schoen** reports no relationships with ophthalmic companies. **Dr. Donaldson** has consulting relationships with Alcon, Johnson & Johnson Vision, Baush & Lomb, and Zeiss. **Dr. Chu** is an investigator for Zeiss, Bausch & Lomb, BVI Medical, Johnson & Johnson Vision, and Glaukos. He's also a consultant for Zeiss, Bausch & Lomb, and RxSight, a maker of the Light Adjustable Lens. **Dr. Heckman** is a consultant for RxSight.

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Data: *Animal Data*: Pregnant rats and rabbits received varenicline succinate during organogenesis at oral doses up to 15 and 30 mg/kg/day, respectively. While no fetal structural abnormalities occurred in either species, maternal toxicity, characterized by reduced body weight gain, and reduced fetal weights occurred in rabbits at the highest dose (4864 times the MRHD on a mg/m^2 basis).

In a pre- and postnatal development study, pregnant rats received up to 15 mg/kg/day of oral varenicline succinate from organogenesis through lactation. Maternal toxicity, characterized by a decrease in body weight gain, was observed at 15 mg/kg/day (1216 times the MRHD on a mg/m^2 basis). Decreased fertility and increased auditory startle response occurred in offspring at the highest maternal dose of 15 mg/kg/day.

Lactation: Risk summary: There are no data on the presence of varenicline in human milk, the effects on the breastfed infant, or the effects on milk production. In animal studies varenicline was present in milk of lactating rats. However, due to species-specific differences in lactation physiology, animal data may not reliably predict drug levels in human milk.

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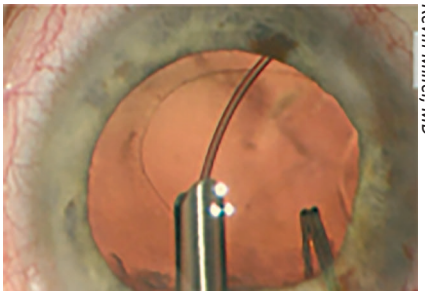
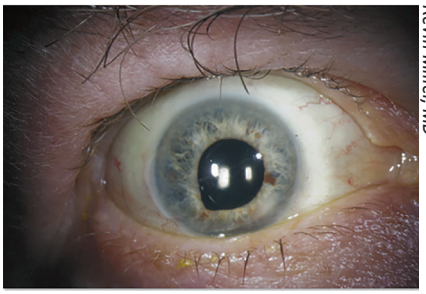


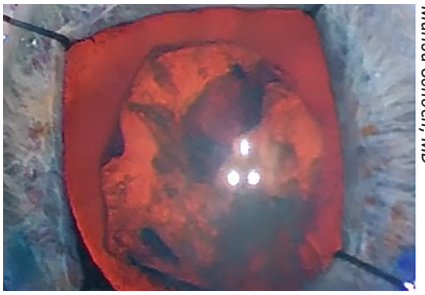
Kevin Miller, MD

Figure 2. In the eye from Fig. 1, with the capsule bag fully inflated by highly viscous OVD, a capsular tension ring is injected and a capsule retractor that's no longer needed is removed.



Kevin Miller, MD

Figure 3. The patient from Figs. 1 and 2's postop eye retains a dilated appearance from a 50-year-old pupil sphincter that wasn't repaired. He's thrilled nonetheless, having gone from counting figures at three feet to 20/20 uncorrected vision.



Marisa Schoen, MD

Figure 5. As soon as the anterior capsule was punctured in this case, the capsule split with a tear that extended out of view under the iris.

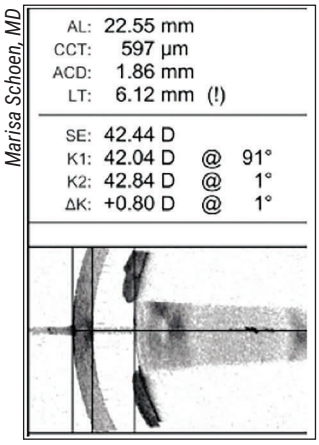
injecting toward the zonulopathy. After doing this, I had the support I needed. I removed the capsule retractor through the phaco incision." A small amount of sub-incisional cortex remained. Dr. Miller gently polished the capsule—arguably a bold move, considering its vulnerability. "I just couldn't help it," admits Dr. Miller. "I had to get that stuff out of there."

Which Type of IOL?

In such a challenging case, many surgeons might've reasonably placed a three-piece IOL in the sulcus, knowing that they wouldn't need to suture unless the lens decentered. "But I felt I could get away with a single-piece acrylic," Dr. Miller says. "Yes, the zonules were weak, but I had the necessary support. If everything started to go south, I could've used the capsule tension ring to stabilize the eye. So I put the optic-haptic junctions of a single-piece acrylic IOL at 3 and 9 o'clock to reduce the chances of negative dysphotopsia. I retrieved the prolene sutures through the Hoffman pocket and tied them together."

There was one last decision for him to make—to suture or not to suture the pupil sphincter where it had ruptured 50 years earlier. Dr. Miller decided to leave it alone. "I infused Miostat (carbachol 0.01% intraocular solution, Alcon) and let the pupil come back. I knew that, if necessary, once the capsule had fibrosed, I could go back later and suture the pupil sphincter."

But it wasn't necessary. "Cosmetically, the eye, with a dilated appearance, wasn't ideal," Dr. Miller admits *(See Figure 3)*. "But the patient was very happy, seeing 20/20 uncorrected."



Marisa Schoen, MD

Figure 4. Optical biometry reveals an anterior chamber depth of only 1.86 mm and a lens thickness of 6.12 mm.

CASE #2:

What Else Could Go Wrong?

The early-career surgeon had her hands full with this case. A 60-year-old male with a history of proliferative diabetic retinopathy and anatomically narrow angles was referred for cataract evaluation. The preop exam revealed a small pupil with 360-degree posterior synechiae and a dense cataract. Optical biometry revealed an anterior chamber depth of only 1.86 mm and a lens thickness of 6.12 mm *(See Figure 4)*.

"My biggest concern was the risk of an anterior capsule tear, given the big lens and shallow chamber," explains Marisa Schoen, MD, a cataract and cornea surgeon at Ophthalmic Partners in Bala Cynwyd, Pennsylvania.

Challenging Start

Before starting the case, she administered IV mannitol to dehydrate the vitreous. After releasing the posterior synechiae and placing iris hooks, she painted trypan onto the anterior capsule. She then filled the anterior chamber with Healon GV and initiated the capsulotomy with a cystotome. "As soon as I punctured the anterior capsule, it split with a tear that extended out of view under the iris *(See Figure 5)*. So I switched to a can-opener technique to complete the rhexis."

Before proceeding with phaco, Dr. Schoen avoided hydrodissection and lowered the bottle height to reduce pressure that could've worsened the tear. "Once an anterior capsule tear occurs, every effort must be made to reduce the risk of posterior extension," she says. "I knew that posterior extension could lead to a worst-case scenario, with the whole lens falling into the vitreous cavity, requiring a vitrectomy and lensectomy." After removing all of the nuclear fragments, she saw that, fortunately, the posterior capsule was intact and that the anterior capsular tear hadn't extended posteriorly.

The next step was cortical cleanup. "In the setting of a tear, it's important to pull cortical material toward—not away from—the tear to avoid stress that would cause the tear to extend, raising the possibility of vitreous prolapse," says Dr. Schoen. "I also made sure I removed cortical material closest to the tear last to further minimize stress on the tear."

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Dr. Schoen notes that the patient had a dense posterior subcapsular cataract, which often leaves behind fibrous material that can be polished intraoperatively with the I/A handpiece. "Because of his compromised anterior capsule, I wasn't as aggressive in cleaning the posterior capsule, recognizing that I could use a YAG laser to deal with it postop," she explains. Dr. Schoen next placed a three-piece IOL in the capsule bag. "When placing an IOL in the bag in these situations, the haptics should be oriented 90 degrees away from the anterior capsular tear," she notes.

Doing Very Well

Two months postop, Dr. Schoen performed a YAG capsulotomy. "The patient achieved an uncorrected distance vision of 20/50 that improved to 20/30 with a slightly myopic manifest refraction," explains Dr. Schoen. "It was a pretty good result, considering how challenging the case had been, plus his underlying diabetic retinopathy. These cases can pose a lot of consequential challenges and complications, but if you recognize the potential for this preop and prepare yourself accordingly, a patient can still do very well."

CASE #3:

Contact Lens Confusion

Kendall Donaldson, MD, MS, recalls the frustration and horror she felt when she draped the patient's left eye and placed the lid speculum, revealing a contact lens. The 60-year-old female patient, who'd undergone radial keratotomy 35 years earlier, had experienced a progressive decline in vision for two years. With severe irregular astigmatism (left eye worse than right), she'd worn both soft and scleral contact lenses. But she'd been instructed to discontinue all contact lens wear to prepare for surgery.

"When was your last contact lens wear?" asked Dr. Donaldson, medical director of Bascom Palmer Eye Institute in Plantation, Florida.

"Oh, I haven't worn lenses in at least two months," the patient replied, insisting, emphatically, that she wasn't wearing a lens during her preop measurements three weeks earlier.

Keratometry over Time

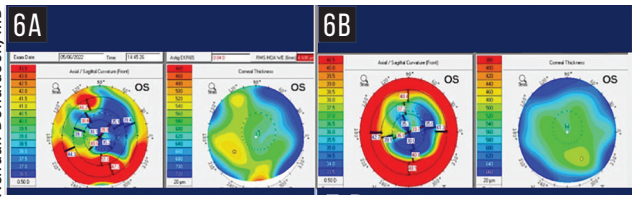
Date	05/06/2022	08/10/2022	03/22/2024	06/04/2024
Refraction	37.35/37.39 @27	33.73/37.58@175	34.19/36.79@015	33.93/37.01 @006
Astigmatism (D)	0.04	3.85	2.60	3.08

Figure 7. Keratometry readings over time from the patient in Fig. 6A show the significant difference between this patient's left-eye astigmatism readings and a left-eye reading affected by contact lens wear.

Surgical Dilemma

In sterile attire, Dr. Donaldson reviewed the patient's measurements and asked for intraoperative aberrometry (ORA, Alcon) to be set up for the case, as she began the surgery with trepidation. She then learned the aberrometer was out of service, awaiting repair. "I thought, 'This patient has 5 D of irregular astigmatism within the central 3 mm of her visual axis, so she will need a new contact lens after surgery anyway. I can't leave her aphakic. Can I?'"

Surgery went perfectly, and Dr. Donaldson implanted the lens according to her preop measurements. But the patient returned postop day one with vision of 20/200. "I advised her to give it time to settle and we would watch her closely," recalls Dr. Donaldson. One week postop, the patient was minimally better at 20/150, with pinhole vision of 20/30 in the left eye. One month postop, she was still extremely hyperopic (+4 +1.25 x 95). With some mild fluctuations, her refraction remained relatively stable, and she resumed soft contact lens wear in the left eye with a best corrected vision of 20/25.



Kendall Donaldson, MD

Figure 6A and 6B. The left corneal topography map (6A) shows true, severe irregular astigmatism that was masked by a contact lens. The other map (6B) reflects true irregular astigmatism found in the same patient at a point in time when she wasn't wearing a contact lens.

About a year later, according to Dr. Donaldson, the patient returned to undergo cataract surgery in the right eye, achieving uncorrected visual acuity of 20/20-2. "Why is my other eye so bad and in need of a contact lens when this eye is now so good?" the patient asked.

"I pointed out that the left eye had eight-cut RK and the right eye only had four-cut RK, so the left eye had a much higher degree of irregular astigmatism," recalls Dr. Donaldson. "And then the patient said, 'Do you think it's because of that contact lens you found during my first surgery?' I had to admit to her that this had in fact made a bad situation worse."

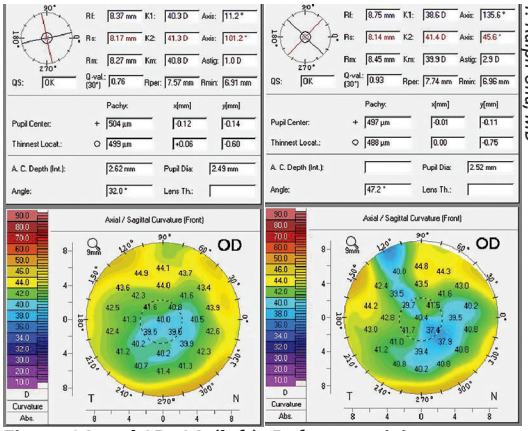
Dr. Donaldson agreed to perform a lens exchange in the troublesome left eye. "I wasn't very confident," she recalls, noting that the previous surgery had been two years earlier and that very severe irregular astigmatism continued within the visual axis. "I re-measured and re-calculated her lens in many different ways. I back-calculated from the lens in her eye. I used the Barrett Rx formula, and I discussed her case with several colleagues." Dr. Donaldson eventually selected a final lens for the bag and, as a backup, a three-piece lens for the sulcus. Measurements ranged over 8 D. "I planned to use ORA (now functioning) to fine-tune my final lens choice," she notes.

The Solution

Surgery began well. "However, the zonules appeared to be a little loose at the end of the lens dissection," says Dr.

Donaldson. "After considering a capsular tension ring, I placed the backup three-piece lens in the sulcus with a target of -0.75 D. Postop day one, the patient was 20/30-2 and extremely happy. By the time she returned one month postop, she could see both distance and near through her fortuitously multifocal cornea." The patient functioned at both distance and near without glasses or contacts. "We bonded over our success—and our luck," Dr. Donaldson recalls.

She now recommends canceling surgery if you ever encounter a contact lens on an eye in the operating room *(See Figures 6A, 6B and 7)*. "The lens can alter the lens calculations by 4 D (as seen in this case) or potentially even more," she points out.



Y. Ralph Chu, MD

Figure 8A and 8B. 8A (left): Before receiving Light-Adjustable Lens implants, the patient's preop topography shows a myopic LASIK pattern, with up to 2 D of cylinder through the visual axis in her right eye. There is up to 4 D of cylinder through the visual axis in her left eye (not pictured).
8B (right): The topography of the LAL implant patient after the patient's first surgery in the right eye reveals expected flattening at the incision site and increased astigmatism through the visual axis.

CASE #4:

If at First You Don't Succeed . . .

Here's an example of why patients with irregular corneas or a history of refractive surgery can sometimes be challenging, even when Light-Adjustable Lenses are used to enable non-invasive postop refinements.

The 67-year-old female patient was referred for possible cataract surgery at the Chu Vision Institute in Bloomington, Minnesota. She'd begun wearing progressive addition lenses full time a year earlier and had been experiencing difficulty driving at night. In 2001, she underwent LASIK for correction of myopia, and she'd been diagnosed with mild dry macular degeneration. Her preop topography showed a myopic LASIK pattern, with up to 2 D of astigmatism through the visual axis in her right eye *(See Figure 8A)* and up to 4 D of astigmatism through the visual axis in her left eye.

The patient had a BCVA of 20/20 in her right eye with plano sphere refraction and 20/25+ in her left eye with a correction of -3 + 0.50 x 173. With glare testing, her best corrected vision decreased to 20/50 OD and 20/70 OS.

The patient had unplanned monovision with the cataract progression, and she initially wanted to keep a distance target in both eyes. "The decision was made to proceed with cataract surgery with a Light-Adjustable Lens to give the patient a postop option of monovision," says Ralph Chu, MD, the founder and medical director of the Chu Vision Institute.

Surgical Outcome

The patient underwent uncomplicated cataract surgery in both eyes with the implantation of Light-Adjustable Lenses. One week postop, she complained of blurred vision. "Her uncorrected vision was 20/40+ and >J10 in her right eye and it was correctable to 20/20 with a refraction of +1.75 +2.00 x 026," explains Jessica Heckman, OD, vice president of clinical affairs and optometric residency director at Chu Vision. "The left eye was uncorrected at 20/50+ and >J10 but correctable to 20/20 with a manifest refraction of -1.50 +3.50 x 021. Her postop topography showed expected flattening at the incision site and increased astigmatism through the visual axis." *(See Figure 8B)*

The refractive findings were concerning, considering the patient's degree of hyperopia OD and astigmatism OS. "Her postop refractive error was pushing her lenses' adjustability limits," explains Dr. Chu. "We chose to perform an IOL exchange to reduce the refractive error to within a more adjustable range for her right eye. Incisional keratotomy or laser vision correction wasn't possible." No IOL exchange was planned for the left eye because of its possible use for monovision.

A 19.5 D LAL was exchanged for a 21.5 D LAL. At one week postop, the patient's uncorrected vision measured 20/60—with a manifest refraction of 1.50 +2.75 x 035. "The patient said her vision felt slightly better, but she remained frustrated with her blurred distance vision," says Dr. Chu. A prescription for glasses was written for functional vision until her right eye and refraction were stable enough for LAL adjustments.

Monovision Correction

The patient ended up needing two light-adjustment treatments on both eyes after the initial implantation. During this process, she found that she preferred more balanced distance vision in both eyes, instead of monovision. She ended up with uncorrected visual acuity of 20/20 and J3 in her right eye and 20/20 and J3 in her left eye. She also had J2 near vision in both eyes, with a +0.25 sphere manifest refraction in each. "She was very happy with her functional result," Dr. Chu says.

"This case provides a good reminder that, even with the use of light-adjustable intraocular lens technology, patients with previous refractive surgery or irregular corneas may have a longer or more complicated journey after cataract surgery," says Dr. Chu. In these cases, he recommends emphasizing to patients the possible need for additional surgery and the possible need to temporarily wear prescription glasses between surgeries. ◀

Pearls for Ciliary Body Ablation

How and when to employ these procedures in your glaucoma practice.

OSAMAH SAEEDI, MD, MS
BALTIMORE

The right ciliary body ablative procedure is a valuable tool for managing pressures in glaucoma. Endoscopic cyclophotocoagulation and micropulse cyclophotocoagulation are gentler approaches that may be used in mild to moderate glaucoma. Traditional transscleral cyclophotocoagulation is generally considered more effective at pressure lowering, depending on the settings used, but is most commonly reserved for patients with poor vision (e.g., count fingers at one inch) and later-stage disease.

There are numerous indications for ciliary body ablation. Here, I'll review scenarios where ciliary ablation may be beneficial, discuss the best laser settings to use and share tips for success.

Additional Subconjunctival Surgery or Cycloablation?

In certain situations, performing another filtering procedure may be unpalatable to the patient or may put them at additional risk for complications. For patients in their 90s, for example, my interest in doing an incisional procedure is lower because they have a higher risk of suprachoroidal hemorrhage. Ciliary ablation may be a good option for such patients.

Here are some more examples of patient scenarios suited to a ciliary body ablative procedure:

• ***Failed tube.*** After a failed tube shunt surgery, patients may not wish to undergo an additional tube shunt surgery or deal with potential tube-related complications such as choroidal hemorrhage (*Figure 1*). While ciliary body ablation has associated risks of its own (discussed below), transscleral CPC or MPC are non-invasive and ECP is minimally invasive.

> **Choose ECP or micropulse for eyes with better vision and earlier-stage disease and reserve traditional CPC for eyes with worse vision or end-stage glaucoma.**

• ***Severe blepharitis.*** If a patient has severe blepharitis, they may have a higher risk for infection with surgery, particularly trabeculectomy. Ciliary body ablation carries a lower risk of endophthalmitis.

• ***Risk of falling.*** If you're concerned that the patient may fall and ultimately cause some damage to a bleb or cause some sort of issue with the tube, this is a potential candidate for ciliary ablation rather than a tube shunt or trabeculectomy.

• ***Poor follow-up.*** Patients who are institutionalized or in nursing homes may not be able to attend follow-up visits with regularity or use their drops as directed. Additionally, it's difficult to account for the types of risks that may be present in their environment.

• ***Ocular tumors.*** When you want to avoid cutting into the eye for risk of seeding or worsening the tumor, a transscleral ciliary ablation laser procedure is a fantastic option.

• ***Lack of transportation.*** If there's no one who can take the patient home, they may be better suited to a cycloablative procedure under local anesthesia with a retrobulbar block.

For these procedures, I'd rather avoid the greater risk of hypotony or vision loss associated with overtreating. In contrast, undertreatment may require repeat procedures.

For any patient undergoing a cycloablative procedure, be sure to counsel them that sometimes it's not a one-time thing; that if their pressures go up later, we may need to do the procedure again.

The Options

When and how should you use CPC, micropulse CPC and ECP? Here's a rundown of the three options:

• ***Traditional transscleral cyclophotocoagulation.*** Typically reserved for eyes with poor visual potential, CPC is an effective pressure-lowering alternative to more invasive glaucoma surgeries and can reduce IOP by 10

This article has no commercial sponsorship.

Dr. Singh is a professor of ophthalmology and chief of the Glaucoma Division at Stanford University School of Medicine. He is a consultant to Alcon, Allergan, Santen, Sight Sciences, Glaukos and Ivantis. **Dr. Netland** is Vernah Scott Moyston Professor and Chair at the University of Virginia in Charlottesville.

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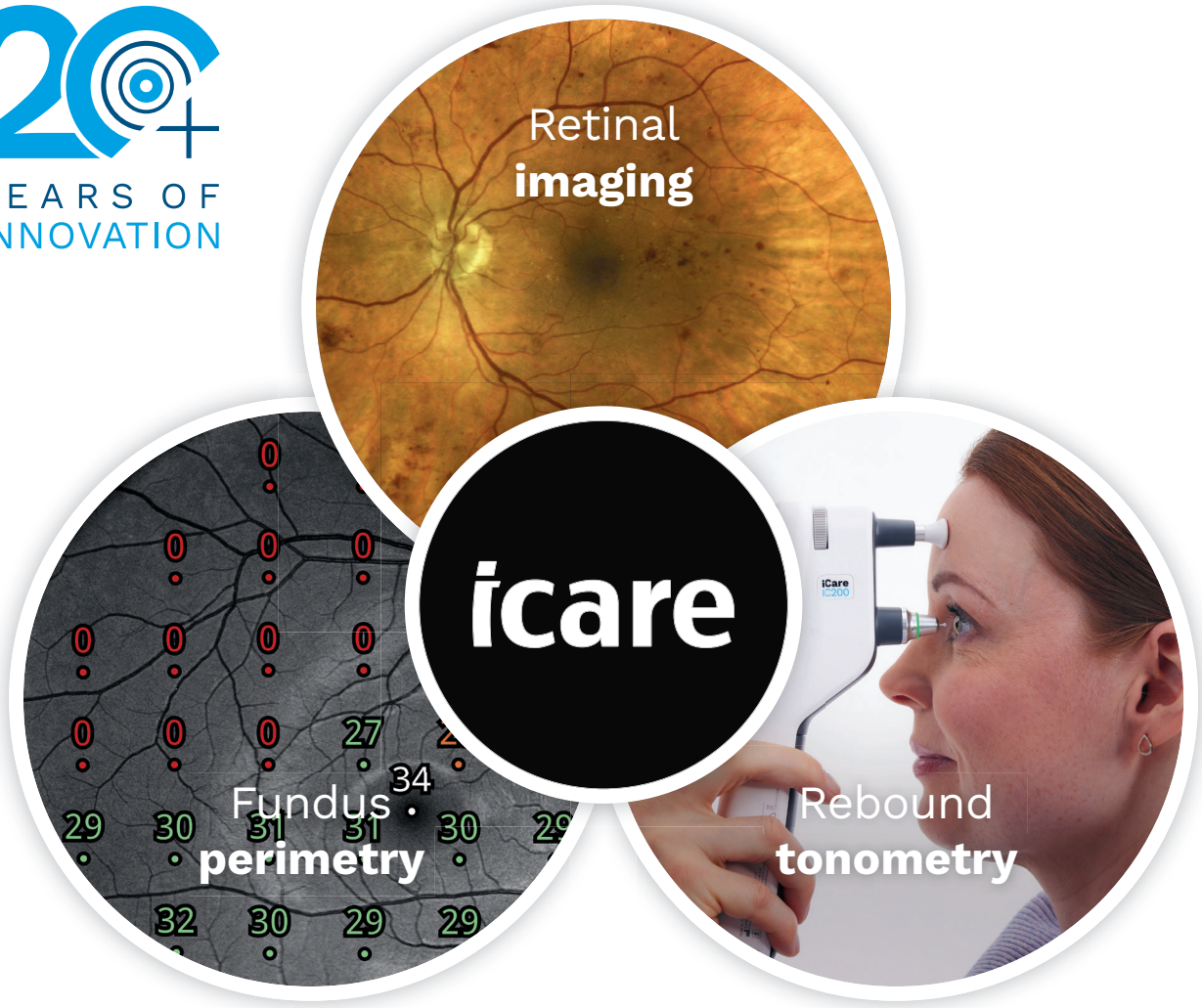

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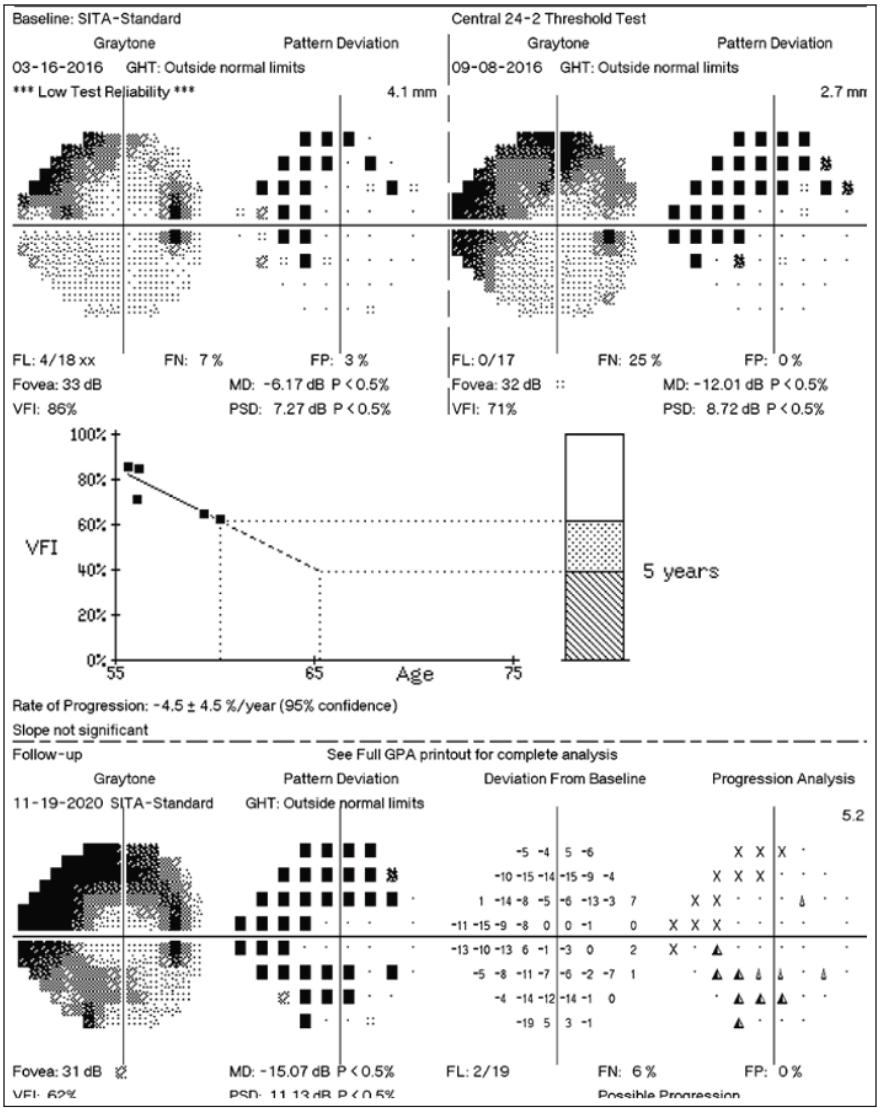

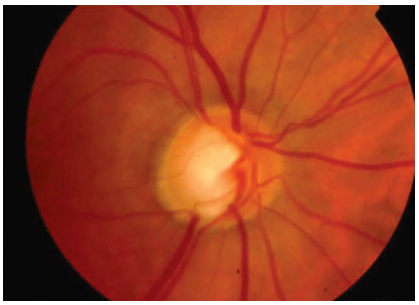

Osamah Saeedi, MD, MS

Figure 1. A 60-year-old African American male patient with open-angle glaucoma in the right eye is allergic to multiple drops. His surgical history includes trabeculectomy, bleb revision x2 and Ahmed Clearpath 350 implantation. Best-corrected visual acuity is 20/25. His T-max is 23 mmHg and his pressures are persistently in the high teens on a preservative-free PGA. Target IOP is 14 mmHg. A 360-degree ECP was completed with two incisions. At postop month four, his IOP was at the target of 14 mmHg on a preservative-free prostaglandin analog.

to 20 mmHg or more. If the outflow facility is poor, then more laser may be needed to reduce the IOP to the normal range. If extensive cycloablation is required to reach the desired IOP outcome, there may be increased risk of phthisis and vision loss.

The traditional transscleral CPC technique involves a G probe. Laser energy is applied evenly spaced around the limbus for 360 degrees, though there are some surgeons who prefer to leave one quadrant open and treat 75 percent of the way around the limbus. I aim for 20 spots total.

The conventional CPC treatment is 2,000 mW for 2,000 ms. I've found this to be a little less effective. In this technique, it's generally advised to titrate up until you hear a pop and then titrate back down. However, the pops are bursting ciliary bodies and can result in inflammation, so I try to avoid this and instead use the lower and slower technique.[1] The lower and slower technique uses anywhere between 1,000 to 1,500 mW for 3,000 to 4,000 ms, or four seconds per spot.

There are certain areas surgeons should avoid treating when performing this procedure, including areas with a functional trabeculectomy or tube. Areas of darker pigmentation should also be avoided. The laser applies energy that passes through the sclera and is absorbed by melanin in the pigmented ciliary body. However, if there's pigment on the eye—such as a particularly large nevus, or there's some blood (e.g., from an injected red eye or a small hemorrhage at the point where you cut down for a sub-Tenon's block)—the laser energy can be absorbed and, in rare cases, even create a hole in the sclera.

Some cases may require altering the laser settings. For example, with a neovascular glaucoma patient with pressures in the 70s, much higher than your normal diode patients, performing traditional CPC at a higher setting may be suitable. Using the lower and slower technique, I'll increase the energy from 1,000 mW to 1,500 or even 1,700 mW.

• ***Micropulse.*** Like traditional CPC, micropulse CPC is a quick procedure, taking about five to 10 minutes, with fast recovery time and no activity restrictions for patients. However, it can be used in patients with better vision. Micropulse provides a modest IOP reduction of 20 to 45 percent and lowers IOP in about four to six weeks. Patients will likely need to continue using some glaucoma medications. Micropulse is less effective in treating secondary glaucomas such as neovascular

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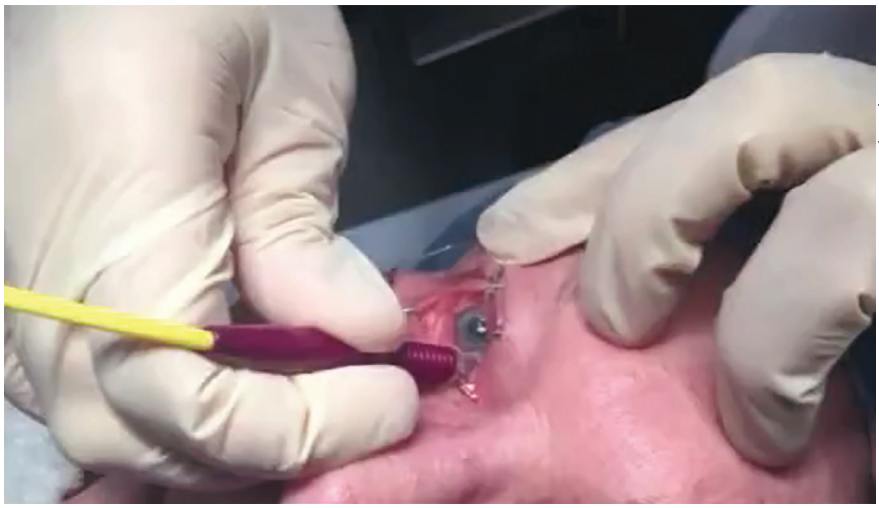
glaucoma, uveitic glaucoma as well as congenital glaucomas.

The micropulse technique is different from that of traditional CPC (*Figure 2*). When applying the G probe for traditional CPC in one location, it produces continuous energy. In this situation, micropulse pulses, as the name implies. It delivers the energy in the duty cycle for 31 percent of the time. This type of pulsation delivers less energy but still potentially offers adequate efficacy.

Rather than treating in discrete spots, sweep the micropulse P3 probe along the edge of the limbus. The recommended settings are 1500-2,500 mW at a 31.3-percent duty cycle. You can change this by 20 to 25 percent, if you want to increase or decrease the energy for whatever reason. A consensus panel suggested four sweeps of 20 seconds per hemisphere for a total of 160 seconds per eye (*Figure 3*).[2] Another option is to do four sweeps of 10 to 15 seconds per quadrant.

A slow sweep does the trick. For comparison, a fast sweep would be a 10-second sweep, or 2 mm per second. A slow sweep is a quarter of that, let's say 0.5 mm per second, or a 40-second sweep. Going too fast is a mistake as it reduces the amount of energy applied to the ciliary body. That may be one reason many surgeons have moved away from micropulse, not finding it to be effective. The slower you go, the greater the efficacy.



Ahmad Aref, MD, MBA

Figure 2. The new micropulse P3 probe has two bunny ears which must be pointed toward the limbus in order for the probe to work properly.

Like CPC, micropulse is an external procedure. While it can be performed in clinic, potentially with a retrobulbar block, I usually perform it in the operating room where patients can be administered propofol and perform the micropulse procedure while they're asleep. Postoperatively, I give them a drop of atropine and that generally addresses postoperative pain.

One of the benefits of the newer cycloablative procedures—micropulse and ECP—is that the patient doesn't necessarily need a retrobulbar block and hence wouldn't need to be patched. For a monocular patient, this is particularly advantageous. A

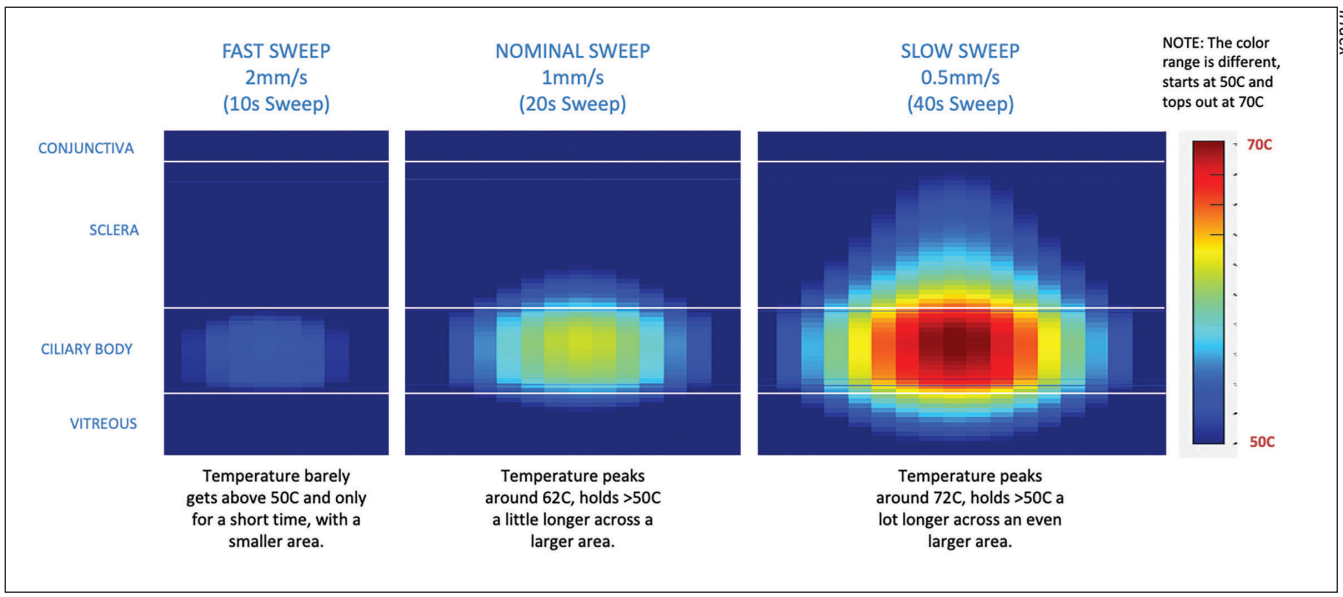


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Figure 3. Micropulse is more effective when performed using slower sweep speeds. Recommended settings for the micropulse technique are 2,500 mW at a 31.3-percent duty cycle, involving four sweeps of 20 seconds per hemisphere (four sweeps of 10 seconds each per quadrant).

micropulse procedure is preferable in this scenario. A heavier micropulse may be suitable if more pressure lowering is required, and in that case, you could increase the energy a little bit or try to go even slower with the sweeps. However, I tend to use the recommended settings with the micropulse.

• ***Endoscopic cyclophotocoagulation.*** ECP may be used as a replacement for medical therapy in conjunction with other surgery (especially cataract surgery), post-trabeculectomy or post-GDD, for poor bleb candidates, in corneal transplant patients, those with congenital glaucomas and in aphakic or vitrectomized eyes, or for any indication where traditional CPC was used prior.

ECP uses a continuous mode at 0.25 watts with a straight or curved probe. In this procedure, first make an incision, fill the sulcus with viscoelastic such as Healon. Then, insert the probe underneath the sulcus. Adjust the illumination to visualize the aiming beam. Ablate the ciliary body. The endpoint is whitening and shrinking of the ciliary processes (*Figure 4*). Avoid applying so much energy as to cause a pop. This causes a lot of inflammation which can be counterproductive and take longer to heal or cause edema. Ensure you have a good view and good alignment. Your view should include three ciliary processes—that's how close you should be. Apply the laser almost as if you're painting the ciliary processes, 270 to 360 degrees, and try to get to this endpoint of whitening.

The use of ECP as a minimally invasive glaucoma surgery employs a different approach than its use for treating an advanced glaucoma patient who's already had a tube, for example. While I don't use it in this context, for ECP as a MIGS procedure, many will treat ciliary body three to six clock hours, not the full 360 degrees. When performing ECP more aggressively for an advanced glaucoma patient, I'll make two separate incisions. I usually make one incision temporally and one superiorly.

Steroid Recommendations

Cycloablative procedures can cause persistent inflammation, so you want to get that under control quickly. Some surgeons recommend using intracameral steroids at the end of the case. For traditional CPC, I'll typically give subconjunctival dexamethasone at the time of the procedure, followed by topical steroids afterwards. For micropulse, a less intense steroid regimen may be used due to concern for steroid response. Post-procedure, I use prednisolone acetate with a fast taper, and others suggest using a weaker steroid such as loteprednol. ECP can generally be treated with intraoperative and postoperative steroids according to the surgeon's preference, taking into

Malik Kahook, MD

Figure 4. The endpoint of ECP is whitening of the ciliary body. Note the difference in color between the ablated ciliary processes to the left and the untreated ones to the right.

consideration the need for steroid therapy required for other concomitant procedures.

Complications

Any cycloablative procedure can also cause cataract, phthisis and vision loss. Common complications with traditional CPC include hypotony, macular edema and central vision loss, with one study reporting that up to 33 percent of patients lose two lines of vision on the Snellen chart with CPC.[3] This is one of the reasons CPC is reserved for worse-seeing eyes. Macular edema is a potential complication of micropulse and ECP as well, although the risk is less. It's uncommon to have central vision loss with these procedures. Since ECP requires an incision, there's a small albeit extremely low risk of infection. Postoperative care includes antibiotic prophylaxis against infection, in addition to steroids.

All three procedures can cause significant inflammation. ECP can even result in aggressive inflammation causing fibrin in the anterior chamber. This commonly resolves with steroids, but inflammation is a big risk with any of these cycloablative procedures.

Other Approaches

Here are a few alternative but less common ways of performing ciliary body ablation:

• ***Transilluminating the sclera.*** Transillumination involves placing a bright white light on the sclera, which will in most cases cause the ciliary body to transilluminate. You can then see the individual ciliary processes and target where you do your transscleral CPC.[4]

• ***ECP Plus.*** This approach targets the posterior ciliary processes, unlike regular ECP which treats the anterior portion. Typically, to access the posterior processes, you'd need to perform a vitrectomy, which most glaucoma specialists aren't comfortable with. ECP Plus involves a limited vitrectomy followed by ECP.[5] After the vitrectomy, some retina specialists sclerally depress the ciliary body and use their traditional retinal lasers on it.[6]

• ***Transpupillary ciliary ablation.*** In unusual situations, one or more ciliary processes may be visible at the slit lamp or on gonioscopy, such as when you've done a large iridectomy for a trabeculectomy or the patient has a wide dilation, is aphakic or has had a procedure whereby the iris was removed or reduced. In these cases, a transpupillary argon ciliary laser ablation can be performed in the clinic.[7]

In summary, ciliary body ablation has a variety of indications and can be performed in eyes that see well. Choose ECP or micropulse for eyes with better vision and earlier-stage disease and reserve traditional CPC for eyes with worse vision or end-stage glaucoma. ◀

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A Review of Tyrosine Kinase Inhibitors

A look at the mechanism of action and results for a new kind of VEGF inhibitor in the pipeline.

REEDA BOU SAID, MD, TIMOTHY XU, MD, AND SOPHIE J. BAKRI, MD
ROCHESTER, MINN.

Vascular endothelial growth factors are 40kDa dimeric glycoproteins[1] implicated in the pathophysiology of multiple leading causes of blindness, including neovascular, or wet, age-related macular degeneration and diabetic retinopathy,[2] among others. These molecules play a vital role in angiogenesis[3] and have been detected in ocular fluid samples in proliferative diabetic retinopathy, iris neovascularization and ischemic central vein occlusion.[4] Thus, they have been the target of multiple medications for the last two decades after the approval of the first anti-VEGF, pegaptanib, in ophthalmic use in the early 2000s.[5,6] Since then, other anti-VEGF medications have been developed and have been used in a multitude of retinal diseases. Here, we'll explore one of the newest drugs being studied in the battle against these diseases: tyrosine kinase inhibitors.

The Anti-VEGF Landscape

The current limitations of anti-VEGF injections lie in the frequency at which they have to be administered. Even with treat-and-extend protocols, the number of patients maintained at prolonged intervals is variable,[7] and the average number of injections with this protocol is around 13 for the first two years.[7-9] The frequency of injections can place a psychological and financial burden on the patients and caregivers, affecting treatment compliance.[10] Furthermore, there are possible complications associated with the injections, including endophthalmitis, intraocular inflammation, vasculitis, tractional/rhegmatogenous retinal detachment, increased intraocular pressure and ocular hemorrhage.[11,12]

This led to the attempt to reduce the treatment burden and to develop sustained delivery systems.[13] For example, the port delivery system for ranibizumab (Susvimo) was FDA approved for the treatment of nAMD, as a surgically implanted refillable reservoir of anti-VEGF.[14] However, it was associated with a higher risk of endophthalmitis and hemorrhage with earlier surgical techniques, and was temporarily recalled due to reported septum dislodgment[15] prior to recirculation.

Moreover, like VEGF, platelet-derived growth factor (PDGF) is important in angiogenesis.[16] It plays a role in pericyte recruitment and vascular maturation,[17,18] and we know from animal models that the paucity of pericytes made vessels more prone to regression with VEGF inhibitors.[19] In fact, a recent clinical trial (Phase IIb) on dual VEGF/PDGF inhibition in wet AMD showed favorable results relative to anti-VEGF monotherapy.[20]

TABLE 1. THE CURRENT MOST-STUDIED TKIs

TKI		Axitinib	Vorolanib	Sunitinib
IC50 (nM)	VEGFR2	0.2	52	43
	Others	VEGFR1: 0.1 PDGFR: 1.6 C-KIT: 1.7	VEGFR1: 10 PDGFR: 260 Flt3: 6 C-KIT: 160	PDGFR: 160 Flt3: 3 C-KIT: 160
Formulation[99]		PEG-based hydrogel implant, micronized axitinib crystals (intravitreal)/ suspension (suprachoroidal)	Bioerodible implant-Durasert	Microparticles, mPEG-PLGA*
Byproducts			Dissolved PVA polymer chains	Lactic and glycolic acid
Infectious		Biodegradation via ester hydrolysis	0 order kinetics, drug embedded in bioerodible matrix	Microparticle aggregation (depot), slow release

IC50 is the half maximal inhibitory concentration

*Sunitib GB-102 components: poly(lactic-co-glycolic acid), methoxy-polyethylene glycol. The presence of the hydrophilic methoxy-polyethylene glycol aims to prevent inflammation seen with poly(lactic-co-glycolic acid).[56]

**Axitinib showed higher inhibition of tie2 than other TKIs, normal tie2 function is essential for vascular stability [38]

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TABLE 2. CURRENT TRIALS INVOLVING AXITINIB

Axitinib	OTX-TKI[42]	OTX-TKI[100]	OTX-TKI[43]	OTX-TKI (HELIOS)[44]	CLS-AX (OASIS)[45]	CLS-AX (ODYSSEY)[46]	CLS-AX (OASIS)-extension[49]
ID	NCT04989699	NCT03630315	NCT06223958	NCT05695417	NCT04626128	NCT05891548	NCT05131646
Phase	I	I	III	Ib	I/IIa	IIb	I/IIa
Mode of administration	Intravitreal, 25 to 27 ga.	Intravitreal, 25 to 27 ga.	Intravitreal, 25 to 27 ga.	Intravitreal, 25 to 27 ga.	Suprachoroidal, 30 ga.	Suprachoroidal, 30 ga.	Suprachoroidal, 30 ga.
Dose	0.6 mg OTX-TKI, aflibercept 2 mg four weeks later	Dose escalation Cohorts: 1: 1 x 0.2 mg 2: 2 x 0.2 mg (0.4 mg) 3a: 3 x 0.2 mg (0.6 mg) 3b: 2 x 0.2 mg (0.4 mg) + anti-VEGF 4a: 1 x 0.6 mg 4b: 1 x 0.6 mg + anti-VEGF	NA	600 µg	Dose escalation, 0.03 to 1 mg	1 mg	Dose escalation, 0.1 to 1 mg
Control group	Aflibercept/Sham	None	Aflibercept	Sham	Aflibercept	Aflibercept	Aflibercept
Number of patients	21	29	300 (estimated)	21	27	60 (estimated)	15
Pathology	nAMD	nAMD	nAMD	Moderately severe to severe NPDR	nAMD	nAMD	nAMD
Treated vs tx naive	Treated, at least 3 anti-VEGF, evidence of response	Either	Naïve	NA	Previously treated	Previously treated, 2 to 4 anti-VEGF	Previously treated
Planned follow up	1 year	9 months	36 weeks (primary) to 104 weeks (secondary)	52 weeks	12 weeks	36 weeks	12 weeks extension following original OASIS study
Primary outcome	TEAE	TEAE	BCVA	TEAE	Treatment-emergent and serious adverse events	BCVA	Treatment-emergent and serious adverse events
Secondary outcomes	BCVA, CST, rescue therapy, absence of fluid, number of injections	Maximum dose tolerated	TEAE	BCVA, CST, rescue therapy, DRSS	IOP, BCVA, CST, needing/qualifying for additional IVT injections, maximum plasma concentration of axitinib	Fluid on OCT, lesion size on FFA, supplemental injections, serious and treatment-emergent adverse events	IOP, BCVA, CST, needing/qualifying for additional IVT injections
(Prelim) Results	Sustained BCVA and CST, comparable to aflibercept Well tolerated 80 percent rescue-free at 7 months	Well-tolerated >60 percent durability of ≥6 months Stable CST in cohort 1; decreased in 2 and 3a 101	Recruiting	Pending	No serious adverse events Stable CST and BCVA	Pending	No serious adverse events Stable CST and BCVA Reduction in treatment burden

However the Phase III clinical trial didn't achieve its primary endpoint.

Other potential culprits are the angiopoietins (Ang) which have also been implicated in angiogenesis[22] and increased inflammatory signaling.[23] Dual inhibition of VEGF and Ang2 (Faricimab) has shown visual and anatomic benefits at more extended intervals in nAMD and DME in recent trials.[24,25] Thus emerged the importance of inhibiting multiple targets in these pathologies.

What are Tyrosine Kinase Inhibitors?

The VEGF family includes VEGF A, B, C, D and E, as well as placental growth factor (P1GF), which bind to different forms of VEGF receptors (VEGFR) that have been identified. These include VEGFR 1, 2 and 3. The most important players in angiogenesis are VEGF-A and its receptors VEGFR-1 (fms-like tyrosine kinase-1 or Flt-1) and 2 (kinase insert domain-containing receptor or KDR), both receptor tyrosine kinases (RTK).[2,26–28] This family of receptors has been implicated in angiogenesis, tumorigenesis

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Dear Resident Program Director and Coordinator,

We would like to invite you to review the upcoming 2nd-Year Ophthalmology Resident Wet Lab Programs for the 2024–2025 Residency Year in Fort Worth. These programs offer a unique educational opportunity for second-year residents. To better familiarize beginning ophthalmologists with cataract surgery, these programs will consist of both didactic lectures and a state-of-the-art, hands-on wet lab experience. Technology and technique will be explained and demonstrated and surgeons will leave better prepared to optimize outcomes and manage complications when they arise. The programs also serve as an opportunity for your residents to network with residents from other programs.

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.

Best regards,
Derek DelMonte, MD, Kourtney Houser, MD, and Jonathan Rubenstein, MD

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CME courses are restricted to 2nd-year residents enrolled in an ophthalmology residency program at the time of the course. There is no registration fee for this activity. Air, ground transportation in Forth Worth, hotel accommodations, and modest meals will be provided through an educational scholarship for qualified participants.

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and metastasis.[29] P1GF can also play a role through synergism with VEGF in pathological conditions, thus increasing angiogenesis and plasma extravasation.[30]

The previously mentioned PDGF and angiopoietins bind to PDGF receptors (α and β, belonging to the class III receptor tyrosine kinases[16]) and the Tie (tyrosine kinase with immunoglobulin and epidermal growth factor homology domains[31]) receptor family, respectively. While Ang1 promotes vascular stability in physiological conditions through binding to Tie2, the increase of Ang2 in disease conditions, eg., hyperglycemia, leads to vascular destabilization and enhanced response to VEGF A, thus increasing vascular leakage and neovascularization.[31,32] Inhibition of Ang2 in animal models leads to inhibition of neovascularization promoted by VEGF.[33]

Other factors involved in angiogenesis include fibroblast growth factor (FGF) which also binds to an RTK.[34] Animal models with pancreatic cancer subjected to treatment with VEGF inhibitors showed the appearance of resistance to this treatment in late stages, with reactivation of angiogenesis.[35] This was due to the presence of other factors which promoted angiogenesis, including FGF.[35]

Similar to the initial development of VEGF inhibitors in cancer treatment, tyrosine kinase inhibitors were studied in oncology to target angiogenesis. Instead of blocking the ligand, TKIs exhibit their effects through inhibition of downstream intracellular signaling that follows ligand-receptor binding.[27] The first approved drug in this family was imatinib, which paved the way for targeted medicine, and improved survival rates and quality of life.[36] This family of drugs can range in selectivity, and some can target multiple receptors.[29] In fact, TKIs that targeted both VEGFR and PDGFR showed better results than inhibition of either separately.[37]

TKIs in Retinal Diseases

Several tyrosine kinase inhibitors have recently been studied in retinal diseases. These include axitinib, sunitinib, vorolanib, anlotinib and pazopanib. The three mainly studied drugs, and their formulations and affinities can be found in Table 1. While all show potent inhibition of VEGFR, axitinib had the strongest effect.[38] The different formulations aim to ensure prolonged release, and therefore longer-lasting effect, of the active drug.

• ***Axitinib.*** Axitinib is a potent inhibitor of VEGFR 1, 2, and 3, with its oral formulation approved in the treatment of renal cell carcinoma, and used in the treatment of other malignancies as well.[39] It also targets PDGFR, though is a less potent inhibitor of this receptor than initially found in *in vitro* studies.[40]

Clinical trials involving this drug can be seen in Table 2. In a Phase I U.S.-based clinical trial of axitinib in nAMD, a single bioresorbable hydrogel implant of the drug (OTX-TKI, Ocular Therapeutix), followed by an injection of aflibercept at one month, showed similar outcomes in visual acuity and central thickness in comparison with aflibercept every eight weeks.[41,42] Axitinib was well-tolerated with no reported adverse events, and with a decrease in treatment burden, demonstrated by 80 percent rescue-free participants in the treatment arm at 24 weeks and 60 percent rescue-free at week 52. Safety data showed the implant was well-tolerated.

A Phase III trial (SOL-1 is currently recruiting subjects with treatment-naïve nAMD for axitinib injection with 151 subjects enrolled as of June 2024; results have yet to be reported.[43] Other trials underway for this drug include moderately severe to severe non-proliferative diabetic retinopathy; a Phase I trial (HELIOS) demonstrated that 23.1 percent (n=3) of subjects receiving an axitinib implant had ≥2-step improvement in the diabetic retinopathy severity scale compared to zero in the sham group at week 48.[44]

Other modes of administration of axitinib currently in trial include suprachoroidal injection (CLS-AX, Clearside Biomedical).[45,46] The advantages of this minimally invasive method are numerous, including decreased risk of infection, potential prolonged release of the drug, compartmentalizing the drug near the target tissue and decreased floaters.[47] Phase I/IIa trials (OASIS) of CLS-AX have demonstrated that in anti-VEGF treatment-exposed sub-responders, 83 percent of patients went ≥4 months without additional treatment, 67 percent went ≥6 months without additional treatment, and 50 percent didn't require additional treatment for >6 months. In the extension of this study, the different axitinib dose cohorts showed no adverse events and a decrease in treatment burden at six months.[48,49] A Phase IIb randomized, double-masked multicenter clinical trial comparing CLS-AX 1 mg suprachoroidal injection to intravitreal 2 mg aflibercept injection for neovascular AMD in eyes previously treated with standard of care intravitreal anti-VEGF is currently underway. Outcome measures will report change in best-corrected visual acuity over 36 weeks, need for supplemental treatment, and treatment burden as quantified by total number of injections over study period.

• ***Sunitinib.*** Sunitinib targets VEGFRs, PDGFR, stem cell growth factor receptor (KIT) and FLT3.[50] It's used in oncology in the treatment of metastatic renal cell carcinoma, gastrointestinal stromal tumors, lung cancer and pancreatic neuroendocrine tumors.[50–53] Preclinical trials investigated biodegradable microparticles of sunitinib, which aggregated in a depot in the inferior vitreous after intravitreal injection, and slowly released the active drug. The trials showed that this medication was nontoxic and retained active levels of the drug at the level of the retina and RPE/choroid for at least four months.[54] In fact, due to its reversible binding to melanin, sunitinib was found to remain up to six to seven months in the RPE/choroid of pigmented rabbits.[55]

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PROGRAM ON ADVANCED ANTERIOR SEGMENT SURGERY

PROGRAM & WET LAB

PROGRAM DATES
JANUARY 17–18, 2025
(FRIDAY & SATURDAY)

Didactic sessions
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11950 Dublin Canyon Road
Pleasanton, California 94588

Wet Labs
Zeiss Innovation Center
5300 Central Pkwy
Dublin, California 94568

Yousuf Khalifa, MD
Madeline Yung, MD
Course Co-Directors

Program Highlights Include

- Intimate meeting (limited to the first 28 residents registered)
- Hands-on wet lab
- Refractive Surgery (LASIK, PRK (refract lenticule extraction)
- MIGs
- Yamane technique
- Capsular Tension Segments
- Complex/dense cataract mgmt

Dear Resident Program Director and Coordinator,

We are excited to announce the upcoming CME Accredited Resident Wet Lab Program on Advanced Anterior Segment Surgery (PAASS). PAASS is an intimate meeting (limited to the first 28 residents registered maximum) designed to help prepare third-year ophthalmology residents to transition successfully into a private practice setting in ophthalmology or their chosen fellowship program, or into an educational environment. The 3rd Year PAASS & Wet Lab will be approved for *AMA PRA Category 1 Credits*™ and will have an emphasis on successful outcomes by concentrating on building diagnostic, medical and advanced surgical skills in the wet lab (including Yamane, Capsular Tension Segments, MIGs, etc). The course directors and the faculty create a "safe" environment, so the third-year residents feel comfortable discussing questions, new technology, and complications in an atmosphere that strongly encourages interactive participation. **We are capping the number of residents to 28 so that the residents are fully immersed in the learning environment along with a one-to-one (faculty-to-resident) ratio in the wet lab to maximize learning curve with the advanced surgical skills wet lab.**

Ophthalmology residencies in the United States strive to introduce their residents to advanced surgical techniques and technologies in an environment characterized by rapid innovation. Due to continuously evolving technological developments, best practices are constantly changing. As such, there are too few opportunities to gain hands-on training. This meeting will concentrate on advanced techniques and technologies geared towards residents approaching the end of their 3rd Year (PGY4) residency. The meeting will cover topics specifically in the areas of refractive surgery, minimally invasive glaucoma surgery, management of aphakia, new technologies for dense cataract management, intraocular lens selection technologies, heads-up displays, and progression tracking software.

This 2-day course will include one day of didactic and one day of hands-on wet lab experience. The meeting will be led by a faculty comprised of renowned key opinion leaders and specialized surgeons with a background in resident education. The wet lab will feature nationally recognized leaders with one-on-one wet lab mentorship.

We believe this program offers a unique opportunity for residents to gain hands-on experience on advanced anterior segment surgery techniques. We hope that you will select and encourage your 3rd-year residents (PGY-4) to attend this CME accredited program.

Sincerely,
Yousuf M. Khalifa, MD, and Madeline Yung, MD

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In animal models, sunitinib microparticles also reduced photoreceptor cell death,[56] and in a separate study, sunitinib had protective effects on retinal ganglion cells in an animal model of nonarteritic optic neuropathy.[57] Clinical trials involving sunitinib can be seen in Table 3, including trials in wet AMD, diabetes and retinal vein occlusion. A Phase I study showed tolerability of sunitinib (GB-102, Graybug vision), an injection formulated for twice-yearly dosing. However, there was evidence of migration of bioabsorbable particles into the anterior chamber in 28 percent of patients, which was self-limited.[58] A Phase IIb study (ALTISSIMO) of the drug versus aflibercept showed that the median time to rescue was five months for the GB-102 1 mg group. The lower dose was well-tolerated with mild-to-moderate adverse events. It was also noted that there was a decrease in injection frequency by 58 percent compared to before enrollment. The CST was comparable in both groups, while the BCVA showed lower numbers in the GB-102 arm by approximately nine ETDRS letters. This was speculated to be influenced by a number of patients within the study arm that either had prior poor response to anti-VEGF, or had ocular adverse events during the study, whether related or not to the microparticles.[59–61] With changes to the drug formulation in this phase, there were fewer cases of migration into the anterior chamber: <10 percent in the 1-mg arm.

At the conclusion of this initial "core study" of GB-102, an "extension study" was performed, with a six-month follow-up without additional treatment.[62] This included patients who didn't require additional therapy at the 12-month follow-up, of which 11 patients were in the GB-102 1-mg arm. Fifty-five percent of this arm retained a treatment duration of 12 months or longer, with stable BCVA and CST.[62] For those patients, the yearly injection burden was reduced by 73 percent. This led to the discontinuation of the work on GB-103, a second-generation formulation with a potential annual injection of the drug, which maintained active levels for five months in the retina and RPE/choroid, and thus supplementary five to six months relative to GB-102.[63] However, more recently, Graybug, now acquired by CalciMedica, stopped the development of GB-102.

• ***Vorolanib.*** Vorolanib is a small molecule TKI, based on the sunitinib scaffold, aiming for lower tissue accumulation.[64] It inhibits VEGFRs, PDGFR and cKIT, but not Tie2, and is used in multiple types of solid tumors.[64,65] Clinical trials with vorolanib in retinal pathology included an oral formulation, which will be discussed later, and in-office intravitreal injections using the sustained release Durasert platform (EYP-1901, EyePoint Pharmaceuticals). This platform can be found in other drug formulations (e.g., Yutiq and Iluvien), where in contrast to EYP-1901 for vorolanib, it's covered with a non-erodible polyimide shell.[66] The Durasert E used for vorolanib is biodegradable.

A Phase I study (DAVIO) on the safety of vorolanib (EYP-1901; Duravyu) in wet AMD, reported no drug-related adverse events, with

TABLE 3. CURRENT TRIALS INVOLVING SUNITINIB

Sunitinib	GB-102 (ADAGIO)[58]	GB-102 (ALTISSIMO)[59]	GB-102[102]
ID	NCT03249740	NCT03953079	NCT04085341
Phase	I/IIa	IIb	II
Mode of administration	Intravitreal, 27 ga.	Intravitreal, 27 ga.	Intravitreal, 27 ga.
Dose	Part 1: dose escalating (4 groups: 0.25, 0.5, 1, and 2 mg), single injection Part 2: low or high dose every six months	1 mg or 2 mg, baseline and at six months (2 mg discontinued after 1st injection and all switched to 1 mg)	1 mg or 2 mg, single injection
Control group	Part 2: Aflibercept every two months	Aflibercept every two months	None
Number of patients	32	56	21
Pathology	nAMD	nAMD	DME/RVO
Treated vs. tx-naive	Treated, at least 3 anti-VEGF, evidence of activity	Treated, at least 3 anti-VEGF	Treated, at least 3 anti-VEGF, evidence of response
Planned follow up	Phase I: 8 months Phase II: 12 months	12 months	6 months
Primary outcome	Phase I: adverse events Phase II: BCVA	Time to first rescue treatment	Adverse events
Secondary outcomes	Phase I: BCVA, subretinal thickness, retinal fluid, lesion and leakage area, rescue therapy, plasma sunitinib level, SHRM height Phase II: absence of fluid, BCVA loss or gain, adverse events, BCVA, plasma sunitinib level, subretinal thickness, rescue medication	Time till and number of times one rescue criterion is met, number of treatments, BCVA, BCVA < 20/200, CST, absence of exudation	BCVA, CST, and time to rescue
(Prelim) Results	No reported drug-related serious adverse events. 88 percent stayed on a single dose at 3 months, and 68 percent at 6 months. In 28 percent migration of bioabsorbable particles into AC (self-limited)	1mg dose was well tolerated. Median time to rescue (GB-102 group): 5 months 48/30 percent rescue-free at 6/12 months, respectively CST: comparable vs control BCVA: lower compared to control (by ~9 ETDRS letters)	3 cases of uveitis in the 2 mg group, other AE mentioned Decrease in BCVA in both groups

TABLE 4. CURRENT TRIALS INVOLVING VOROLANIB

Vorolanib	EYP-1901 (DAVIO)[68, 69]	EYP-1901 (DAVIO2)[70]	EYP-1901 (PAVIA)[71]
ID	NCT04747197	NCT05381948	NCT05383209
Phase	I	2	2
Mode of administration	Intravitreal, 22 ga.	Intravitreal, 22 ga.	Intravitreal, 22 ga.
Dose	Dose escalating (440, 1,060, 2,060 and 3,090 µg), single injection	2 groups: 2,060 µg and 3,090 µg, single injection	2 groups: 2,060 µg and 3,090 µg, single injection
Control group	None	Aflibercept 2 mg every 8 weeks	Sham
Number of patients	17 (16 at last follow up: 1 withdrew at week 16)	160	105
Pathology	nAMD	nAMD	Moderately severe to severe NPDR
Treated vs. tx-naive	Treated, at least 3 anti-VEGF, evidence of response	Treated, at least 2 anti-VEGF	Naïve
Planned follow up	48 weeks	56 weeks	48 weeks
Primary outcome	TEAE	BCVA	Improvement in DR
Secondary outcomes	BCVA and CST	BCVA, central retinal thickness, rescue injections	Improvement in DR, TEAE, diabetes-related vision threatening complications
(Prelim) Results	No reported TEAE Stable VA and CST Median time to rescue: 6.5 months 81%/50%/41%/31% rescue free at 3/6/9/12 months respectively	Active, not recruiting	Recruiting

stable CST and more than a 70-percent reduction in treatment burden at six and 12 months.[67–69] Phase II trials of this drug in wet AMD and moderately severe to severe NPDR are ongoing,[70,71] and are expected to start recruiting in diabetic macular edema.[72] Six-month results from a Phase II trial in nAMD (DAVIO2) showed noninferiority of Duravyu to aflibercept in the two dose groups and more than 80-percent decrease in treatment burden.[73] There was a favorable safety profile. The Phase III program for EYP-1901 for wet macular degeneration is planned to commence in the second half of 2024. Phase II trials are currently underway for the use of Durasert for NPDR and DME.

Other formulations of TKIs

Besides the aforementioned formulations of the TKI in the form of injections, sunitinib, pazopanib, and axitinib aqueously dispersed eye-drops were compared to aflibercept in an animal model of wet AMD.[77] They showed comparable efficacy to aflibercept in reducing the size of the CNV, and statistically significant efficacy relative to regular sunitinib eye drops. In contrast, a Phase II trial of an ophthalmic oily suspension of regorafenib, a TKI that targets VEGFRs, PDGFR, tie2, KIT and FGFR,[78] was terminated because of lack of efficacy, likely related to poor absorption of the drug into the back of the eye.[79,80] Despite promising results on CNV in animal models,[81] the prior eye-drop form of pazopanib, though well tolerated, showed a lack of efficacy at 12 months in wet AMD and the trial was terminated.[82,83]

Another trial comparing pazopanib drops with ranibizumab injections failed to demonstrate a benefit in reducing the injection burden with the former treatment.[84] Oral pazopanib, a TKI targeting VEGFRs, PDGF, cKIT and FGF,[85] was also studied in the treatment of AMD, and a Phase I trial showed tolerability of the drug and promising results.[86–88] However, it was limited by the length of the follow-up and the number of participants.

Oral vorolanib (X-82, CM082) has also been studied in wet AMD and myopic CNV,[89–93] and while there have been reductions in CST and CNV area, the trials have recorded systemic treatment-related adverse events.[94,95] Moreover, oral sunitinib, while potentially helpful in certain cases of peripapillary retinal capillary hemangioblastomas in von Hippel Lindau, resulted in multiple side effects that might limit its use in this formulation for retinal disease.[96]

It's also worth noting, however, that while rare, oral TKIs have been associated with ocular complications, including serous retinal detachment[97] and delayed healing in a case of rhegmatogenous retinal detachment with multiple tears following surgical repair.[98]

In conclusion, tyrosine kinase inhibitors are promising treatments for a multi-targeted approach to retinal disease. Targeting multiple receptors, and thus affecting common downstream responses, as well as their various sustained-release formulations can prove effective in prolonging the therapeutic effect and decreasing treatment burden in, among other diseases, exudative AMD, DME and retinal vein occlusion. ◀

The full bibliography is available in the online version of the article on reviewofophthalmology.com.

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eyes on EYECARE REVIEW of OPHTHALMOLOGY

A 78-year-old man presents with strobe lights and blurred vision in both eyes.

ERIC KIM, MD, NIKHIL BOMMAKANTI, MD, JORDAN DEANER, MD
PHILADELPHIA

Presentation

A 78-year-old Caucasian male presented to the Wills Eye Emergency Room after seeing "strobe lights" followed by progressively blurred vision in both eyes over a one-week period.

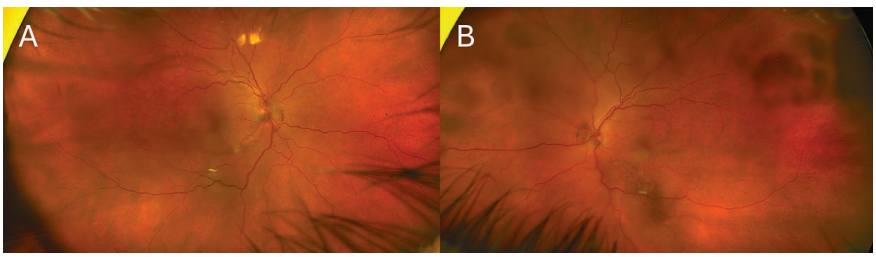

Figure 1. Ultra-widefield fundus photographs of right (A) and left (B) eyes at presentation showing bilateral multilobulated serous retinal detachments.

History

The patient's past ocular history was pertinent for a remote history of cataract surgery in both eyes. His medical history was notable for hyperlipidemia, hypothyroidism, gastroesophageal reflux disease, hypertension, spinal stenosis relieved after a lumbar laminectomy, chronic urinary tract infections and bladder incontinence. Previous investigation of his urinary symptoms revealed a high-grade urothelial carcinoma with lymph node involvement diagnosed one year before ophthalmic presentation. His urothelial cancer was treated with a right nephroureterectomy and three cycles of adjuvant chemotherapy with dose-dense methotrexate, vinblastine, doxorubicin and cisplatin (ddMVAC). He was most recently treated with a single dose of maintenance pembrolizumab therapy, just one month prior to presentation.

Review of systems was positive for tinnitus, low back pain and lower extremity edema. He denied trauma, photophobia, ocular pain, vitiligo, headache, scalp tenderness, jaw claudication and unintentional weight loss.

Initial Examination and Work-up

In the Eye Emergency Room, visual acuity was 20/40 in the right eye and 20/50 in the left. Intraocular pressures were within normal limits. Pupils were reactive with no relative afferent pupillary defect. Ishihara color plates were 6/8 in both eyes. Confrontational visual fields appeared to demonstrate a right homonymous hemianopia. Extraocular motility was full in both eyes without ptosis or proptosis.

Anterior segment examination revealed 2+ anterior chamber cell, a well-centered posterior chamber intraocular lens, and trace anterior vitreous cell OU. Dilated fundus examination revealed a posterior vitreous detachment, multilobulated subretinal fluid in the posterior pole and macular edema OU.

MRI brain and orbits with and without contrast showed mild microangiopathy without any optic nerve pathology, intracranial infarct or mass. Quantiferon gold and Treponemal antibody tests were negative. The patient was started on topical 1% prednisolone acetate six times daily to both eyes and referred to the retina service the next day.

Follow-up examination the next day remained unchanged. Pseudocolor ultra-widefield fundus images demonstrated a hazy media with serous retinal detachments OU *(Figure 1)*. Optical coherence tomography of the macula revealed a thickened choroid and multiple, loculated pockets of subretinal fluid OU and a bacillary layer detachment OD *(Figure 2)*. Fluorescein angiography demonstrated late leakage from the optic nerves, multifocal areas of pinpoint leakage, and pooling in the areas of subretinal fluid in both eyes *(Figure 3)*.

What's your diagnosis? What management would you pursue? The diagnosis appears on page 71.

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Diagnosis and Treatment

We diagnosed this patient with a Vogt-Koyanagi-Harada-like reaction secondary to pembrolizumab therapy for his urothelial carcinoma. Given the important role of pembrolizumab in controlling this patient's cancer we opted to control the ocular inflammation with local steroids, allowing the patient to continue his cancer immunotherapy without interruption.

A 0.7-mg intravitreal dexamethasone implant was placed into each eye. Two weeks later, visual acuity improved to 20/25 OD and remained stable at 20/50 OS. There was notable improvement in the anterior and posterior segment inflammation. On OCT there was resolution of the subretinal fluid and bacillary layer detachment *(Figure 4)*.

Discussion

We present a case of VKH-like syndrome following treatment of the patient's urothelial cancer with pembrolizumab which responded well to local steroid therapy, allowing the patient to continue his cancer therapy uninterrupted. A VKH-like syndrome is a known adverse effect of checkpoint inhibitors and has been reported after therapy with ipilimumab, nivolumab, cemiplimab and pembrolizumab.[1-4] Notably, upon review of the literature, this is the first case of VKH-like syndrome secondary to pembrolizumab therapy used in the treatment of urothelial cancer.

The body has intrinsic mechanisms to prevent autoimmunity, such as inhibitory receptors on T-cells that, when activated, lead to T-cell apoptosis.[5,6] Cancer cells can evade the immune system by activating these receptors, which include cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1). Immune checkpoint inhibitors (ICI) are a new class of medications that work by blocking these intrinsic down regulators of the immune system. Pembrolizumab is an ICI and is a monoclonal antibody targeted against PD-1, enhancing the ability of T-cells to detect and eliminate cancer cells. Cancer therapy with ICI has resulted in improved outcomes and survival for many kinds of cancers and are being used more frequently in oncology. However, upregulating the immune system can also lead to inadvertent autoimmunity, which results in immune-related adverse events (irAE).[7]

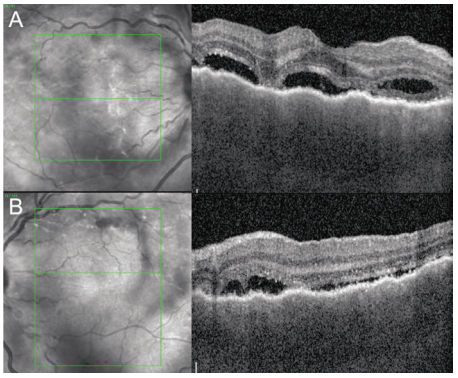

Figure 2. Enhanced-depth imaging optical coherence tomography of the macula of right (A) and left (B) eyes at presentation showing irregularly thickened choroid and subretinal fluid in both eyes and a bacillary detachment in the right eye.

IrAEs typically occur within weeks to months of initiating therapy, but can develop at any time, even after cessation. They most commonly involve the skin, gastrointestinal tract, liver and endocrine glands but can occur in any organ, including the eyes.[8,9] The incidence and type of irAEs varies greatly depending on the duration and dose of therapy, specific agent used and tumor type. Up to 70 percent of patients treated with a PD-1 or PD-L1 (the ligand that PD-1 binds) inhibitors experience irAEs; however, most of these irAEs are mild to moderate in severity.[10,11] Yet, severe and even fatal irAEs have been reported to occur in up to 2 percent of patients.[12,13] Fortunately, most irAEs can be successfully managed with corticosteroids.

Ocular side effects from ICIs occur in approximately 1 to 3 percent of patients and most commonly include dry eye, inflammatory uveitis and ocular myasthenia.[14-16] There have been relatively few reports of inflammatory orbitopathy, optic neuropathy, retinal vasculitis and VKH-like reactions.[17,18] VKH syndrome is an autoimmune condition with ocular, cutaneous and central nervous system manifestations that is believed to result from a T-cell-mediated response to melanocyte antigens.[19] A VKH-like syndrome in patients receiving ICIs (as in our patient) is thought to result from T-cell recognition of antigens of non-cancerous melanocytes.

Generally, ICI-related uveitis has been shown to respond

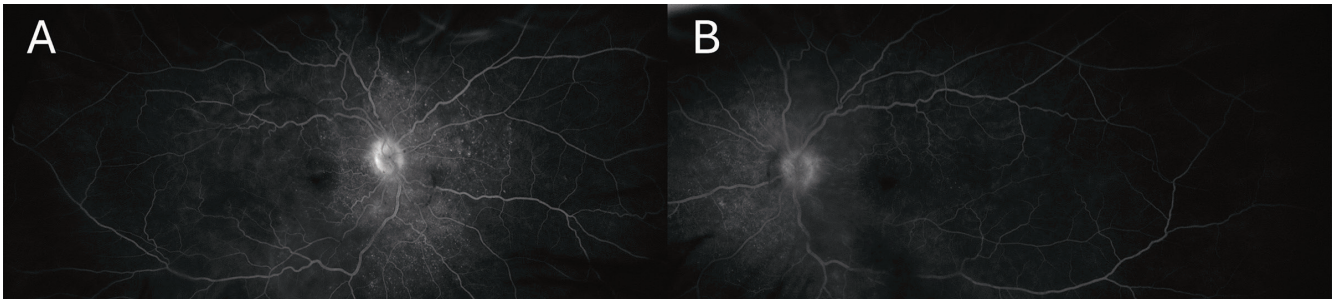

Figure 3. Late phase ultra-widefield fluorescein angiography of the right (A) and left (B) eyes revealing optic nerve leakage, multifocal areas of pinpoint leakage, and pooling in the areas of subretinal fluid in both eyes.

well to corticosteroids, but the preferred administration route varies based on type and severity of ocular inflammation as well as individual practice patterns. Immunotherapy toxicity is staged using the Common Terminology Criteria for Adverse Events (CTCAE):[20] Grades 1 and 2 consist of anterior uveitis with trace and 1-2+ cell, respectively. Grade 3 denotes anterior uveitis with 3+ cell or intermediate, posterior or panuveitis. Grade 4 is reserved for uveitis causing significant vision loss, visual acuity <20/200.

Major oncology guidelines suggest cautious continuation of ICI in Grade 1 and temporary cessation in Grade 2 until inflammation reverts to Grade 1. While most agree with permanent discontinuation of ICI and initiation of systemic corticosteroids in Grade 4 toxicity, the management of Grade 3 events is less clear.[21]

In a large review of 126 patients with ICI-related uveitis, ICIs were suspended in 11.4 percent and discontinued in 51.4 percent of patients. Topical corticosteroids were the sole treatment in 36.9 percent of cases while 53.2 percent of patients required systemic corticosteroids.[22] Yet, in a separate case series of eight patients, all patients (three of which had Grade 3 inflammation) were successfully treated using topical steroids without cessation of immunotherapy.[23] As ophthalmologists, having several ways to administer corticosteroids locally, including via a topical, sub-Tenon's, suprachoroidal or intravitreal approach, may allow for a more nuanced strategy to treat moderate to severe inflammation while avoiding temporary or permanent discontinuation of potentially lifesaving ICIs. We prefer this to systemic corticosteroid treatment given the possibility of systemic immunosuppression interfering with immunotherapy and the increased risk for opportunistic infections.[4]

In conclusion, we present a case of VKH-like syndrome secondary to pembrolizumab therapy used in the treatment of urothelial cancer with great response to local steroids. This case highlights the importance of taking a thorough history and screening medications in patients with uveitis, especially for medications associated with uveitis like immune checkpoint inhibitors. Additionally, our case highlights the important role of local steroids in these cases, allowing for good control of inflammation and continuation of the patient's cancer therapy which can be life prolonging or lifesaving. ◀

Dr. Deaner has the following disclosures outside of the submitted work: Consultant for Alimera, EyePoint, Regeneron, and Genentech.

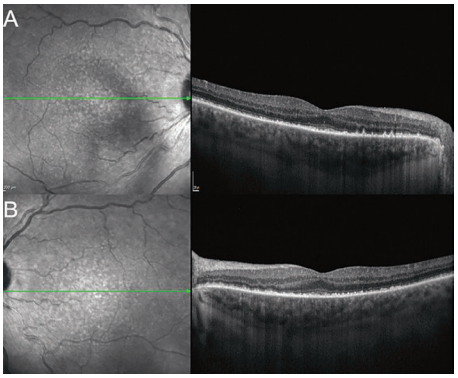

Figure 4. Enhanced depth imaging optical coherence tomography of the macula of right (A) and left (B) eyes showing improvement in choroidal thickening and resolution of the subretinal fluid and bacillary layer detachments after placement of a 0.7-mg dexamethasone implant into each eye.

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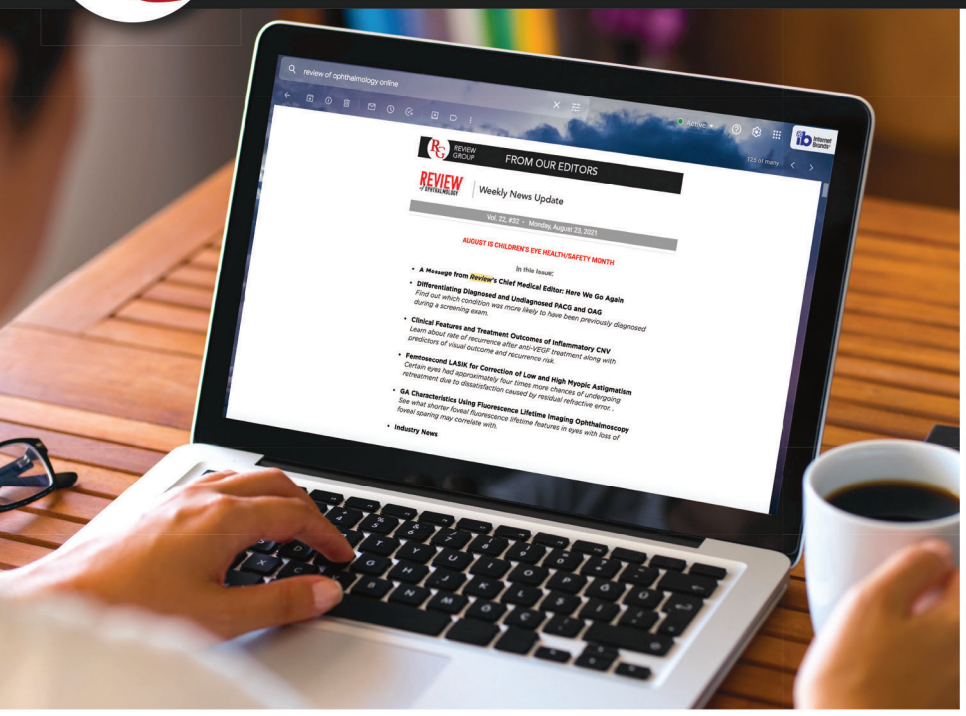

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REVIEW GROUP FROM OUR EDITORS

REVIEW of OPHTHALMOLOGY | Weekly News Update

Vol. 25, #33 • Monday, August 19, 2024

AUGUST IS CHILDREN'S EYE HEALTH/SAFETY MONTH

In this Issue:

- **Corneal Epithelial Damage Findings After Switching from Concomitant Use of Brinzolamide and Brimonidine to Fixed-dose Combination**
  Find out if the fixed-dose combination had efficacy.
- **Effect of Brolucizumab and Aflibercept on Maximum Thickness of PEDs and sub-RPE fluid, in HAWK and HARRIER**
  Learn which agent achieved greater reductions in pigment epithelium fluid and sub-retinal pigment epithelium fluid thickness.
- **Outcomes of Donor Corneas of Different Thicknesses from Endothelial Keratoplasty in DALK for Keratoconus**
  Find out if there was parity among the corneas.
- **Digital Histology of Retinal Microaneurysms as Provided by Dense B-scan (DART) OCTA: Relevance in DR**
  Researchers determined that Dense Automatic-RealTime OCTA technology provided several new insights on retinal microaneurysm characteristics and their blood flow network connectivity.
- **Industry News**

Corneal Epithelial Damage Findings After Switching from Concomitant Use of Brinzolamide and Brimonidine to Fixed-dose Combination

Researchers assessed the effectiveness of switching from the concomitant use of brinzolamide 1% (BZM) and brimonidine 0.1% (BMD) to a BZM/BMD fixed-dose combination (BBFC) for the reduction of corneal epithelial damage.

The retrospective cohort study involved 52 eyes of 52 glaucoma patients (26 women, 26 men; mean

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SYFOVRE® (pegcetacoplan injection), for intravitreal use
BRIEF SUMMARY OF PRESCRIBING INFORMATION
Please see SYFOVRE full Prescribing Information for details.

INDICATIONS AND USAGE

SYFOVRE is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

CONTRAINDICATIONS

Ocular or Periocular Infections
SYFOVRE is contraindicated in patients with ocular or periocular infections.
Active Intraocular Inflammation
SYFOVRE is contraindicated in patients with active intraocular inflammation.

WARNINGS AND PRECAUTIONS

Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with SYFOVRE, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering SYFOVRE in order to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.
Retinal Vasculitis and/or Retinal Vascular Occlusion
Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of SYFOVRE. Cases may occur with the first dose of SYFOVRE and may result in severe vision loss. Discontinue treatment with SYFOVRE in patients who develop these events. Patients should be instructed to report any change in vision without delay.
Neovascular AMD
In clinical trials, use of SYFOVRE was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (12% when administered monthly, 7% when administered every other month and 3% in the control group) by Month 24. Patients receiving SYFOVRE should be monitored for signs of neovascular AMD. In case anti-Vascular Endothelial Growth Factor (anti-VEGF) is required, it should be given separately from SYFOVRE administration.
Intraocular Inflammation
In clinical trials, use of SYFOVRE was associated with episodes of intraocular inflammation including: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, and anterior chamber flare. After inflammation resolves patients may resume treatment with SYFOVRE.
Increased Intraocular Pressure
Acute increase in IOP may occur within minutes of any intravitreal injection, including with SYFOVRE. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

ADVERSE REACTIONS

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 the clinical trials of another drug and may not reflect the rates observed in practice.
A total of 839 patients with GA in two Phase 3 studies (OAKS and DERBY) were treated with intravitreal SYFOVRE, 15 mg (0.1 mL of 150 mg/mL solution). Four hundred nineteen (419) of these patients were treated in the affected eye monthly and 420 were treated in the affected eye every other month. Four hundred seventeen (417) patients were assigned to sham.
The most common adverse reactions (≥5%) reported in patients receiving SYFOVRE were ocular discomfort, neovascular age-related macular degeneration, vitreous floaters, and conjunctival hemorrhage.

Table 1: Adverse Reactions in Study Eye Reported in ≥2% of Patients Treated with SYFOVRE Through Month 24 in Studies OAKS and DERBY

Adverse Reactions	PM (N = 419) %	PEOM (N = 420) %	Sham Pooled (N = 417) %
Ocular discomfort*	13	10	11
Neovascular age-related macular degeneration*	12	7	3
Vitreous floaters	10	7	1
Conjunctival hemorrhage	8	8	4
Vitreous detachment	4	6	3
Retinal hemorrhage	4	5	3
Punctate keratitis*	5	3	<1
Posterior capsule opacification	4	4	3
Intraocular inflammation*	4	2	<1
Intraocular pressure increased	2	3	<1

PM: SYFOVRE monthly; PEOM: SYFOVRE every other month
*The following reported terms were combined:
Ocular discomfort included: eye pain, eye irritation, foreign body sensation in eyes, ocular discomfort, abnormal sensation in eye
Neovascular age-related macular degeneration included: exudative age-related macular degeneration, choroidal neovascularization
Punctate keratitis included: punctate keratitis, keratitis
Intraocular inflammation included: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, anterior chamber flare

Endophthalmitis, retinal detachment, hyphema and retinal tears were reported in less than 1% of patients. Optic ischemic neuropathy was reported in 1.7% of patients treated monthly, 0.2% of patients treated every other month and 0.0% of patients assigned to sham. Deaths were reported in 6.7% of patients treated monthly, 3.6% of patients treated every other month and 3.8% of patients assigned to sham. The rates and causes of death were consistent with the elderly study population.

Postmarketing Experience
The following adverse reactions have been identified during postapproval use of SYFOVRE. 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. Eye disorders: retinal vasculitis with or without retinal vascular occlusion.

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary
There are no adequate and well-controlled studies of SYFOVRE administration in pregnant women to inform a drug-associated risk. The use of SYFOVRE may be considered following an assessment of the risks and benefits.
Systemic exposure of SYFOVRE following ocular administration is low. Subcutaneous administration of pegcetacoplan to pregnant monkeys from the mid gestation period through birth resulted in increased incidences of abortions and stillbirths at systemic exposures 1040-fold higher than that observed in humans at the maximum recommended human ophthalmic dose (MRHOD) of SYFOVRE (based on the area under the curve (AUC) systemically measured levels). No adverse maternal or fetal effects were observed in monkeys at systemic exposures approximately 470-fold higher than that observed in humans at the MRHOD.
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.
Lactation
Risk Summary
It is not known whether intravitreal administered pegcetacoplan is secreted in human milk or whether there is potential for absorption and harm to the infant. Animal data suggest that the risk of clinically relevant exposure to the infant following maternal intravitreal treatment is minimal. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when SYFOVRE is administered to a nursing woman.
Females and Males of Reproductive Potential
Contraception
Females: It is recommended that women of childbearing potential use effective contraception methods to prevent pregnancy during treatment with intravitreal pegcetacoplan. Advise female patients of reproductive potential to use effective contraception during treatment with SYFOVRE and for 40 days after the last dose. For women planning to become pregnant, the use of SYFOVRE may be considered following an assessment of the risks and benefits.
Pediatric Use
The safety and effectiveness of SYFOVRE in pediatric patients have not been established.
Geriatric Use
In clinical studies, approximately 97% (813/839) of patients randomized to treatment with SYFOVRE were ≥ 65 years of age and approximately 72% (607/839) were ≥ 75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies. No dosage regimen adjustment is recommended based on age.

PATIENT COUNSELING INFORMATION

Advise patients that following SYFOVRE administration, patients are at risk of developing endophthalmitis, retinal detachments, retinal vasculitis with or without retinal vascular occlusion and neovascular AMD. If the eye becomes red, sensitive to light, painful, or if a patient develops any change in vision such as flashing lights, blurred vision or metamorphopsia, instruct the patient to seek immediate care from an ophthalmologist. Patients may experience temporary visual disturbances associated either with the intravitreal injection with SYFOVRE or the eye examination. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

Manufactured for:
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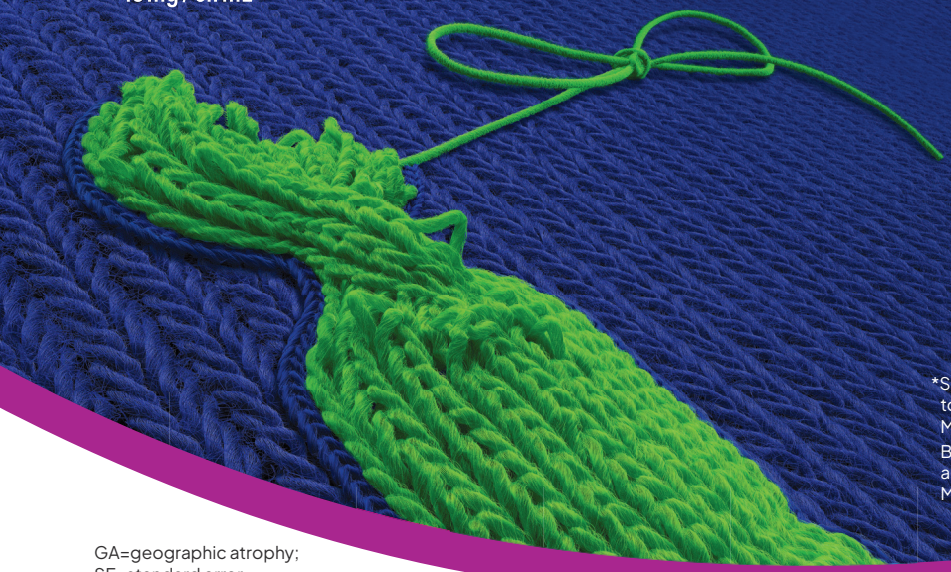
SYF-PI-30NOV2023-2.0

12/23 US-PEGGA-2200163 v4.0

SYFOVRE®
(pegcetacoplan injection)
15 mg / 0.1 mL



GA unravels so much
SAVE RETINAL TISSUE BY SLOWING PROGRESSION[1-3]

SYFOVRE achieved continuous reductions in mean lesion growth rate* vs sham pooled from baseline to Month 24[1,4]

Monthly	Every Other Month (EOM)
OAKS trial (mm^2): (3.11 vs 3.98) **22%**	OAKS trial (mm^2): (3.26 vs 3.98) **18%**
DERBY trial (mm^2): (3.28 vs 4.00) **18%**	DERBY trial (mm^2): (3.31 vs 4.00) **17%**

SE in trials (monthly, EOM, sham pooled): OAKS: 0.15, 0.13, 0.14; DERBY: 0.13, 0.13, 0.17.

*Slope for baseline to Month 24 is an average of slope of baseline to Month 6, Month 6 to Month 12, Month 12 to Month 18, and Month 18 to Month 24.[1]

Based on a mixed effects model for repeated measures assuming a piecewise linear trend in time with knots at Month 6, Month 12, and Month 18.[1]

GA=geographic atrophy;
SE=standard error.

Explore the long-term data

The CMS-assigned permanent J-code for SYFOVRE is J2781—effective 10/1/23[1]

INDICATION

SYFOVRE® (pegcetacoplan injection) is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- SYFOVRE is contraindicated in patients with ocular or periocular infections, and in patients with active intraocular inflammation

WARNINGS AND PRECAUTIONS

- **Endophthalmitis and Retinal Detachments**
  - Intravitreal injections, including those with SYFOVRE, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering SYFOVRE to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.
- **Retinal Vasculitis and/or Retinal Vascular Occlusion**
  - Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of SYFOVRE. Cases may occur with the first dose of SYFOVRE and may result in severe vision loss. Discontinue treatment with SYFOVRE in patients who develop these events. Patients should be instructed to report any change in vision without delay.
- **Neovascular AMD**
  - In clinical trials, use of SYFOVRE was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (12% when administered monthly, 7% when administered every other month and 3% in the control group) by Month 24. Patients receiving SYFOVRE should be monitored for signs of neovascular AMD. In case anti-Vascular Endothelial Growth Factor (anti-VEGF) is required, it should be given separately from SYFOVRE administration.
- **Intraocular Inflammation**
  - In clinical trials, use of SYFOVRE was associated with episodes of intraocular inflammation including: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, and anterior chamber flare. After inflammation resolves, patients may resume treatment with SYFOVRE.
- **Increased Intraocular Pressure**
  - Acute increase in IOP may occur within minutes of any intravitreal injection, including with SYFOVRE. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

ADVERSE REACTIONS

- Most common adverse reactions (incidence ≥5%) are ocular discomfort, neovascular age-related macular degeneration, vitreous floaters, conjunctival hemorrhage.

Please see Brief Summary of Prescribing Information for SYFOVRE on the adjacent page.

Trial Design: SYFOVRE safety and efficacy were assessed in OAKS (N=637) and DERBY (N=621), multi-center, 24-month, Phase 3, randomized, double-masked trials. Patients with GA (atrophic nonexudative age-related macular degeneration), with or without subfoveal involvement, secondary to AMD were randomly assigned (2:2:1:1) to receive 15 mg/0.1 mL intravitreal SYFOVRE monthly, SYFOVRE EOM, sham monthly, or sham EOM for 24 months. Change from baseline in the total area of GA lesions in the study eye (mm^2) was measured by fundus autofluorescence (FAF).[1,4]

References: 1. SYFOVRE (pegcetacoplan injection) [package insert]. Waltham, MA: Apellis Pharmaceuticals, Inc.; 2023. **2.** Pfau M, von der Emde L, de Sisternes L, et al. Progression of photoreceptor degeneration in geographic atrophy secondary to age-related macular degeneration. *JAMA Ophthalmol*. 2020;138(10):1026–1034. **3.** Bird AC, Phillips RL, Hageman GS. Geographic atrophy: a histopathological assessment. *JAMA Ophthalmol*. 2014;132(3):338–345. **4.** Data on file. Apellis Pharmaceuticals, Inc.

Apellis

From the makers of the #1-prescribed dry eye brand in Europe*

Covering the spectrum of Dry Eye Relief

Over-the-counter iVIZIA® lubricant eye drops protect the ocular surface and deliver a unique combination of immediate and long-lasting relief in a **preservative-free** formulation.

- A unique formulation–including povidone (active), trehalose (inactive), and hyaluronic acid (inactive)
- Proprietary, **multi-dose preservative-free (MDPF) bottle**

Safe for use with contact lenses‡

Chronic Dry Eye Patient Usage Study†:

Up to
8 hours
of relief

as well as improved comfort during computer work, reading, and driving[1]

84%

of users reported iVIZIA worked better than their previous eye drops[1]

Recommend iVIZIA and request samples by visiting iVIZIA.com/ECP

Scan here.

*Prescription market data, Dec. 2022 – S01K without cyclosporine.
†In a chronic dry eye patient usage study, participants from a variety of socioeconomic backgrounds answered questions about their experience with iVIZIA lubricant drops. In the study, 203 chronic dry eye patients, 28-80 years old, switched from their dry eye artificial tears to iVIZIA for a month.[1]
‡To limit blurriness when using contact lenses, remove contacts, apply drops, then insert contacts.

Reference: 1. Thea Data on File.

Thea
let's open our eyes