Wills Eye Resident Series: A case of worsening vision and fluctuating IOP, *p. 87*

REVIEW of OPHTHALMOLOGY®

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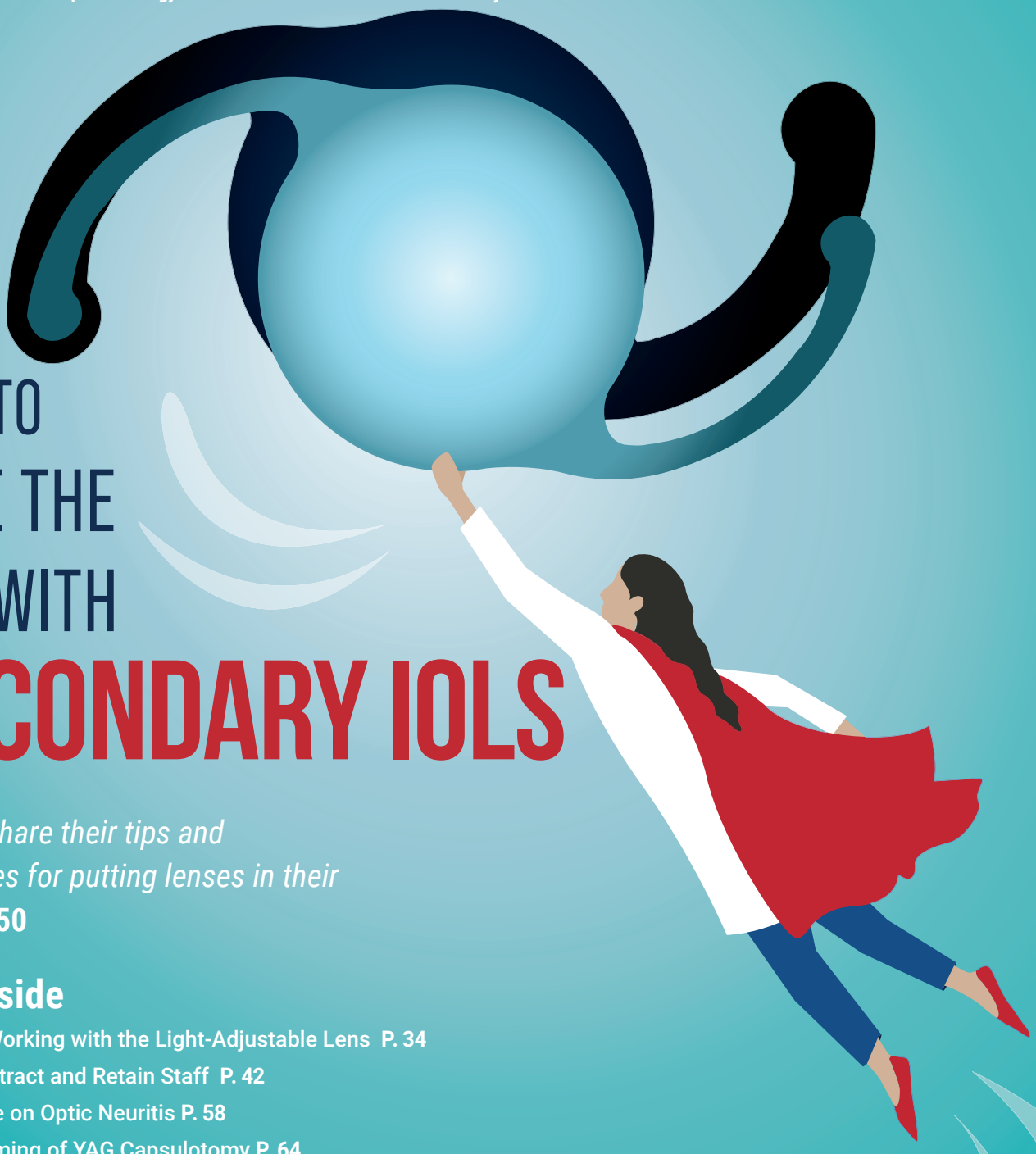

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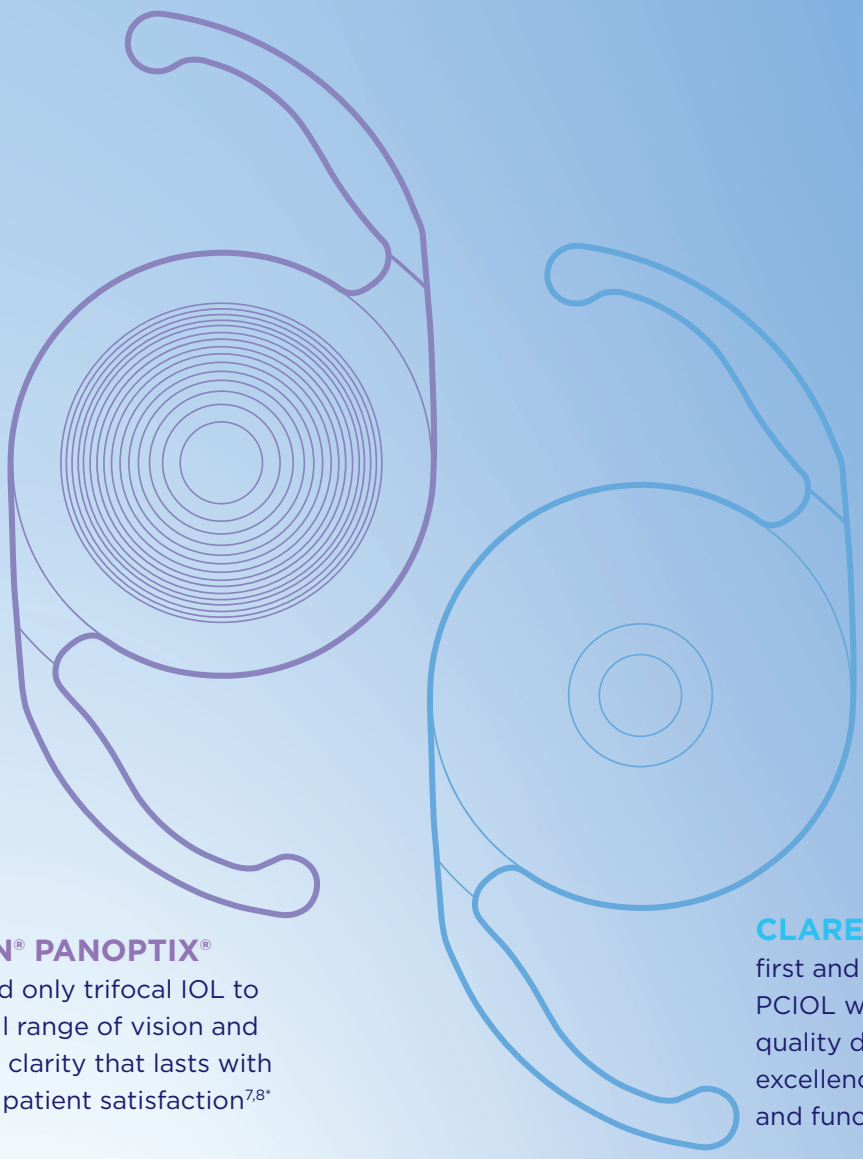

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REFERENCES: 1. Market Scope 2023 Premium Cataract Surgery. **2** Alcon, Data on File, 2022. **3**. Alcon, Data on file 2024. **4**. Oshika T, Fujita Y, Inamura M, Miyata K. Mid-term and long-term clinical assessments of a new 1-piece hydrophobic acrylic IOL with hydroxyethyl methacrylate. *J Cataract Refract Surg*. 2020 May;46(5):682-687. **5**. Maxwell A, Suryakumar R. Long-term effectiveness and safety of a three-piece acrylic hydrophobic intraocular lens modified with hydroxyethyl-methacrylate: an open-label, 3-year follow-up study. *Clin Ophthalmol*. 2018;12:2031-2037. **6**. Clareon® Vivity® Extended Vision Hydrophobic IOL (CNWET0) Directions for Use – US. **7**. Clareon® PanOptix® Trifocal Hydrophobic Acrylic IOL Model: CNWTT0 DFU. **8**. Lehmann R, Maxwell A, Lubeck DM, Fong R, Walters TR, Fakadej A. Effectiveness and Safety of the Clareon® Monofocal Intraocular Lens: Outcomes from a 12-Month Single-Arm Clinical Study in a Large Sample. *Clin Ophthalmol*. 2021;15:1647-1657. Published 2021 Apr 20.

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VOLUME XXXI • NO. 10
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Study Delves into the Risk Factors for Broken Capsules

Modern cataract surgery is extremely safe, but the sheer volume of procedures performed—roughly four million each year in the United States alone—means that adverse events will affect a sizable number of people. As the intraoperative complication of posterior capsular rupture can negatively impact final visual outcome for patients, researchers and clinicians alike would like to know what risk factors are present for PCR during cataract surgery.

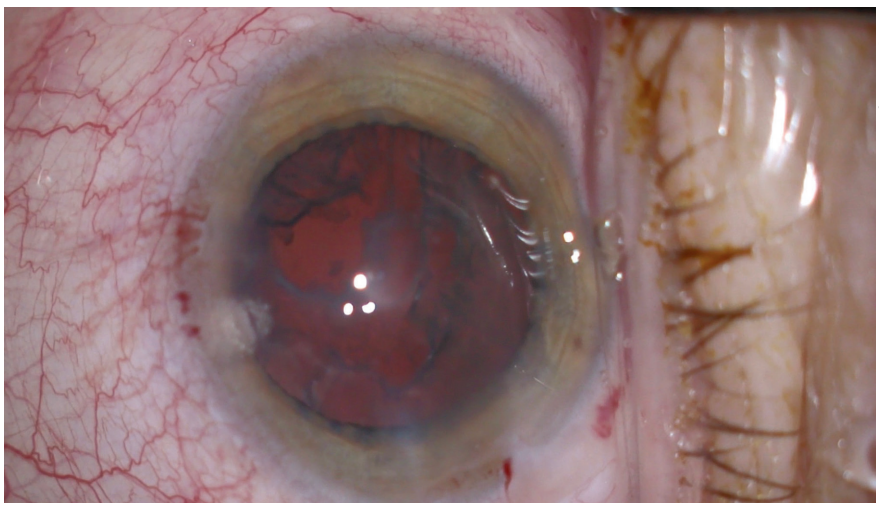
A shallow anterior chamber depth of <2.2 mm was associated with increased PCR rates, possibly due to iris prolapse being more common, thus surgeons making longer tunnels and increasing corneal distortion and impairing visualization, or more directly increasing proximity of instruments to the posterior capsule in a shallow anterior chamber.

Included in a new investigation were eligible operations from centers supplying data to the U.K. national cataract audit with complete data, including patients' sex, age at surgery, anterior chamber depth and preoperative visual acuity. A model was designed to identify risk factors and calculated the odds ratios of factors on PCR likelihood. Results were recently published in the British journal *Eye*.[1]

A significant 961,208 cataract operations were included, performed on 682,381 patients from 136 different centers and with 3,198 different surgeons. Only 1.01 percent of these surgeries had PCR occur, with a median age of 75.7 for the first eye surgery and 76.7 for the second among affected patients. Of those who had PCR occur, 53 percent were women. The highest risk factors for PCR included a less experienced trainee surgeon, pseudoexfoliation/phacodonesis, younger men and brunescent/white/mature cataract. Other identified risk factors were glaucoma, worse preoperative visual acuity, previous intravitreal therapy, high myopia, previous vitrectomy, systemic diabetes, diabetic retinopathy, amblyopia, older age, shallower anterior chamber depth and an inability to lie flat and cooperate.

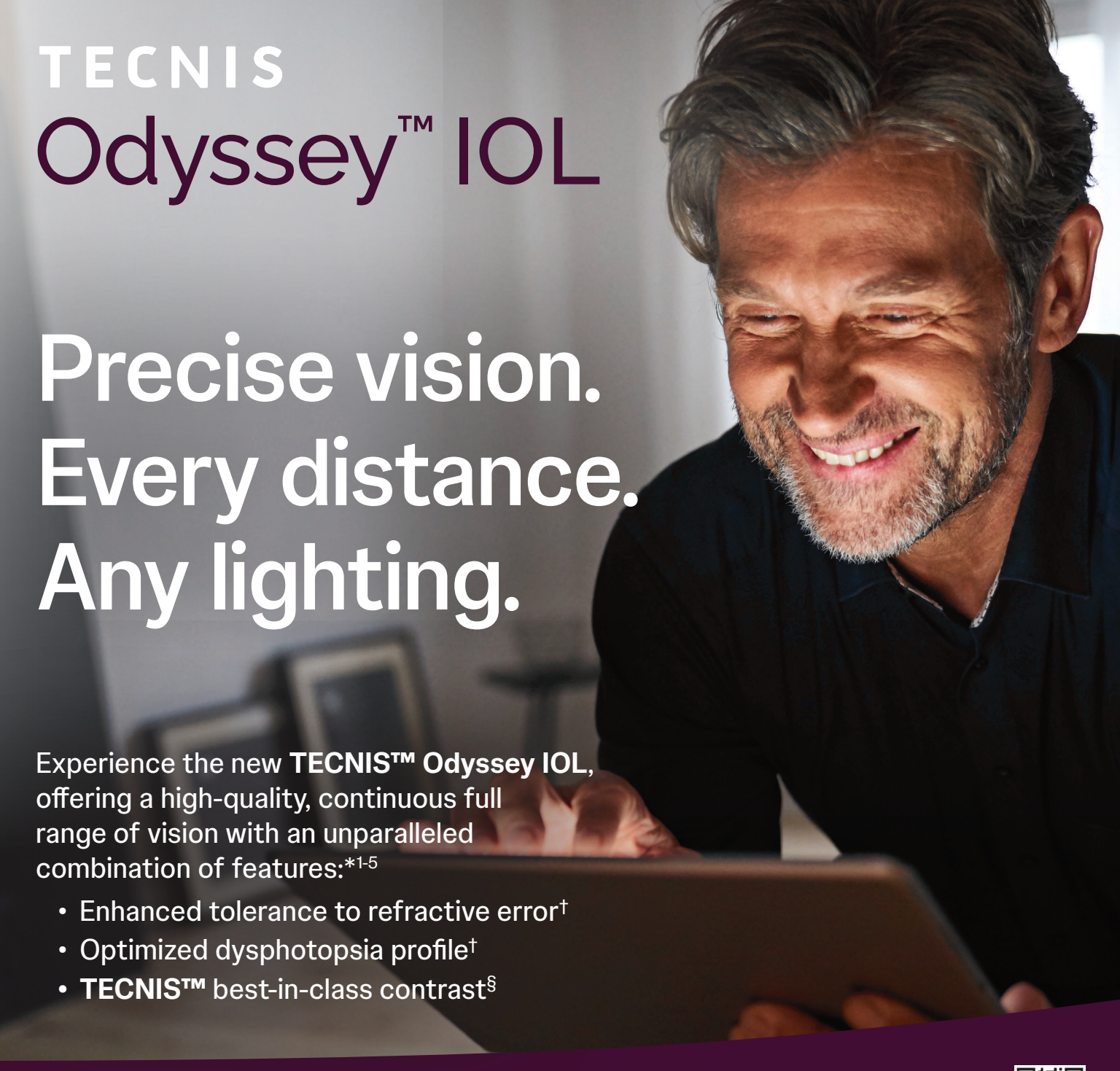
As part of their discussion, the study authors relay that these findings confirmed previously known risk factors of increasing age, trainee surgeon, male sex, inability to lie flat and cooperate, systemic diabetes, diabetic retinopathy, smaller pupil size, mature cataract, glaucoma and pseudoexfoliation/phacodonesis, with corroboration of more recently reported risk factors, too, of previous intravitreal anti-VEGF therapy and worse preoperative visual acuity. What's more interesting are the novel risk factors identified of high myopia, previous vitrectomy, shallow anterior chamber depth and amblyopia.

They elaborate more on individual risk factors, stating that one of the highest odds ratios was in younger men; however, they note that the age/sex interaction term diminished this ratio in older patients, with similar risk in sexes by age 85, and even a switch of women having greater risk after 90 years of age.



Douglas Grayson, MD

Investigators from the United Kingdom have identified possible novel risk factors for posterior capsular rupture during cataract surgery.



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The authors theorize that the novel risk factor of high myopia might affect PCR by a longer axial length making surgery more challenging, but previous literature hasn't found an association between axial length specifically and PCR, thus suggesting other mechanisms at play, like higher cataract density.

Those who had a pervious vitrectomy may have had higher PCR risk due to altered fluid dynamics, unstable posterior capsules or posterior lenticular touch during vitrectomy, with the underlying increased PCR risk in these eyes potentially overlapping with high myopia, since the two possess a strong correlation.

Generally, the authors convey that "this analysis provides an update to the current risk adjustment model for PCR with the quantification of additional risk factors."

As they explain, this information "will facilitate a bespoke, contemporary risk assessment tailored to an individual patient's operation, thereby allowing more informed patient counseling, appropriate case allocation and adoption of precautionary measures to minimize the risk of posterior capsular rupture during surgery."

1. Sim PY, Donachie PHJ, Day AC, Buchan JC. The Royal College of Ophthalmologists' National Ophthalmology Database study of cataract surgery: A risk factor model for posterior capsule rupture. Eye (Lond). September 19, 2024 [Epub ahead of print].

First Whole-eye Transplant at One Year

In *JAMA*, surgeons at NYU Langone Health in New York City recently provided an update on the first whole-eye transplant that they performed a year ago.[1]

In their paper, the surgeons note that whole-eye transplantation has been stymied in the past "by a lack of microsurgical techniques for vascular anastomosis and a modern understanding of immunosuppression leading to transplant failures." They add that there hasn't been a workable surgical approach to such transplants, and that "retinal ischemia/reperfusion, and absence of optic nerve regeneration with restoration of oculocortical-visual pathways have remained substantial impediments to whole eye transplant."

They say that recent studies, however, have explored the concept of whole eye transplant in the context of craniofacial transplant, adding that, "Vascularized composite allotransplantation (VCA) has revolutionized the paradigm of craniofacial reconstruction by recapitulating the lost anatomic and functional units that otherwise are insufficiently addressed with conventional reconstructive techniques."

It's with this VCA technique that they approached the treatment of a 46-year-old patient who had unfortunately sustained a high-voltage electrical injury in June 2021, resulting in loss of his left eye, left eyelid, nose, lips, and a large volume of facial tissue including skin and mimetic musculature.[1]

The patient ultimately underwent a combined whole eye and face transplant from a compatible donor with primary optic nerve coaptation and conventional postoperative immunosuppression. The physicians say that, per fluorescein angi-

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ography, globe and retinal perfusion were maintained throughout the immediate postoperative period.

Optical coherence tomography showed atrophy of the inner retinal layers and attenuation and disruption of the ellipsoid zone. Serial electroretinography confirmed retinal responses to light in the transplanted eye. The surgeons say that structural and functional magnetic resonance imaging demonstrated the integrity of the transplanted visual pathways and potential occipital cortical response to light stimulation of the transplanted eye. At one year post transplant (postoperative day 366), there was no perception of light in the transplanted eye, the physicians say.

"The globe transplant remained viable in the context of a face transplant including orbital bony anatomy," the surgeons say in their paper, "although with time and greater understanding, there may be potential for isolated globe transplant."

1. Ceradini DJ, Tran DL, Dedania VS, et al. Combined whole eye and face transplant: Microsurgical strategy and 1-year clinical course. JAMA. September 9, 2024 [Epub ahead of print].

Combined Treatment for PDR: Sequence Matters

Initial treatment of patients with proliferative diabetic retinopathy often involves a combined approach using panretinal photocoagulation and anti-VEGF injections. Large randomized clinical trials usually prefer monotherapy, limiting the information available on the outcomes of combined treatment approaches and whether the sequence of PRP and anti-VEGF therapy has an effect. A new study published in *JAMA Ophthalmology* aimed to close this research gap by comparing the need for pars plana vitrectomy among patients treated with PRP first then anti-VEGF injections and vice versa.

The retrospective cohort study included more than 3,000 patients with new PDR diagnoses from the TriNetX EHR network, stratified by therapy with PRP and subsequent anti-VEGF or anti-VEGF and subsequent PRP. While the primary outcome was the need for PPV, secondary outcomes included incidence of PPV, vitreous hemorrhage or tractional retinal detachment. After propensity score matching, which controlled for baseline demographic characteristics and medical comorbidities, there were 1,377 patients in each of the two treatment groups. The average age was 63 years in both groups, and the sex ratio was nearly 50:50.

The results showed that patients in the PRP-first group demonstrated a higher risk of needing PPV over the course of five years compared to those in the anti-VEGF-first group, with similar associations at six months, one year and three years. This group also had higher rates of vitreous hemorrhage and tractional retinal detachment at the same four time points.

"While combined therapy for the treatment of PDR has

(Continued on p. 12)

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INDICATIONS AND USAGE

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IMPORTANT SAFETY INFORMATION:

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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.

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DEPARTMENTS

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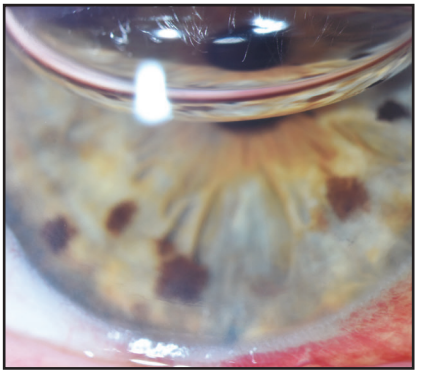

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WARNINGS: Careful preoperative evaluation and sound clinical judgment should be used by the surgeon to decide the risk/benefit ratio before implanting an IOL in a patient with any of the conditions described in the Light Adjustable Lens and LDD Professional Use Information document. Caution should be used in patients with eyes unable to dilate to a pupil diameter of ≥ 7 mm to ensure that the edge of the Light Adjustable Lens can be visualized during LDD light treatments; patients who the doctor believes will be unable to maintain steady fixation that is necessary for centration of the LDD light treatment; patients with sufficiently dense cataracts that preclude examination of the macula as patients with preexisting macular disease may be at increased risk for macular disease progression; and patients at high risk for future vitreoretinal disease that may require silicone oil as part of therapy. The Light Adjustable Lens must be implanted in the correct orientation with the back layer facing posteriorly.

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ADVERSE EVENTS: The most common adverse events (AEs) reported in the randomized pivotal trial included cystoid macular edema (3 eyes, 0.7%), hypopyon (1 eye, 0.2%), and endophthalmitis (1 eye, 0.2%). The rates of AEs did not exceed the rates in the ISO historical control except for the category of secondary surgical interventions (SSI); 1.7% of eyes (7/410) in the Light Adjustable Lens group had an SSI ($p < .05$). AEs related to the UV light from the LDD include phototoxic retinal damage causing temporary loss of best spectacle corrected visual acuity (1 eye, 0.2%), persistent induced tritan color vision anomaly (2 eyes, 0.5%), persistent induced erythropsia (1 eye, 0.3%), reactivation of ocular herpes simplex Infection (1 eye, 0.3%), and persistent unanticipated significant increase in manifest refraction error (≥ 1.0 D cylinder or MRSE) (5 eyes, 1.3%).

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RxSIGHT

(Continued from p. 7)

gained popularity in clinical practice, as shown by the ASRS PAT surveys, if this study's approach is considered, it is unknown if the order of treatment modalities affects outcomes," the researchers explained in their paper. They cited one previous study that found "PRP after intravitreal conbercept injections (Lumitin; Kanghong Biotechnology) was associated with a reduced number of subsequent anti-VEGF injections compared with eyes treated with PRP before intravitreal conbercept at two years [six vs. 8.5 injections], despite no difference in visual and anatomic outcomes between cohorts."

Furthermore, in the present study, which used a large, heterogenous, real-world database of matched patients with proliferative diabetic retinopathy, "administration of PRP first was associated with an increased risk of undergoing PPV, as well as developing vitreous hemorrhage and tractional retinal detachment, compared with anti-VEGF injection [first]," the study authors wrote.

Study co-author Amer Fadel Alsoudi, MD, has some thoughts on what's behind the results. "Combined treatment is preferred practice among ophthalmologists across the world (supported by ASRS PAT surveys and real world practice)," he says, "with some evidence to support better outcomes than monotherapy (though no study that directly compares combined treatment with monotherapy). We recently published that monotherapy anti-VEGF may have improved outcomes than monotherapy PRP in a select cohort of patients. It's perhaps the VEGF sequestration with anti-VEGF therapy that facilitates successful PRP and prevention of PDR complications."

While the literature on this topic is growing, they caution that further research is still warranted to determine the optimal order of panretinal photocoagulation and anti-VEGF injections for treating proliferative diabetic retinopathy, especially considering the increasing popularity of this combined approach.

Dr. Alsoudi notes what actualy surprised him about the results. "[I was surprised by] the magnitude of difference regarding outcomes secondary to the order of treatment that remained significant at every time point observed," he says. "When we ask questions in science, we often don't expect results that support or reject our hypothesis—rather to better inform the public one way or the other. When we find a signal that hasn't been explained yet, we're surprised.

In terms of limitations, Dr. Alsoud notes that, "Without belaboring the point, de-identified large database studies that require accurate clinical coding are limited by the possibility of inaccurate coding—though physician compensation is reliant on accurate coding." ◀

1. Alsoudi AF, Wai KM, Koo E, et al. Initial therapy of panretinal photocoagulation vs anti-VEGF injection for proliferative diabetic retinopathy. JAMA Ophthalmol. August 29, 2024 [Epub ahead of print].

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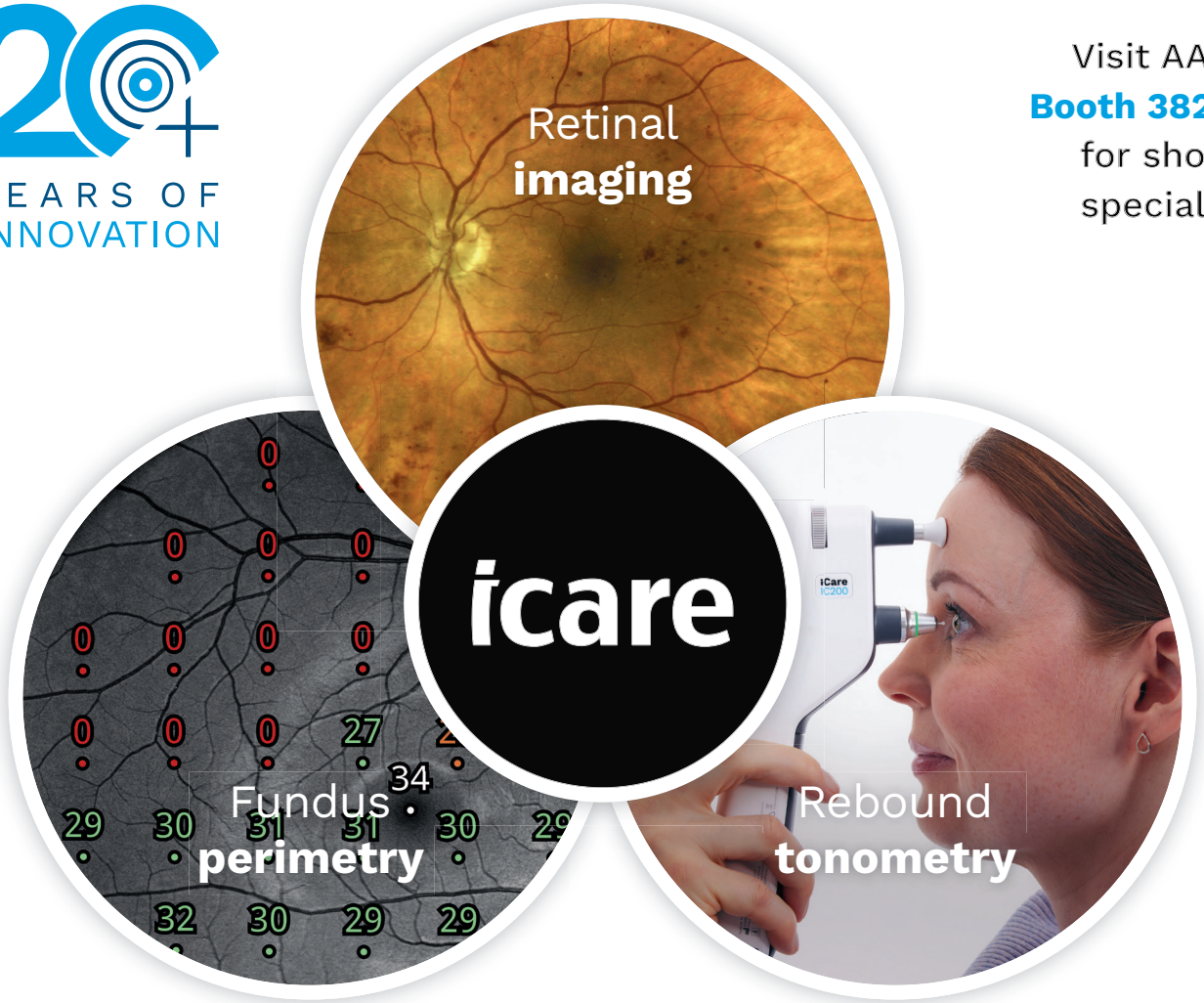

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REVIEW of OPHTHALMOLOGY

WALTER C. BETHKE, EDITOR IN CHIEF

EDITOR'S PAGE

My 30th AAOnniversary

Since this is *Review*'s AAO issue, it got me thinking: It's hard to believe—the time has flown by like a femtosecond burst—but 2024 marks my 30th year attending the American Academy of Ophthalmology meeting. This sparked a bunch of AAO memories ...

Back then, I was a wide-eyed junior editor on *Review*, barely able to spell "capsulorhexis," trying to absorb as much information as I could. In one of the first sessions I walked into Houston's Jack Holladay, MD, was up on stage dissecting a complex optics equation. I broke out into a cold sweat—I was told there'd be no math—but stuck it out anyway. I may not have ever gotten the equation, but I did get a lot of great topics and insights from Dr. Holladay over the years, many of them at the AAO.

Another time, I met with renowned surgeon Theo Seiler to learn more about his corneal collagen cross-linking technique. Near the end of our conversation, he joked, "You've got the most German name ever—'Valtuh Beet-kah' [pronounced like a true German]—but don't speak German." I was going to counter by saying I actually took German in high school and college, but I didn't think that would help my case.

Attending 30 years' worth of meetings also puts you in a position to see therapies come and go, and then come again—usually in the presbyopia and hyperopia treatment realms. A treatment will fail, but another company will pick it up, put a new shade of lipstick on the pig and trot it out several years later under a new name. Surgeons are like, "Isn't that the same pig we kicked out in 2003?" To this, the pig pivots and waddles out. See you in seven years.

But, there were a lot of groundbreaking technologies and techniques that were discussed at the meeting as well over three decades: PRK; LASIK; multifocal IOLs; optical biometry; prostaglandins; toric lenses; tons of phaco techniques; MIGS; and the femtosecond laser, just to name a few. It was exciting to be on the ground floor of all of them.

And, as everyone knows, though the meeting itself is great, a lot of memorable moments happen outside the convention center, in the downtime out in the host city. At my first AAO, which was in San Francisco, a friend and I wandered onto the set of the movie "Nine Months," near where Hugh Grant's and Jeff Goldblum's characters were comisserating about Grant's character's impending fatherhood. A petite, feisty security guard corralled us and moved us back to an acceptable distance. We joked around, asking her to pose for a photo as if she were kicking us off the set, and I recall she said I had a "Forrest Gump thing going on" with the way I spoke. When you're a young guy in his 20s, you don't particularly want to be compared with Forrest Gump, but I guess it's better than nothing.

So if you're at this year's AAO and you see a guy with a really German name who reminds you of Forrest Gump, be sure to say, "Guten Tag!"

(Take that, Dr. Seiler.)

— Walter Bethke
Editor in Chief

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- **Up to 72% of patients** achieved complete corneal healing in clinical trials*†[1-3]
- **80% of these patients** remained healed at 1 year (REPARO trial)*[4]

*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

Dompé

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

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 Long Goodbye

Musings on life, medicine and the practice of ophthalmology.

MARK H. BLECHER, MD
CHIEF MEDICAL EDITOR

It's that time of year … again. Fall. So many mixed emotions. Sad for the summer to be over. Excited for pumpkin spice lattes. And maybe time to start decorating for Christmas. But one thing we can all agree on is that it's uniquely a season of change. Change in the weather of course, and a change in our daily routine. With a sense that the year is rushing away from us, also a need to be sure we've accomplished what we wanted. Up here at my farm, Lambs Hollow, the changes are stark. A switch is flipped on Labor Day and the leaves start to turn, and it no longer feels like pool weather even if the temperatures are still warm. I think back to previous autumns at Lambs Hollow, and see the rest of the year playing out in front of me. Familiar, predictable and a bit melancholy.

For more than three decades I've spent my weekends away from the city and the madding crowd at Lambs Hollow, which had previously been a farm for almost 200 years in Northwest New Jersey, nestled among the rolling hills, horse farms and small towns. Yes, New Jersey. You should visit sometime. It's not just Newark. It's been my place of refuge. And now that I'm contemplating retirement, its time is coming to an end. Many of you share the dread of having to close up for winter. There's a lot to do. And I'll admit I'm tired of the work—and the cold. It may surprise many of you, but I've come to appreciate the warmth and relaxation of Florida. I know, so cliché. And surprising to me too. But while I love the peacefulness of Lambs Hollow, the ease and accessibility of Florida is hard to beat. So, today I wander around the farm with Tobey this chilly early fall morning with the knowledge that this will be my last. By this time next year, it'll belong to someone else. Tobey won't be happy; he loves strolling the fields sniffing for critters. Chasing iguanas in Florida isn't the same.

In addition to great beauty what I see are chores to be done, expenses to be paid and a steep 18th century staircase waiting to get me. It's time. Time to shake things up. Time to move on. Time to simplify, and make things easier. To do new things, and to create a new norm. I've been here for 35 years, crafted an existence that worked for me for a very long time. But I can't escape the feeling that I need to break out of my routine, not be captive to the place and the obligations it brings.

How do you process all those years of memories? Of a place I've lived longer than any other? Every corner is familiar, every view, every tree. I'm only just acknowledging the pending reality of leaving. What do I need to do to pay sufficient tribute to how well this place has served me, and supported me? Is it enough to just go through the motions of the season? I want to turn it over in optimal condition, to show the next owners how it needs to be kept. But I have no way to convey how special it was/is to me. I'm starting to clean it out. Thirty-five years of stuff, which at some point I thought was important. There's no room in Florida to keep anything. A few boxes of photos, some financial records. What else is there that I haven't already replicated down there? Surprisingly little, so the purge goes on. And for every item I find to throw out, another memory springs up.

While I had hoped for a growing sense of freedom, what I'm getting is a sense of loss. I guess this is to be expected and the price to pay for change. I know it's what needs to happen and I'm left searching for how to properly close the chapter. I want to close it with satisfaction, a sense of accomplishment and, hopefully, only a little remorse. ◀

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

LASIK in Patients with Systemic Disease

For those with conditions such as rheumatoid arthritis and ocular HSV, do the risks outweigh the benefits?

LIZ HUNTER
SENIOR EDITOR

Autoimmune diseases and other systemic conditions, such as rheumatoid arthritis and ocular herpes simplex virus are considered relative contraindications for laser vision correction, according to the U.S. Food and Drug Administration, as well as the American Academy of Ophthalmology.[1,2] This recommendation was based on potential surgical complications and unpredictable healing responses, yet there are limited case reports of LVC on patients with these conditions.

"The lack of large-scale studies on laser vision correction for patients with autoimmune diseases like RA and HSV contributes to the uncertainty," says Nichelle Warren, MD, an anterior segment surgeon at Georgia Eye Partners in Atlanta. "There are no large sample sizes to draw definitive conclusions, which makes it challenging to form clear guidelines. Most available data come from smaller studies and reviews. Continued research would be beneficial, but currently, that's probably not a reality due to the risks."

Surgeons say there needs to be clarification of the risks associated with refractive surgery in patients with these conditions. "Although some case series suggest that such surgeries can be safe, there are many case reports of poor outcomes," notes David S. Chu, MD, who's the medical director at Metropolitan Eye Research and Surgery Institute in Palisades Park, New Jersey, and a clinical associate professor of ophthalmology at Rutgers University. "This discrepancy indicates a need for more detailed research to balance risks and benefits more accurately. No one is disputing that the risks in these patients are higher, but we just don't know how much higher.

> **Although refractive surgery is possible for patients with rheumatoid arthritis, it likely increases the risk. There are case reports of complications such as severe dry eyes, non-healing corneal ulceration and corneal melting.**
>
> ***– David S. Chu, MD***

"Despite the risks, people with rheumatoid arthritis undergo refractive surgery regularly," he continues. "As clinicians, the goal is to carefully select patients and weigh the risks and benefits."

Without standardized guidelines, refractive surgeons have to make decisions on a case-by-case basis. We asked these experts to chime in on the patient presentations that would give them cause for concern, and on whom they'd proceed with laser vision correction. Here's what they shared.

Rheumatoid Arthritis and Autoimmune Involvement

RA is a systemic autoimmune disease that can affect more than a person's joints. Its ophthalmic manifestations can include scleritis, peripheral ulcerative keratitis, uveitis, corneal melt and severe dry eyes, says Dr. Chu.

Historically, patients with RA were often excluded from FDA trials for LASIK and other refractive procedures due to concerns about safety, says Brad Feldman, MD, a cornea/cataract/refractive surgeon at Wills Eye Hospital in Philadelphia and a clinical instructor in ophthalmology at the Sidney Kimmel Medical College at Thomas Jefferson University. "Over time, case series have examined the safety of LASIK for these patients, but there was a degree of cherry picking on which patients were included. RA remains a relative contraindication because there are different types of RA patients. Some have RA that isn't well-controlled with active inflammation, while others may have only joint disease without additional systemic manifestations, such as skin and eyes."

This caution isn't limited to RA; other rheumatic diseases such as lupus, scleroderma and inflammatory bowel disease also fall under this spectrum, Dr. Feldman continues. "For these patients, my general rule of thumb is to avoid offering LASIK if the patient has extra-arthritic manifestations or systemic involvement. This is because these patients are at higher risk for oc-

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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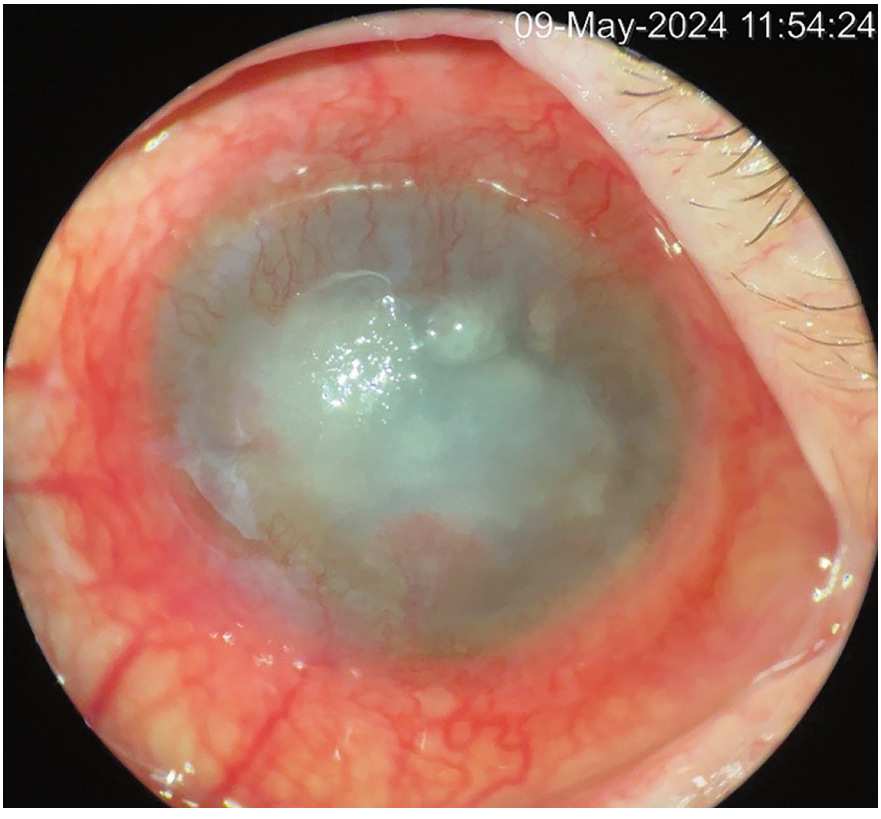
ular complications either immediately postoperatively or down the road. We aim to select patients who present the lowest risk for complications."

Small case series have reported some of the risks associated with performing LVC on these patients. "Although refractive surgery is possible for patients with rheumatoid arthritis, it likely increases the risk," Dr. Chu says. "There are case reports of complications such as severe dry eyes, non-healing corneal ulceration and corneal melting etc., in the literature," Dr. Chu says. "There have been instances where photorefractive keratectomy in patients with rheumatoid arthritis has gone terribly wrong."

"A particularly alarming complication is necrotizing scleritis, which can lead to perforation," says Dr. Warren. "Corneal melt also poses a risk of perforation. Given these risks, it's crucial to be very cautious about performing any laser vision correction on RA patients. They're already at a higher risk for possible infection if they're immunosuppressed. Up to 25 percent of RA patients also have secondary Sjögren's syndrome, which exacerbates their dry eye. If LASIK is performed, it will further worsen their dry eye symptoms."

Dr. Chu says it's important to be aware of overlapping conditions in RA patients. "Regarding autoimmune diseases like Sjögren's syndrome, patients with severe dry eyes—a common manifestation of Sjögren's—generally do poorly with refractive surgery," he says. "Sjögren's patients who show significant loss of tear production or a very inflamed or dry ocular surface are particularly problematic. These patients, especially those with overlapping conditions such as rheumatoid arthritis, should be thoroughly evaluated and avoided if the ocular surface is excessively dry. Some patients with very dry surfaces may not have been diagnosed with Sjögren's, so they may not be aware that they have it."



David S. Chu, MD

This patient with Sjögren's syndrome underwent PTK for a corneal scar and was then referred to David S. Chu, MD, with a non-healing corneal ulcer, which can be a common complication of those with autoimmune diseases who undergo laser vision correction.

Despite these warnings, only four retrospective studies on this topic have been published in the past 20 years, according to a paper co-authored by Dr. Chu, in which he summarized those findings.[1] The largest and most recent was published in 2016, and it included 1,226 eyes of 622 patients with underlying collagen vascular or autoimmune diseases. Among them, 315 patients had RA. LASIK was performed on a majority of the eyes in the study, with PRK on the remainder, and the authors concluded that no sight-threatening complication such as corneal perforation was reported.[3]

With this in mind, some surgeons will consider performing LASIK on RA patients under specific guidelines. "If you decide to proceed with laser vision correction for these patients, it's crucial to first evaluate their tear film using Schirmer's, staining and tear breakup time," Dr. Warren advises. "Additionally, a thorough corneal exam should be performed to ensure there are no signs of staining or scarring from previous issues. Ideally, the patient's disease should be well-controlled for at least six months before considering any surgical interventions. Any uncontrolled disease condition is an absolute contraindication for laser surgery, as it could lead to severe complications."

Although a Schirmer's test may be routine on all patients, Dr. Feldman says there are some nuances when RA is involved. "A borderline low Schirmer score is more concerning than it would be for a patient who otherwise has no signs or symptoms of dry-eye disease," he says. "If a patient with RA has a low Schirmer score but no other findings or symptoms of dryness, I would be more suspicious that this patient may be someone who will have chronic ocular surface disease after surgery. However, if on that same patient, the Schirmer score is borderline but other tests are normal, I might have a more detailed discussion

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References: 1. TRIESENCE Prescribing information. Harrow IP, LLC; 2023

INDICATIONS AND USAGE

TRIESENCE® Suspension is indicated for:

- Treatment of the following ophthalmic diseases: sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids.
- Visualization during vitrectomy.

IMPORTANT SAFETY INFORMATION

Contraindications

- TRIESENCE® Suspension is contraindicated in patients with systemic fungal infections.
- TRIESENCE® Suspension is also contraindicated in patients with hypersensitivity to corticosteroids or any component of TRIESENCE® Suspension. Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroid therapy.

Warnings and Precautions

- *TRIESENCE® is a suspension; it should not be administered intravenously.*
- *Ophthalmic effects: May include cataracts, infections, and glaucoma. Monitor intraocular pressure.*
- *Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome and hyperglycemia: Monitor patients for these conditions and taper doses gradually.*
- *Infections: Increased susceptibility to new infection and increased risk of exacerbation, dissemination, or reactivation of latent infection.*
- *Elevated blood pressure, salt and water retention, and hypokalemia: Monitor blood pressure and sodium, potassium serum levels.*
- *GI perforation: Increased risk in patients with certain GI disorders.*
- *Behavioral and mood disturbances: May include euphoria, insomnia, mood swings, personality changes, severe depression, and psychosis.*
- *Decreases in bone density: Monitor bone density in patients receiving long term corticosteroid therapy.*
- *Live or live attenuated vaccines: Do not administer to patients receiving immunosuppressive doses of corticosteroids.*
- *Negative effects on growth and development: Monitor pediatric patients on long-term corticosteroid therapy.*
- *Use in pregnancy: Fetal harm can occur with first trimester use.*
- *Weight gain: May cause increased appetite.*

Adverse Reactions

- Based on a review of the available literature, the most commonly reported adverse events following ocular administration of triamcinolone acetonide were elevated intraocular pressure and cataract progression. These events have been reported to occur in 20-60% of patients.
- Less common reactions occurring in up to 2% of patients include: endophthalmitis (infectious and non-infectious), hypopyon, injection site reactions (described as blurring and transient discomfort), glaucoma, vitreous floaters, detachment of retinal pigment epithelium, optic disc vascular disorder, eye inflammation, conjunctival hemorrhage and visual acuity reduced. Cases of exophthalmos have also been reported.

Drug Interactions

- *Anticoagulant Agents* – Corticosteroids may enhance or diminish the anticoagulant effect of anticoagulant agents. Coagulation indices should be monitored.
- *Antidiabetic Agents* – Corticosteroids may increase blood glucose concentrations. Dose adjustments of antidiabetic agents may be required.
- *CYP 3A4 Inducers and Inhibitors* – CYP 3A4 inducers and inhibitors may respectively increase or decrease clearance of corticosteroids, necessitating dose adjustment.
- *NSAIDs* – Concomitant use of NSAIDS, including aspirin and salicylates, with a corticosteroid may increase the risk of GI side effects.

For additional Important Safety Information about TRIESENCE® Suspension, please see the Brief Summary of Full Prescribing Information on the following page.

HARROW™

Triesence®
(triamcinolone acetonide injectable suspension) 40 mg/mL

BRIEF SUMMARY – PLEASE SEE THE TRIESENCE® PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE:

TRIESENCE® is a synthetic corticosteroid indicated for:

- Treatment of the following ophthalmic diseases: sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids.
- Visualization during vitrectomy.

CONTRAINDICATIONS

- Patients with systemic fungal infections.
- Hypersensitivity to triamcinolone or any component of this product.

DOSAGE AND ADMINISTRATION:

- Initial recommended dose for all indications except visualization: 4 mg (100 microliters of 40 mg/mL suspension) with subsequent dosage as needed over the course of treatment.
- Recommended dose for visualization: 1 to 4 mg (25 to 100 microliters of 40 mg/mL suspension) administered intravitreally.

WARNINGS AND PRECAUTIONS

- TRIESENCE® is a suspension; it should not be administered intravenously.
- Ophthalmic effects: May include cataracts, infections, and glaucoma. Monitor intraocular pressure.
- Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and hyperglycemia: Monitor patients for these conditions and taper doses gradually.
- Infections: Increased susceptibility to new infection and increased risk of exacerbation, dissemination, or reactivation of latent infection.
- Elevated blood pressure, salt and water retention, and hypokalemia: Monitor blood pressure and sodium, and potassium serum levels.
- GI perforation: Increased risk in patients with certain GI disorders.
- Behavioral and mood disturbances: May include euphoria, insomnia, mood swings, personality changes, severe depression, and psychosis.
- Decreases in bone density: Monitor bone density in patients receiving long term corticosteroid therapy.
- Live or live attenuated vaccines: Do not administer to patients receiving immunosuppressive doses of corticosteroids.
- Negative effects on growth and development: Monitor pediatric patients on long-term corticosteroid therapy.
- Use in pregnancy: Fetal harm can occur with first trimester use.
- Weight gain: May cause increased appetite.

ADVERSE REACTIONS

- Based on a review of the available literature, the most commonly reported adverse events following ocular administration of triamcinolone acetonide were elevated intraocular pressure and cataract progression. These events have been reported to occur in 20-60% of patients.
- Less common reactions occurring in up to 2% of patients include: endophthalmitis (infectious and non-infectious), hypopyon, injection site reactions (described as blurring and transient discomfort), glaucoma, vitreous floaters, detachment of retinal pigment epithelium, optic disc vascular disorder, eye inflammation, conjunctival hemorrhage and visual acuity reduced. Cases of exophthalmos have also been reported.

DRUG INTERACTIONS

- *Anticoagulant Agents* – Corticosteroids may enhance or diminish the anticoagulant effect of anticoagulant agents. Coagulation indices should be monitored.
- *Antidiabetic Agents* – Corticosteroids may increase blood glucose concentrations. Dose adjustments of antidiabetic agents may be required.
- *CYP 3A4 Inducers and Inhibitors* – CYP 3A4 inducers and inhibitors may respectively increase or decrease clearance of corticosteroids, necessitating dose adjustment.
- *NSAIDs* – Concomitant use of NSAIDS, including aspirin and salicylates, with a corticosteroid may increase the risk of GI side effects.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Two prospective case control studies showed decreased birth weight in infants exposed to maternal corticosteroids in utero. Triamcinolone acetonide was shown to be teratogenic in rats, rabbits, and monkeys at inhalation doses of 0.02 mg/kg and above and in monkeys, triamcinolone acetonide was teratogenic at an inhalation dose of 0.5 mg/kg (1/4 and 7 times the recommended human dose)..Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Infants born to mothers who received corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Nursing Mothers

Corticosteroids are secreted in human milk. The risk of infant exposure to steroids through breast milk should be weighed against the known benefits of breastfeeding for both the mother and baby.

Pediatric Use

The efficacy and safety of corticosteroids in the pediatric population are based on the well-established course of effect of corticosteroids which is similar in pediatric and adult populations. The adverse effects of corticosteroids in pediatric patients are similar to those in adults.

Geriatric Use

No overall differences in safety or effectiveness were observed between elderly subjects and younger subjects, and other reported clinical experience with triamcinolone has not identified differences in responses between the elderly and younger patients.

PATIENT COUNSELING INFORMATION

Patients should discuss with their physician if they have had recent or ongoing infections or if they have recently received a vaccine.

Patients should be advised of common adverse reactions that could occur with corticosteroid use such as elevated intraocular pressure, cataracts, fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite, and weight gain.

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about dry-eye disease with the patient, but I may still offer them laser vision correction, though this is done with greater caution."

Patients should be asymptomatic for dry eye before proceeding, say surgeons. "There should be no staining on their cornea, and their topography and refraction should be stable," Dr. Warren says. "Ideally, the patient shouldn't be on high-dose steroids, and preferably not on any steroids at all. If they're on immunosuppressants, caution is required because these patients are at increased risk for infection. Additionally, patients need to be fully informed about the potential for future issues, as autoimmune diseases like RA can wax and wane. Even if the disease has been controlled for the past six months, there's a possibility of problems arising later on."

Dr. Feldman says he's hypervigilant in the postop period for these patients. "My approach involves careful monitoring and follow-up," he says. "I make it a point to examine these patients daily after surgery myself to ensure that any issues are promptly addressed. I wouldn't co-manage these patients."

Treating physicians need to be aware of potential complications. "They should monitor for unusual inflammation, such as diffuse lamellar keratitis, or issues with corneal epithelium healing or increased inflammation in the eye, including uveitis or scleritis, which are not typical after laser refractive surgery," says Dr. Chu. "Any abnormal inflammation should be treated proactively, and consultation with additional specialists might be necessary if issues arise."

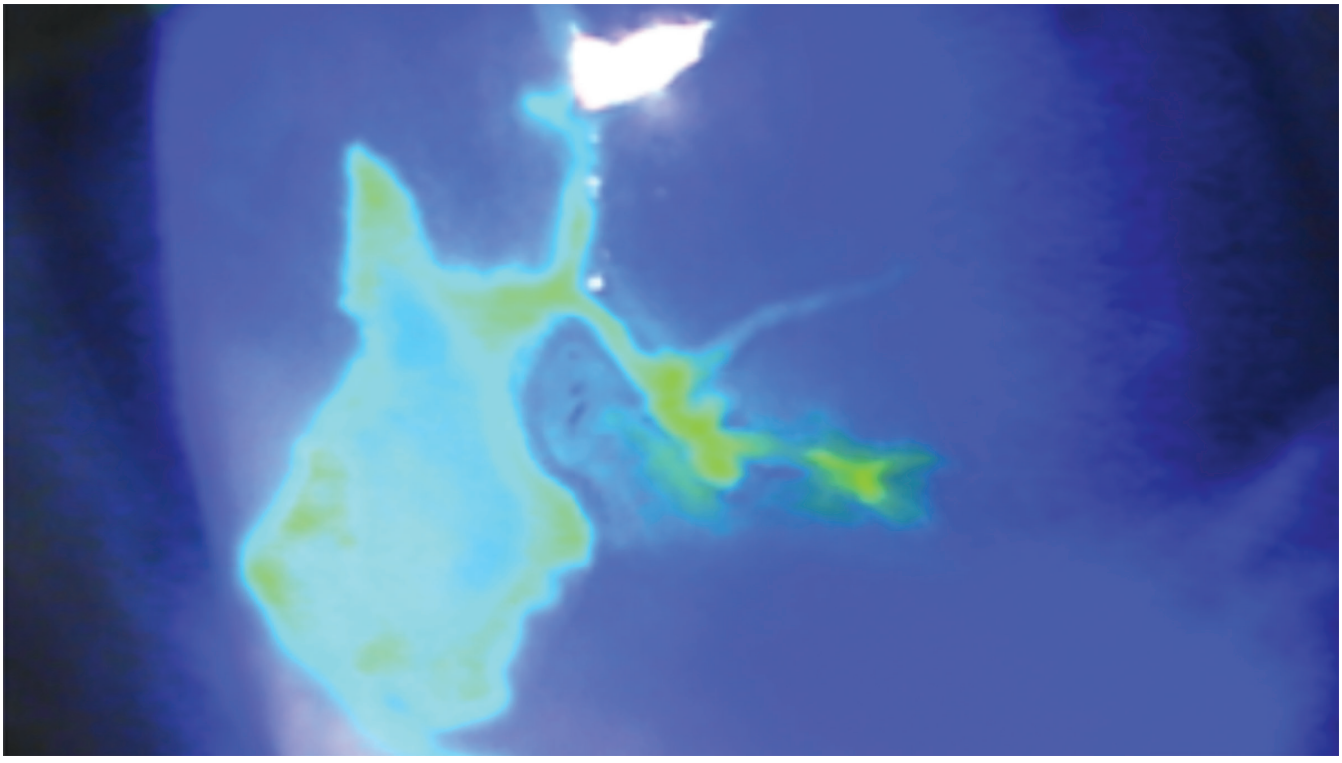
Dr. Warren also says to monitor for any corneal opacifications which could be a scar, the start of a sterile ulceration or potential infection. "It's also important to look for signs of exacerbation of their dry-eye symptoms, such as increased staining and signs of epithelial basement membrane dystrophy or other complications," she says, echoing Dr. Chu's warning about DLK and adding RA patients specifically are at risk of developing peripheral ulcerative keratitis.

"If an epithelial defect is detected, I'm more likely to place a bandage contact lens to promote healing," says Dr. Feldman, "although I usually have a low threshold for this regardless of the patient's condition."

Finally, don't overlook the role of patient counseling in these situations. "I find that you can help decrease your chair time if you spend the time upfront managing their expectations and educating the patient on the disease and potential problems they might encounter down the road," Dr. Warren says. "When you educate them ahead of time, it can prevent a patient from blaming their problems on the surgery itself."

Ocular HSV

Although these surgeons say that LVC on RA patients may be pursued under the right circumstances, they feel differently when it comes to



Nichelle Warren, MD

In those with ocular HSV, laser vision correction surgeries, including PRK, combined with the use of steroids, can lead to non-healing defects or geographic ulcers, as seen here. Surgeons say the risk of haze and scarring remains high even if the patient is on antivirals, and laser vision correction is generally avoided in these patients.

ocular HSV.

"For me, HSV is an absolute contraindication for LASIK or PRK," says Dr. Feldman. "I won't perform these surgeries on anyone with a history of ocular HSV. My decision is based on a specific case I inherited where a patient with a remote history of documented HSV went into surgery on valacyclovir and had no early complication. This person developed severe interface haze after surgery, leading to legal blindness and required a corneal transplant. She then had complications in her transplant due to HSV as well. This case highlighted the unacceptable risk associated with performing LASIK in such patients."

Dr. Chu also says he avoids refractive surgery on patients with HSV due to the risks and complications associated with the disease.

Ocular HSV is a broad diagnosis. "The primary occurrence is often blepharoconjunctivitis," says Dr. Warren. "However, as cornea specialists, we see more issues related to recurrent infections. These recurrences can lead to stromal opacification, stromal keratitis, epithelial keratitis and endotheliitis, which can cause permanent damage to the cornea and long-term vision loss."

The main concern with laser vision correction in HSV patients is the risk of reactivating the virus, she continues. "HSV remains dormant in the nerve tissue after the initial infection. If a patient has already had one recurrence, they're at risk for more. Applying a laser to their cornea could increase this risk. Additionally, the postoperative use of steroids can suppress the immune system in the cornea, increasing the risk of reactivation," continues Dr. Warren.

Case studies on this topic involving humans are limited, and surgeons have supplemented their research with animal models. PRK has been found to be a particular trigger for reactivation, according to research. In one animal study, de-epithelialization coupled with the excimer laser resulted in a 66.67 percent HSV keratitis reactivation rate.[2,4]

"For patients with HSV, PRK is particularly risky," says Dr. Feldman. "The large epithelial defect associated with PRK, combined with the use of steroids, can lead to non-healing defects or geographic ulcers. Even if the patient is on antiviral medication at the time of surgery, the risk of haze and scarring remains high. PRK is generally avoided in HSV patients due to these risks."

Similar concerns apply to corneal collagen cross-linking, he continues. "I've encountered HSV in patients who underwent cross-linking without a known history of HSV," says Dr. Feldman. "Those things can happen, but in these situations, these patients are prone to haze or scarring in the area of delayed epithelialization. Stromal haze is another risk, and in the worst-case scenario, patients can develop corneal ulceration and melts. Even if they don't have corneal structural defects, they can have chronic dry eye, which is exacerbated by LASIK or PRK. The procedure itself often leads to dry eye for at least three to six months, which can be particularly

(Continued on p. 63)

Mastering DMEK Graft Manipulation

How to troubleshoot common graft problems and advice for approaching complex eyes.

CHRISTINE YUE LEONARD
SENIOR ASSOCIATE EDITOR

DMEK has earned its reputation as a tricky transplant procedure for good reason. "Every case is very different," says Jack Parker, MD, of Parker Cornea in Birmingham, Alabama. "When you're doing other challenging eye surgeries, they typically proceed algorithmically. You may be faced with a difficult scenario, but there are published steps and tactics for each of those potential challenges. With DMEK, it's not always obvious what to do next, even for experienced DMEK surgeons, and you need to have a feel for how the tissue behaves in the eye. It's problem solving on a timer, and it's not easy to develop a sense for how to solve that problem without lots and lots of practice."

In the absence of virtual simulations and eye models, Dr. Parker recommends watching DMEK videos. "You can to some extent recapitulate the process using tissue obtained from an eye bank to practice in a wet lab, but probably the best way to learn the dynamics of the graft behavior is to watch videos, especially your own," he says. "Play them back and observe how the tissue responds to various stimuli and manipulations."

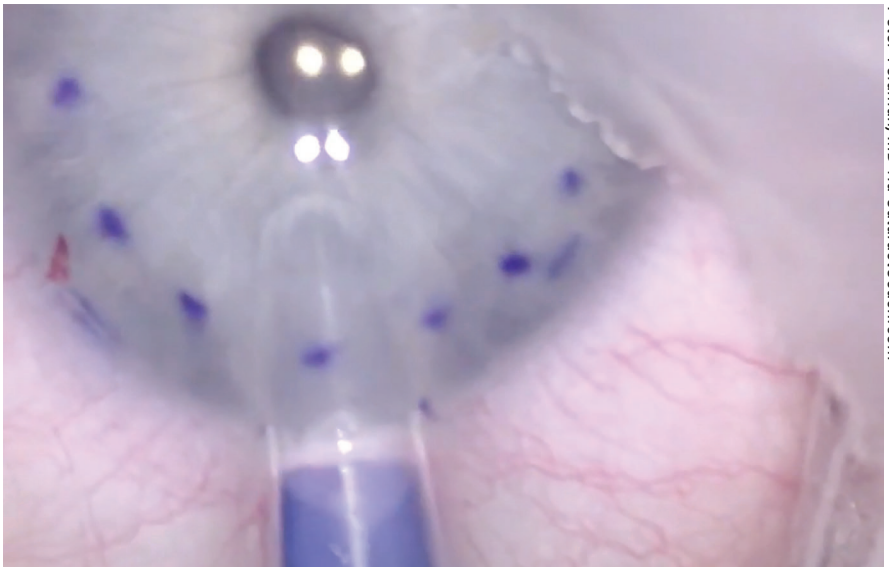
The learning curve for DMEK is long and takes commitment, surgeons say. "DMEK presents one of the steepest learning curves among eye surgeries," says Ahmed Bardan, MSc, MD, PhD, a consultant ophthalmic surgeon at St. James University Hospital in Leeds, United Kingdom. "The tissue involved is fragile, and numerous anatomical, surgeon-related and patient-related factors must be considered."

Here, Dr. Parker and Dr. Bardan share tips for when graft unfolding doesn't go as planned, and discuss how they handle the graft in complex cases with variable eye anatomy.

Eye Anatomy

The depth of the recipient anterior chamber plays a key role in the success of DMEK graft manipulation during surgery. "In a shallow anterior chamber, everything is mashed together and it's difficult to unfold the edges of the DMEK tissue," Dr. Parker says. "In a hyper-deep anterior chamber, such as an eye that's been previously vitrectomized, the chamber can be so deep that the graft just spins around in the eye, and it's difficult to unfold because there's no compression between the back of the cornea and the front of the patient's iris. Each of these extremes presents challenges."

"We advise surgeons about to start doing DMEK to choose 'standard' eyes," Dr. Bardan says. "A standard eye won't be extremely myopic or hyperopic. The anterior chamber won't be too deep or too shallow. Avoid vitrectomized eyes, aphakic eyes that had previous complicated surgery, eyes with previous glaucoma surgeries or eyes with any device in the anterior chamber such as an AC IOL. These additional factors make the surgery



Peter Veldman, MD via CataractCoach.com

Figure 1. Starting out with the graft in the correct orientation will help to ensure smooth delivery and unfolding of the graft.

This article has no commercial sponsorship.

Dr. John is a clinical associate professor at Loyola University at Chicago and is in private practice in Oak Brook, Tinley Park and Oak Lawn, Illinois. He can be reached at 708-429-2223; email: tjconference@gmail.com.

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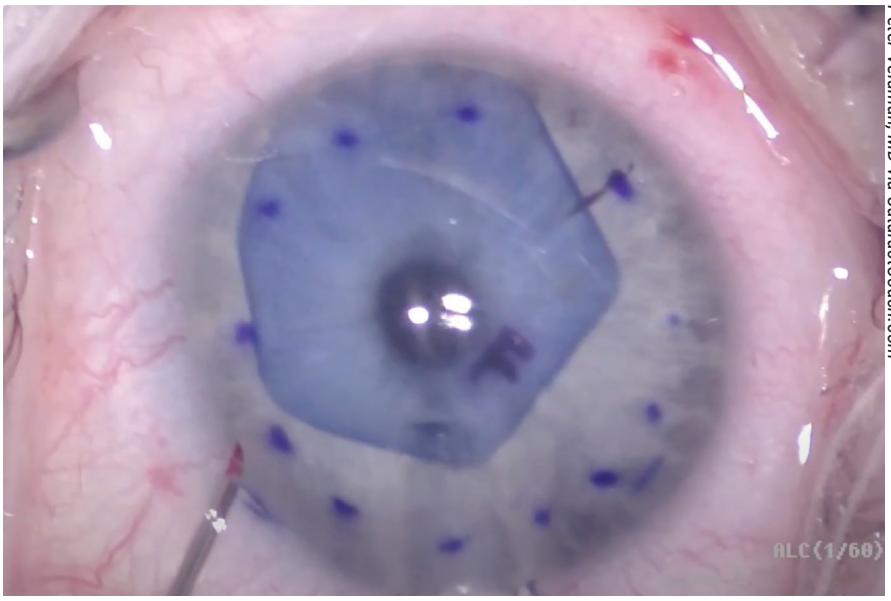

Peter Veldman, MD via CataractCoach.com

Figure 2. Shallowing the anterior chamber after graft delivery encourages the graft to flatten out.

more complicated."

He adds that patients on antiplatelet medications for cardiac disorders are more likely to bleed and have fibrin released during surgery. "Once you get fibrin, it makes the graft adhere to itself, and it's very difficult to unfold," Dr. Bardan says. "Fibrin is your enemy when you do DMEK."

DMEK Technique

Striving to establish a degree of standardization in the DMEK technique—acknowledging the inherent variability of each case—can assist surgeons in developing a robust foundation and gaining confidence in this sophisticated keratoplasty procedure, Dr. Bardan explains. "The complexity of certain eyes, particularly those affected by conditions such as peripheral anterior synechiae, prior glaucoma surgeries, aniridia or vitrectomy, renders it nearly impossible to fully standardize the procedure, as there will invariably be additional complicating factors.

"I believe in standardization in general for corneal and refractive surgeries," he continues. "With DMEK, one way to handle the steep learning curve and meet each challenge is to minimize deviation from the steps you perform each time. This also helps minimize the surgery time."

Dr. Bardan says that taking the time to carefully inject the graft in the proper orientation will help the rest of the procedure go more smoothly. "For surgeons just starting DMEK, the injection technique is a common delivery approach. When delivering the graft into the anterior chamber, ensure it's in the correct orientation, facing the correct way with the endothelium side down and the Descemet's side up towards the cornea (*Figure 1*). Delivering the graft in the correct orientation into the center of the anterior chamber, using gentle insertion rather than a gush insertion helps maintain its correct orientation.

"At the end of the graft delivery, I intentionally shallow the anterior chamber (*Figure 2*). This shallowness provides no room for the graft to remain scrolled and it encourages the graft to become flat and open up. If it's not a tight scroll—since today we use donor tissue from older donors—the graft should open up with gentle tapping on the center of the cornea.

"Centration before unfolding is important," he notes. "Once it's unfolded, the graft becomes more difficult to mobilize inside the eye because all or part of the graft will be touching the corneal stroma."

Graft Configurations

Certain graft configurations call for unique unfolding approaches. "One of the things you don't want to do is just bang aimlessly on the surface of the cornea," Dr. Parker says. "This can be deleterious to the outcome because you're wasting time and washing some of the trypan blue off the back of the graft, making it more difficult to unfold."

He notes that though every case is different, there are actually only a few possible graft configurations. "The graft is a circular sheet of cells that tries to curl in on itself," he says. "For the most part, it curls into a handful of more or less identifiable configurations that have names."

These names include:[1]

- single roll;
- double roll;
- bouquet;
- jib;
- paper airplane;
- taco;
- folded edge;
- rolled edge;
- open plaster;
- bulge;
- tricorne hat; and
- square.

"It's useful to name these various configurations because there are different strategies that you can employ depending on how the graft is curled," continues Dr. Parker. "So, if you're struggling to unfold the graft, it can be useful to take a step back and ask yourself, 'What is the name of this configuration?' After you've named it, then ask, 'What are some of the effective strategies for this particular configuration?'"

Two common configurations can be addressed like this: For a double-scrolled graft, which is the standard way the graft scrolls, Dr. Bardan recommends gentle tapping on the center of the cornea, parallel to the axis of the scroll to encourage it to open up

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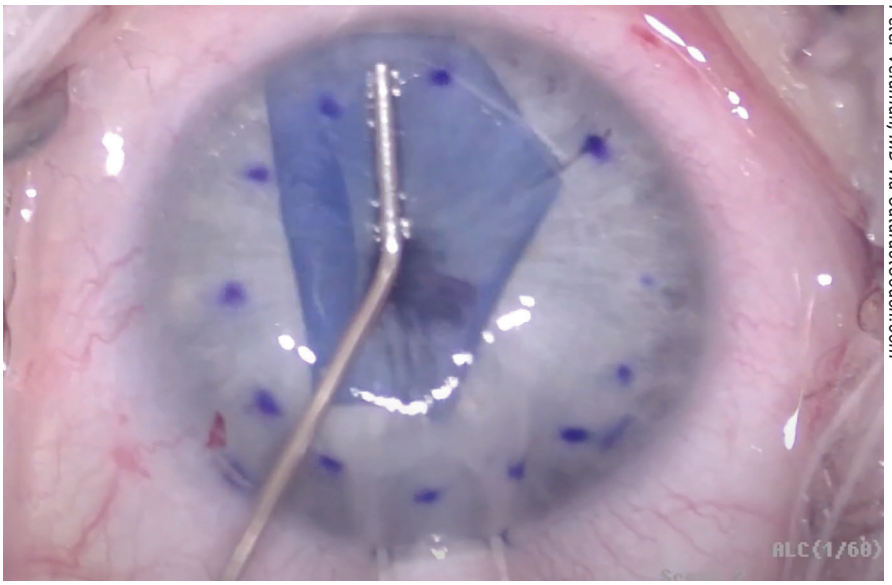


Peter Veldman, MD via CataractCoach.com

Figure 3. To encourage a double-scrolled graft to open up, tap gently on the center of the cornea, parallel to the axis of the graft scroll.

(*Figure 3*). If one side is scrolled and the other is flat, Dr. Parker and Dr. Bardan say the Dirisamer technique can be employed, which involves pressing one cannula on the cornea over the flat part of the graft to keep it flattened, and tapping with a second cannula over the folded part until it unfolds.

Other techniques include bubble bumping for peripheral inward folds; the help-yourself technique, which involves using a single cannula to poke over one edge of a folded graft; and small air bubble-assisted unrolling or the Dapena maneuver. "There are lots of different techniques," says Dr. Parker.

Common Obstacles

Here are a few common roadblocks and pearls for how to handle them:

• ***The patient has atypical anterior chamber depth.*** "For eyes with a deep anterior chamber, you almost always need an air bubble to help unfold [the graft]," Dr. Parker says. "That air bubble supports the graft from the top or from below and artificially shallows the anterior chamber. It gives you a helping hand in unfolding the graft in an eye that it would otherwise be very difficult.

"For an eye with a shallow anterior chamber, one solution to deepen it involves doing a pars plana vitrectomy," he continues. "It can be limited, but often just removing some vitreous from behind the IOL or the limbus can deepen the chamber enough for you to unfold the graft easier."

• ***The graft is upside-down.*** "In a situation in which you feel like you're struggling, one effective strategy instead of randomly tapping the corneal surface is to deepen the chamber with saline and flush the graft in the anterior chamber into a more friendly configuration," Dr. Parker says.

For a crumpled graft or an upside-down graft, Dr. Bardan recommends "injecting BSS behind the scroll through one of the side ports and directing it in a way that creates a current in the anterior chamber that encourages the scroll toward the correct orientation. Once you achieve this, shallow the anterior chamber to preserve that orientation and start using one of the tapping techniques to unfold it."

• ***The graft still isn't unfolding as it should.*** Sometimes, the graft still refuses to unfold, and then the surgeon must figure out what's causing the problem. "If it's a combined phaco-DMEK, for example, there could be some residual viscoelastic that's stopping it from unfolding," Dr. Bardan says. "There could be microscopic fibrin in the anterior chamber that's started to entangle parts of the graft—which will prevent it from opening up. It could also be that the space within the anterior chamber, such as a certain part of the angle, doesn't have enough room for the graft to unfold. An arcus senilis or corneal cloudiness could obscure your view. The surgeon should think about what's causing the problem and then have a plan of action to deal with it."

If fibrin is present in the anterior chamber, the situation becomes tricky since it can be challenging to clear the fibrin. "We have access to tissue plasminogen activator or tPA, which you can inject into the anterior chamber to cause fibrinolysis," says Dr. Bardan.

Unfolding Grafts in Complex Eyes

New variables in the mix complicate DMEK surgery, but there are steps you can take to ensure a successful outcome. Here are some tips for the following scenarios:

• ***Previously vitrectomized eyes.*** In an eye that's undergone vitrectomy, the iris-lens diaphragm is pushed backwards, making the anterior chamber much deeper and the DMEK unfolding more challenging. "If you try to unfold the graft in a previously vitrectomized eye, every time the anterior chamber reforms, the graft scrolls back on itself," Dr. Bardan says. "I inject a small air bubble underneath [the graft]. This air bubble occupies part of the anterior chamber volume and leaves no big space in the anterior chamber for the graft to scroll back on itself."

• ***Narrow angles.*** For eyes with narrow-angle glaucoma with PAS, Dr. Bardan says he sizes the DMEK graft based on how much room there is in the anterior chamber rather than cutting the graft and pre-sizing

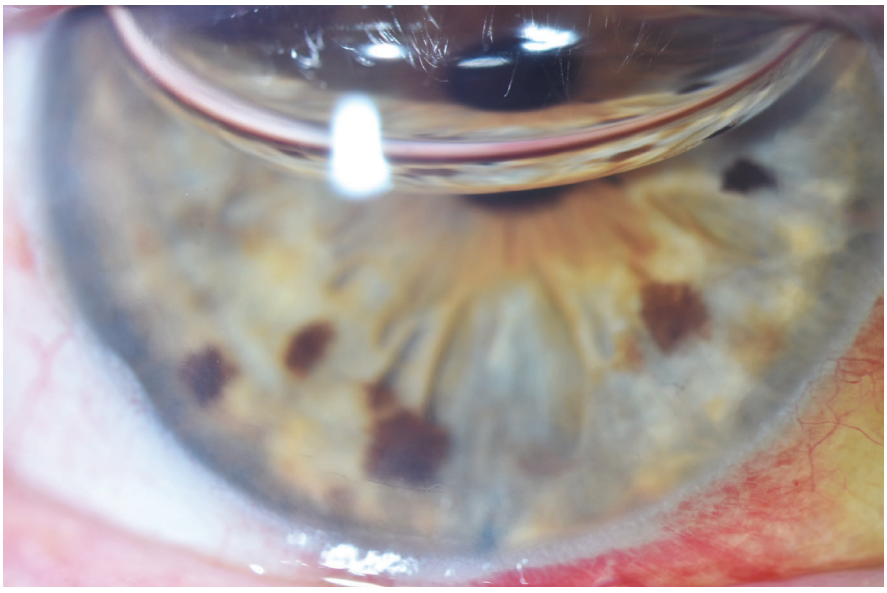
it based on the white-to-white preoperative dimensions. "I don't cut the graft in these cases with complex anterior chambers until I go inside the eye and do the Descemetorhexis," he explains. "I put an air bubble inside the anterior chamber to test for the dimensions. Sometimes there's a very fixed adhesion between the iris and cornea, and that prevents the bubble from expanding to the angle of the anterior chamber. If this bubble is, for example, 7.5 or 7.25 mm, then I adjust the graft size to match and be slightly smaller. This approach can help make these challenging cases easier."

• ***Eyes with a device in the anterior chamber.*** Glaucoma drainage devices and anterior chamber IOLs can complicate DMEK surgery. "If there's a device in the anterior chamber, I've found that the best way is to try to get the procedure done as quickly as possible," Dr. Bardan says. "This is best done by an experienced surgeon who knows how to get the graft to unfold as quickly as possible."

• ***Aphakia.*** In aphakic eyes, the surgeon faces the possibility that the graft might fall into the posterior segment. "If the patient is aphakic, I try to use the iris as a shelf," Dr. Bardan says. "I inject the graft toward the iris shelf to keep it in position to avoid flushing it toward the posterior segment. I use an iris repositor 'spatula' to encourage the graft to open up quickly before tapping, as tapping initially may cause the graft to drop through the pupil.

"It's challenging to get a decent gas bubble or air bubble fill for the anterior chamber in these eyes, since the air or gas keeps escaping toward the back of the eye," he continues. "One thing I do, if the eye has been vitrectomized, is to try to get a gas bubble fill in both the posterior and anterior segments. Leave the tamponade on the table intraoperatively for 10 to 15 minutes and then release it."

Aphakic eyes that are also aniridic or have significantly deficient iris tissue are more challenging. "There's a greater chance of the graft dropping to the posterior segment," Dr. Bardan notes. "Our colleagues at Moorfields Eye Hospital have described a technique using Prolene suture to create a scaffold mesh that replaces the iris diaphragm. If you manage to insert the graft flat on top of these suture lines, then once the graft is unfolded and gas is injected, you can remove the Prolene sutures."



Ahmed Bardan, MSc, MD, PhD

In this photo taken on postoperative day four after a combined phaco, IOL and DMEK procedure, the cornea is clear, the graft is attached and the bubble size is approximately 50 percent of the anterior chamber volume.

• ***Phakic eyes.*** "Our standard technique for all DMEK procedures, whether or not the eye is phakic, involves creating a preoperative YAG laser inferior peripheral iridotomy to avoid iris bleeding and fibrin release," Dr. Bardan says. "This is a must for phakic eyes because there's a higher chance of postoperative pupil block with the air [tamponade] used.

"For phakic eyes, I use preoperative pilocarpine drops to keep the pupil constricted," he continues. "I insert the graft, similar to as I would in aphakic eyes, onto the iris shelf. So, the graft will go to the side rather than the center. Once the graft is in the eye, avoid crossing over the pupillary area with instruments or fluid irrigation to avoid causing any lens trauma or inducing an early cataract."

He says he performs the Descemetorhexis under Healon cohesive viscoelastic to protect the lens and then aspirates it before insertion of the DMEK graft. "Once the graft is unfolded, we use air instead of SF-6 gas to tamponade the graft because SF-6 will have a higher chance of causing pupil block and angle closure, and a higher chance of inducing cataracts," he says. "At the end of the case, be sure to check that the bubble isn't occluding both the pupil and the peripheral iridotomy."

Though DMEK is a challenging procedure, Dr. Parker points out that it's also a very forgiving operation. "It's difficult for things to go horribly wrong," he says. "Surgeons are afraid of starting with it because it's challenging to problem-solve on a timer. But the way to learn is to start. Once you start, you'll pick up insights along the way." ◀

1. Parker J, Parker J, Melles G. DMEK Unfolding Manual. Published September 6, 2019.

DISCLOSURES

Dr. Bardan and **Dr. Parker** have no related financial disclosures.

ADVANCED RETINAL IMAGING SUPPORTS COMPLEX CASES

A hospital clinic has come to rely on the iCare EIDON Ultra-Widefield Module for monitoring retinal pathologies.

By David Sarraf, MD

As a retinal specialist and professor at the Stein Eye Institute at UCLA, I see patients who have been referred by ophthalmologists and other retina specialists. We care for a spectrum of diseases that tend to be complex in nature at my tertiary care teaching facility.

By far and away, the most common cases we deal with in the clinic are AMD patients in intermediate and late stages of disease, both geographic atrophy and neovascular AMD. However, we also see patients with rare genetic dystrophies that can be challenging to identify and follow. Advanced retinal imaging has become indispensable in our ability to diagnose and manage these less common pathologies and care for the patients who present with them.

A "WONDERFUL RESOURCE"

The iCare EIDON imaging system my facility acquired several years ago quickly offered us a wonderful resource to illuminate a wide range of common and less common retinal conditions. Our iCare EIDON Ultra-Widefield (UWF) Module, which offers up to 200° of superior image quality, produces strikingly clear images of the macula and the peripheral retina. We have come to depend on the system's wider field of view, coupled with its TrueColor Confocal Technology offering exceptionally high resolution and color contrast, to help us manage especially challenging cases. The ease of acquiring images with this device adds another layer of benefit.

The iCare EIDON UWF offers us essential information on

CASE #1: BRANCH RETINAL ARTERY OCCLUSION

FIGURE 1

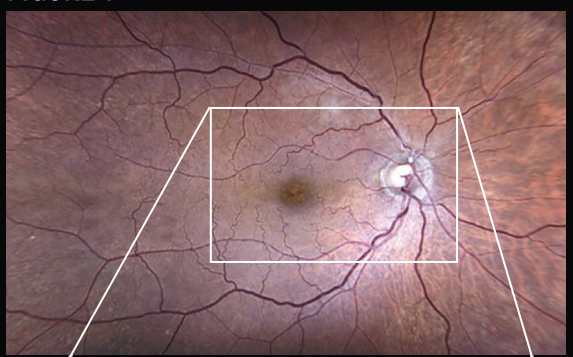


FIGURE 1A

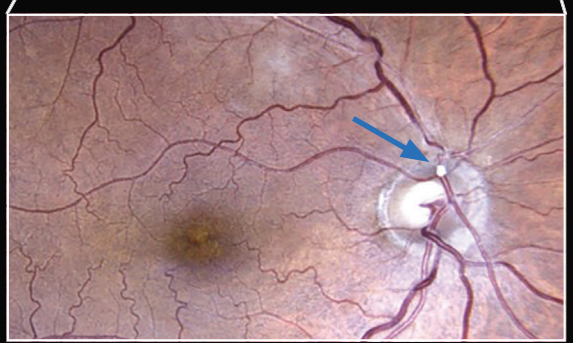


Figure 1. Without the proper contrast and resolution offered by our iCare EIDON UWF, we might have overlooked the retinal whitening indicating the distribution of ischemia and infarction. **Figure 1A.** A closer look reveals the culprit, a plaque, causing non-perfusion and ischemic whitening of the retina.

This case of branch retinal artery occlusion was interesting because the ischemic infarction, located in the macula, showed very subtle changes. Without the proper contrast and resolution offered by our iCare EIDON UWF, we might have overlooked the retinal whitening indicating the distribution of ischemia and infarction. The iCare EIDON UWF helped to capture that wedge of ischemia, or infarction, that was distal to the exact point of arterial occlusion, which helped us to arrive at the diagnosis.

The imaging system also enabled us to identify the culprit embolus, or plaque, causing the non-perfusion and ischemic whitening of the retina. In these patients, the BRAO diagnosis is a critical part of the systemic workup. Determining the source of the embolus, which we identified in the retina with the aid of our iCare EIDON UWF, helped us to make the final diagnosis.

peripheral pathology and macular lesions for common disorders such as AMD, diabetic retinopathy, and diabetic macular edema. The peripheral view is particularly important in diabetics as it helps us to identify more occult retinopathy. This wider field of view also can highlight a broader area of retinal degeneration, neovascular complications, and pattern of changes—insights contributing to our ability to accurately diagnose patients with the disease and assess the status of their progression. At the Stein Eye Institute, we also find the iCare EIDON UWF's ability to help us uncover less common disorders and dysfunction, along with issues such as pentosan polysulfate sodium toxicity, extremely valuable.

A DEVICE TO HELP MANAGE RARE GENETIC DYSTROPHIES

In addition to our iCare EIDON UWF Module, our iCare EIDON AF has been an invaluable asset in helping us manage cases of rare genetic dystrophies. In these kinds of cases, identifying the pattern of maculopathy is a core component to making the diagnosis and monitoring the patients. The color contrast and resolution offered by the iCare EIDON imaging system has improved our ability to identify phenotypes so we can more reliably target them and pinpoint causative genes. The ability to view the macular pattern of atrophy and disruption has helped us to diagnose members of our patient families with mitochondrial maculopathy, as well as to phenotype them and track their disease progression.

Moreover, our iCare EIDON AF has assisted us in identifying hyperfluorescent flecks and peripapillary sparing in Stargardt's disease. Those elements need to be confirmed to successfully diagnose the autosomal recessive retinal dystrophy. Our iCare EIDON AF Module also has given us an efficient way to identify geographic atrophy and AMD patients, and monitor their disease progression. Undoubtedly, our iCare EIDON imaging system has offered my hospital clinic an excellent return on investment for all of the reasons mentioned.

CASE #2: STARGARDT'S DISEASE

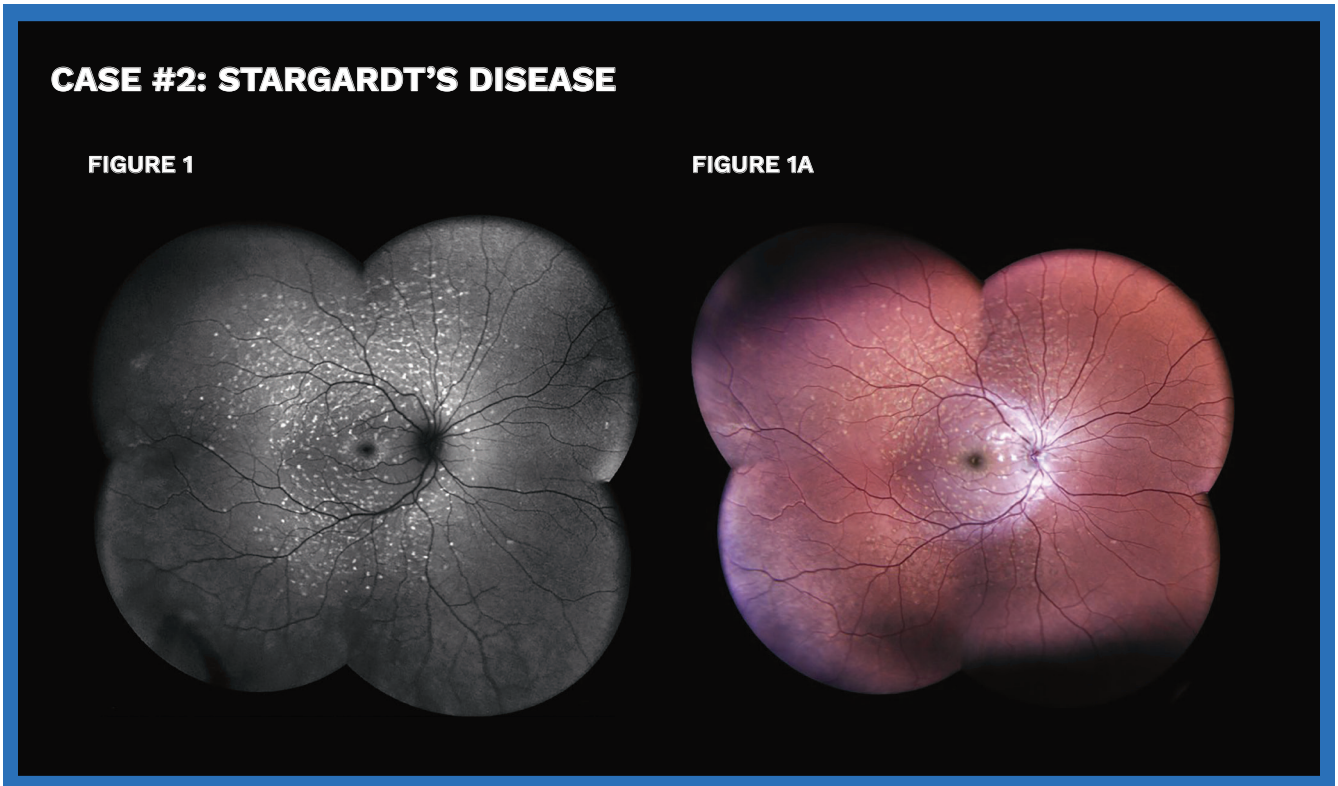


Figure 1. The iCare EIDON Ultra-Widefield AF Module revealed a pattern of hyperfluorescent flecks extending into the periphery consistent with Stargardt's. **Figure 1A.** EIDON UWF reveals in color the extent of this disease across the retina.

In this case of Stargardt's disease, the wide field of view with the iCare EIDON UWF Module played a pivotal role in our evaluation because it revealed the pattern of hyperfluorescent flecks that radiated into the periphery. We also used our iCare EIDON AF to better highlight the pattern of the flecks, along with the evidence of peripapillary sparing, which are vital components in making the final diagnosis for this disease. Our iCare EIDON imaging system was an integral part of determining that this was indeed Stargardt's disease.

THE LIGHT-ADJUSTABLE LENS IN THE REAL WORLD

How surgeons manage patient selection and workflow challenges for successful integration of this novel lens technology.

LIZ HUNTER
SENIOR EDITOR

The introduction of the Light-Adjustable Lens (RxSight) and its customizable technology have generated excitement in the cataract-refractive space. Not only can patients who may have been previously ineligible for anything other than a standard monofocal have an opportunity to achieve excellent vision, but surgeons also have the chance to hit their refractive targets more closely in challenging cases.

Implementing the LAL does take some additional legwork, however, as postop adjustment and lock-in appointments affect clinic workflow. For tips on how to negotiate patient selection, counseling and scheduling, we spoke with seasoned cataract/refractive surgeons who are familiar with the nuts and bolts of this technology. Here, we share their feedback.

Patient Education and Selection

Conversations with patients seeking cataract surgery usually begin with education about the various IOL options. And when it comes to the LAL, patient counseling is just as important as any other lens.

"Patients often don't know what to expect from any lens implant," says John Hovanesian, MD, who's a surgeon practicing in Laguna Hills, California. "Even those who have researched the options may have encountered misleading information that doesn't apply to their specific situation. Therefore, it's essential for the surgeon to educate them thoroughly."

Sumitra Khandelwal, MD, who's a professor of ophthalmology at Baylor College of Medicine in Houston, begins by outlining the various lens options available, including monofocal lenses, astigmatism-correcting lenses, and presbyopia-correcting lenses, which come in multiple categories. "If a patient is concerned about issues such as glare and halos associated with some presbyopia-correcting lenses, I explain that the LAL provides an alternative," she says. "The LAL functions similarly to a monofocal lens but has the added benefit of being adjustable after implantation. This adjustment capability allows us to fine-tune the lens to provide distance, intermediate, and potentially near vision based on the patient's needs and preferences."

An analogy can be effective in this situation, explains Neda Shamie, MD, of the Maloney-Shamie Vision Institute in Los Angeles. "An analogy helps patients and my team understand the technology more easily," she says. "Essentially, it's a lens made from a material that can be adjusted after implantation, allowing patients to 'test drive' their vision. I use the analogy of a designer dress or suit that you would then tailor to fit your exact size or waistline. Similarly, the LAL allows for customization of vision to the exact measurements of the patient's eyes and can allow for test driving blended or monovision before making a commitment. This analogy helps patients grasp the concept of how the LAL can be fine-tuned to their individual needs."

Some patients are better suited to the LAL than others and surgeons should make sure to explain why that is.

"For patients who have undergone previous refractive surgery or have unusual eye characteristics, such as flat corneas or shallow anterior chambers,

This article has no commercial sponsorship.

Dr. Hovanesian discloses stock in RxSight. **Dr. Khandelwal** reports no disclosures. **Dr. Shamie** is a consultant for RxSight.

I emphasize that our standard formulas for calculating IOL power may not be as accurate," Dr. Khandelwal says. "This can lead to refractive surprises. I explain that because their eyes are atypical, the ability to achieve perfect distance vision might be limited compared to other patients. Therefore, if precise focal points are crucial and the patient wishes to avoid glasses for various distances, the LAL could be a suitable option. I stress that the LAL allows for post-implant adjustments, which can be particularly beneficial for these complex cases."

While it has some advantages over non-adjustable IOLs, be mindful to manage expectations for the LAL carefully, advise surgeons. "The LAL's performance can depend on two key variables: whether you're using the LAL+ and whether you're planning for monovision or mini monovision," Dr. Hovanesian says. "The LAL+ is designed to provide a greater range of vision, functioning similarly to an extended depth of focus lens by modifying spherical aberration. This lens adds negative asphericity, which can increase the depth of focus for many patients. However, exercise caution when using this lens for patients who've undergone hyperopic LASIK or have significant corneal aberrations, as it induces some aberration that isn't typically present in spherical lenses."

"Patients who have undergone RK can also be very challenging because their vision fluctuates," Dr. Khandelwal says. "I advise them that achieving stable vision may take longer and involve more frequent adjustments. I make sure to address these challenges upfront so patients are prepared for a potentially longer and more involved process, and they're typically understanding. If they mention it's hard for their doctor to get an accurate glasses prescription, that's sort of a red flag to ask a few follow-up questions. Is it because they're tough to be refracted, is it the cataract? It might be someone who isn't going to be easy to do adjustments on, so you want to have your radar up."

Neda Shamie, MD

Adjustments for the Light-Adjustable Lens are scheduled approximately three weeks after the second eye for post-myopic LASIK or virgin eyes, whereas post-hyperopic or post-RK patients begin adjustments at least six weeks after their second eye to ensure the cornea has stabilized, recommends Neda Shamie, MD.

Tolerance of monovision is an important component of patient criteria. "Many patients may not have ever tried monovision before and may be hesitant about the ability to tolerate the anisometropia," says Dr. Shamie. "A typical LAL candidate in our practice is one who is motivated to have spectacle independence but is concerned about the aberrations related to multifocal lenses or may have eyes that aren't ideal for multifocal implants. They may be a patient who has specifically high visual expectations, or has had corneal-based refractive surgery such as LASIK, PRK or RK. The LAL's advanced technology provides a solution tailored to their needs."

For those who have experienced monovision, whether naturally or with contact lenses, the LAL would be a good fit, continues Dr. Shamie. "Even if they've never had LASIK, PRK or RK, but they've done well with monovision, those patients also understand what it means to optimize the distance vision and have their near at that sweet spot," she says. "In fact, the LAL+ especially is an ideal option because it gives a bit of range of vision with the ability to fine tune it further and to create a blended zone of vision."

Be cognizant of a patient's ocular comorbidities as well, cautions Dr. Shamie. "Initially, we were more aggressive in recommending the LAL for patients with comorbidities such as macular degeneration who wouldn't otherwise be candidates for premium lenses, but we learned that this may not always be the best approach," she says. "The LAL behaves similarly to a monofocal or monofocal toric lens in terms of optical quality, so there are no added visual aberrations as one sees with diffractive multifocal lenses. The reason to hesitate recommending the LAL to patients with visually significant comorbidities such as AMD is mostly to avoid an unhappy outcome when a patient has invested time and money in this advanced lens technology and may have related unrealistic expectations of the visual potential of the eye.

"I'm fully transparent with such patients about my hesitation and paint a realistic picture of what they would achieve to help them understand why the LAL may not be the ideal IOL for them," continues Dr. Shamie. "The time and cost commitment might not be justified if the patient's best possible vision is limited."

Another element to keep in mind is the patient's astigmatism. "The LAL

MANY MANIFESTATIONS OF THYROID EYE DISEASE (TED)

ONE ROOT CAUSE[1-3]

TEPEZZA®
teprotumumab-trbw

TEPEZZA is indicated for the treatment of Thyroid Eye Disease (TED) *regardless* of disease activity or duration[4]

Designed to **target and block IGF-1R**, a key driver of TED pathophysiology

TEPEZZA has shown to:

- Decrease proptosis[4,5,7]
- Improve diplopia[4-7]
- Reduce orbital pain, redness, and swelling[5,7]
- Improve functional vision and patient appearance[5,7†]

†Patient reported based on GO-QOL scale

...in two 24-week, randomized, double-masked, placebo controlled clinical studies of 171 patients with TED.[4]

See how TEPEZZA can help reduce the burden of TED

Teprotumumab-trbw's mechanism of action in patients with TED has not been fully characterized. Teprotumumab-trbw binds to IGF-1R and blocks its activation and signaling.[1]

IGF-1R, insulin-like growth factor-1 receptor.

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INDICATION

TEPEZZA is indicated for the treatment of Thyroid Eye Disease regardless of Thyroid Eye Disease activity or duration.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Infusion Reactions: TEPEZZA may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with TEPEZZA. Reported infusion reactions have usually been mild or moderate in severity. Signs and symptoms may include transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache, and muscular pain. Infusion reactions may occur during an infusion or within 1.5 hours after an infusion. In patients who experience an infusion reaction, consideration should be given to premedicating with an antihistamine, antipyretic, or corticosteroid and/or administering all subsequent infusions at a slower infusion rate.

Preexisting Inflammatory Bowel Disease: TEPEZZA may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

Hyperglycemia: Increased blood glucose or hyperglycemia may occur in patients treated with TEPEZZA. In clinical trials, 10% of patients (two-thirds of whom had preexisting diabetes or impaired glucose tolerance) experienced hyperglycemia. Hyperglycemic events should be controlled with medications for glycemic control, if necessary. Assess patients for elevated blood glucose and symptoms of hyperglycemia prior to infusion and continue to monitor while on treatment with TEPEZZA. Ensure patients with hyperglycemia or preexisting diabetes are under appropriate glycemic control before and while receiving TEPEZZA.

Hearing Impairment Including Hearing Loss: TEPEZZA may cause severe hearing impairment including hearing loss, which in some cases may be permanent. Assess patients' hearing before, during, and after treatment with TEPEZZA and consider the benefit-risk of treatment with patients.

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥5% and greater than placebo) are muscle spasm, nausea, alopecia, diarrhea, fatigue, hyperglycemia, hearing impairment, dysgeusia, headache, dry skin, weight decreased, nail disorders, and menstrual disorders.

Please see Full Prescribing Information or visit TEPEZZAhcp.com for more information.

TEPEZZA®
teprotumumab-trbw

For injection, for intravenous use

Brief Summary - Please see the TEPEZZA package insert for full prescribing information.

INDICATIONS AND USAGE

TEPEZZA is indicated for the treatment of Thyroid Eye Disease regardless of Thyroid Eye Disease activity or duration.

WARNINGS AND PRECAUTIONS

Infusion Reactions

TEPEZZA may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with TEPEZZA. Signs and symptoms of infusion-related reactions include transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache and muscular pain. Infusion reactions may occur during any of the infusions or within 1.5 hours after an infusion. Reported infusion reactions are usually mild or moderate in severity and can usually be successfully managed with corticosteroids and antihistamines. In patients who experience an infusion reaction, consideration should be given to pre-medicating with an antihistamine, antipyretic, corticosteroid and/or administering all subsequent infusions at a slower infusion rate.

Exacerbation of Preexisting Inflammatory Bowel Disease:

TEPEZZA may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

Hyperglycemia:

Hyperglycemia or increased blood glucose may occur in patients treated with TEPEZZA. In clinical trials, 10% of patients (two-thirds of whom had preexisting diabetes or impaired glucose tolerance) experienced hyperglycemia. Hyperglycemic events should be controlled with medications for glycemic control, if necessary.

Assess patients for elevated blood glucose and symptoms of hyperglycemia prior to infusion and continue to monitor while on treatment with TEPEZZA. Ensure patients with hyperglycemia or preexisting diabetes are under appropriate glycemic control before and while receiving TEPEZZA.

Hearing Impairment Including Hearing Loss:

TEPEZZA may cause severe hearing impairment including hearing loss, which in some cases may be permanent. Assess patients' hearing before, during, and after treatment with TEPEZZA and consider the benefit-risk of treatment with patients.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Infusion Reactions *[see Warnings and Precautions]*
- Exacerbation of Preexisting Inflammatory Bowel Disease *[see Warnings and Precautions]*
- Hyperglycemia *[see Warnings and Precautions]*
- Hearing Impairment Including Hearing Loss *[see Warnings and Precautions]*

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.

The safety of TEPEZZA was evaluated in two randomized, double-masked, placebo-controlled clinical studies (Study 1 [NCT:01868997] and Study 2 [NCT:03298867]) consisting of 170 patients with Thyroid Eye Disease (84 received TEPEZZA and 86 received placebo). Patients were treated with TEPEZZA (10 mg/kg for first infusion and 20 mg/kg for the remaining 7 infusions) or placebo given as an intravenous infusion every 3 weeks for a total of 8 infusions. The majority of patients completed 8 infusions (89% of TEPEZZA patients and 93% of placebo patients).

The most common adverse reactions (≥5%) that occurred at greater incidence in the TEPEZZA group than in the control group during the treatment period of Studies 1 and 2 are summarized in Table 1. In addition, menstrual disorders (amenorrhea, metrorrhagia, dysmenorrhea) were reported in approximately 23% (5 of 22 patients) of menstruating women treated with TEPEZZA compared to 4% (1 of 25 patients) treated with placebo in the clinical trials.

Table 1. Adverse Reactions Occurring in 5% or More of Patients Treated with TEPEZZA and Greater Incidence than Placebo

Adverse Reactions	TEPEZZA N=84, N (%)	Placebo N=84, N (%)
Muscle spasms	21 (25%)	6 (7%)
Nausea	14 (17%)	8 (9%)
Alopecia	11 (13%)	7 (8%)
Diarrhea	10 (12%)	7 (8%)
Fatigue[a]	10 (12%)	6 (7%)
Hyperglycemia[b]	8 (10%)	1 (1%)
Hearing impairment[c]	8 (10%)	0
Dysgeusia	7 (8%)	0
Headache	7 (8%)	6 (7%)
Dry skin	7 (8%)	0
Weight decreased	5 (6%)	0
Nail disorder[d]	4 (5%)	0

a - Fatigue includes asthenia

b - Hyperglycemia includes blood glucose increase

c - Hearing impairment including hearing loss (deafness, including sensorineural deafness, eustachin tube dysfunction, hyperacusis, hypoacusis, autophony and tinnitus)

d - Nail disorder (includes nail discoloration, nail disorder and onycholysis)

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay.

In a placebo-controlled study with TEPEZZA, 1 of 42 patients treated with placebo had detectable levels of antidrug antibodies in serum. In the same study, none of the 41 patients treated with TEPEZZA had detectable levels of antidrug antibodies in serum.

Postmarketing Experience

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

Metabolism and Nutrition Disorders: diabetic ketoacidosis, hyperosmolar hyperglycemic state (HHS).

Otologic: severe hearing impairment including hearing loss, which in some cases may be permanent.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action inhibiting insulin-like growth factor 1 receptor (IGF-1R), TEPEZZA may cause fetal harm when administered to a pregnant woman. Adequate and well-controlled studies with TEPEZZA have not been conducted in pregnant women. There are insufficient data with TEPEZZA use in pregnant women to inform any drug associated risks for adverse developmental outcomes. In utero teprotumumab exposure in cynomolgus monkeys dosed once weekly with teprotumumab throughout pregnancy resulted in external and skeletal abnormalities. Teprotumumab exposure may lead to an increase in fetal loss *[see Data]*. Therefore, TEPEZZA should not be used in pregnancy, and appropriate forms of contraception should be implemented prior to initiation, during treatment and for 6 months following the last dose of TEPEZZA. If the patient becomes pregnant during treatment, TEPEZZA should be discontinued and the patient advised of the potential risk to the fetus.

The background rate of major birth defects and miscarriage is unknown for the indicated population. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively.

Data

Animal Data

In an abridged pilot embryofetal development study, seven pregnant cynomolgus monkeys were dosed intravenously at one dose level of teprotumumab, 75 mg/kg (2.8-fold the maximum recommended human dose [MRHD] based on AUC) once weekly from gestation day 20 through the end of gestation. The incidence of abortion was higher for the teprotumumab treated group compared to the control group. Teprotumumab caused decreased fetal growth during pregnancy, decreased fetal size and weight at caesarean section, decreased placental weight and size, and decreased amniotic fluid volume. Multiple external and skeletal abnormalities were observed in each exposed fetus, including: misshapen cranium, closely set eyes, micrognathia, pointing and narrowing of the nose, and ossification abnormalities of skull bones, sternebrae, carpals, tarsals and teeth. The test dose, 75 mg/kg of teprotumumab, was the maternal no observed adverse effect level (NOAEL).

Based on mechanism of action inhibiting IGF-1R, postnatal exposure to teprotumumab may cause harm.

Lactation

Risk Summary

There is no information regarding the presence of TEPEZZA in human milk, the effects on the breast-fed infant or the effects on milk production.

Females and Males of Reproductive Potential

Contraception

Females

Based on its mechanism of action inhibiting IGF-1R, TEPEZZA may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations]*. Advise females of reproductive potential to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

Geriatric Use

Of the 171 patients in the two randomized trials, 15% were 65 years of age or older; the number of patients 65 years or older was similar between treatment groups. No overall differences in efficacy or safety were observed between patients 65 years or older and younger patients (less than 65 years of age).

OVERDOSAGE

No information is available for patients who have received an overdosage.

PATIENT COUNSELING INFORMATION

Embryo-Fetal Toxicity

- Advise females of reproductive potential that TEPEZZA can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy.
- Educate and counsel females of reproductive potential about the need to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

Infusion-related reactions

- Advise patients that TEPEZZA may cause infusion reactions that can occur at any time. Instruct patients to recognize the signs and symptoms of infusion reaction and to contact their healthcare provider immediately for signs or symptoms of potential infusion-related reactions.

Exacerbation of Preexisting Inflammatory Bowel Disease

- Advise patients on the risk of inflammatory bowel disease (IBD) and to seek medical advice immediately if they experience diarrhea, with or without blood or rectal bleeding, associated with abdominal pain or cramping/colic, urgency, tenesmus or incontinence.

Hyperglycemia

- Advise patients on the risk of hyperglycemia and, if diabetic, discuss with the healthcare provider to adjust glycemic control medications as appropriate. Encourage compliance with glycemic control.

Hearing Impairment Including Hearing Loss

- Advise patients that TEPEZZA may cause severe hearing impairment including hearing loss, which in some cases may be permanent. Instruct patients to contact their healthcare provider if they experience any signs or symptoms of hearing impairment or any changes in hearing.

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only corrects for regular astigmatism up to 2 to 3 D; it doesn't correct irregular astigmatism," says Dr. Shamie. "The lens isn't a good option for patients with highly aberrated corneas, such as keratoconus. It's a great lens to correct regular astigmatism up to 3 D but in its virgin state upon implantation, it's essentially a monofocal IOL needing light adjustments to correct the refractive astigmatism. Therefore, it's important for the patient to understand that right after the surgery their vision isn't going to be optimized due to the remaining astigmatism up until the point that they start getting light treatments. They may need a temporary pair of glasses for some activities."

For some patients, the commitment on their end may turn them off, while for others, it can be a rewarding experience.

"I'd put the LAL in everybody, but it requires a few things from the patient, including time, patience and a financial investment," explains Dr. Khandelwal. "Patients need to be aware that achieving optimal results with the LAL involves multiple follow-up visits and may take several months to finalize. This is a contrast to presbyopia-correcting lenses, which generally offer a more straightforward outcome with a quicker recovery period. I make it clear that if a patient isn't willing to commit to the necessary time and follow-up appointments, the LAL might not be the right choice for them.

"When you explain that it could potentially take two to three months for the final lock-in, if not longer for those with RK, there are patients who will decline," she continues. "At that point I direct the conversation to a different lens platform. On the other hand, we'll have patients who go home and read about the LAL and understand the fact that it can be optimized after surgery and it realigns their priorities. They realize this is an investment in the eyes that will last their lifetime and they're willing to put some other things on hold to make it happen."

Understanding patient psychology is crucial in determining who would benefit most from the LAL, according to Dr. Shamie. "It's essential to match the technology to patients who will appreciate the detailed adjustments and fine-tuning," she says. "Those who have enjoyed excellent vision with past refractive surgeries or are highly discerning about their vision are typically the best candidates for the LAL. On the other hand, patients who are less discerning about their visual needs may not find the LAL necessary and would push back on the time commitment."

Those who do commit to the requirements associated with the LAL are treated like partners in the process. "We routinely observe higher satisfaction levels with the LAL compared to other lenses," says Dr. Hovanesian. "This is largely due to the favorable refractive outcomes and the fact that patients are actively involved in the process. They understand from the beginning that they'll need to wear glasses for a while and invest time into achieving a long-term outcome. They appreciate the 'lock-in' process and feel satisfied because they see their results evolve. This creates a sense of accomplishment, similar to preparing for a sports competition, where the effort put in leads to great results. By the end of the treatment, we celebrate with our patients, referring to them as graduates of the process."

Preop Planning and Surgery

The screening process for the LAL is similar to that of any premium lens, according to surgeons, who note there are some important elements not to overlook.

"In terms of preoperative diagnostics, the LAL requires careful assessment to ensure that it's the right choice for the patient," Dr. Shamie says. "This includes using advanced diagnostic tools such as macular OCT to check for any underlying conditions like epiretinal membranes or drusen that could affect vision quality. We also perform topography and tomography to assess the corneal contour and identify any potential limitations due to comorbidities before proceeding with the implantation."

Dr. Hovanesian says signs of dry eye should be managed effectively before surgery.

That therapy will likely have to continue after cataract removal. "I used to think the LAL was going to be the lens implant for patients who couldn't have a multifocal or an EDOF because of their dry eye, but these patients are so hard to refract," Dr. Khandelwal says. "If they have ocular surface disease, they can swing like a pendulum. Not only will you need to optimize them ahead of time, you'll need to make sure they're optimized afterwards. Otherwise, it's tough to lock them in because their cylinder is changing so much."

Dr. Shamie says the LAL requires a pupil dilated to at least 6 mm to allow for effective light adjustments. "If a patient has conditions such as pseudoexfoliation or is on medications that affect pupil dilation, this could limit the ability to perform necessary adjustments," she says.

Intraoperatively, surgeons recommend expanding the traditional cataract incision to 2.8 mm to accommodate the LAL injector.

"The surgical procedure for the LAL is very similar to that of traditional silicone lenses," Dr. Hovanesian says. "It's a three-piece lens, so for surgeons who have only trained with single-piece acrylic lenses, there are some differences. The lens loads differently and requires skill and experience during loading. It's crucial to handle the posterior side of the lens carefully, as it has a fragile ultraviolet-absorbing coating that can be damaged with significant manipulation. When implanted, the lens opens more quickly than an acrylic lens, so surgeons need to be prepared for that."

"In our practice, we have our scrub techs handle the loading because they're used to loading them all day long for different surgeons," adds Dr. Khandelwal. "If your surgical center

doesn't have experienced scrub techs, it's advisable for you to load the lens yourself to avoid scratching the optic. Scratching the optic would necessitate removing and replacing the lens. As surgeons, we're okay with the leading haptic coming out a little awkwardly if we know it's going to happen, but we don't want it to be scratched."

Dr. Shamie advises that the capsule be fully expanded with viscoelastic during implantation. "The slightly rapid nature of how the LAL unfolds could catch on the capsule if the eye is soft, so it's important to make sure there's enough viscoelastic in the eye," she says. "There's a technique of rotating your hand first to the left and then to the right to make sure the haptic opens in a more planar fashion. Going slow is beneficial. While the unfolding process is quicker than with a one-piece lens, it can be learned with practice. Using an artificial anterior chamber to practice lens implantation can be helpful."

When determining a target for the LAL, Dr. Shamie suggests a slightly hyperopic outcome initially and adjusting towards myopic. "This approach provides an extended depth of focus and gives patients a sense of ongoing improvement," she says. "For patients who have tried monovision before, and that's what you're targeting, I tend to pull back on the near correction. If their monovision was a -2.5 D for example in their near eye, I don't go straight to targeting -2.25 D. I start off at maybe 0.75 D less myopic correction in the near eye, because, again, when you adjust towards the near they tend to have some extended range of focus which could mean less anisometropia but still excellent range of vision."

"From my extensive experience, I've found that many patients achieve 20/20 distance vision and often get to J2 or even J1 for near vision," Dr. Hovanesian says. "When combined with a small amount of myopia in the non-dominant eye, say 0.25 or 0.5 D, you often get a full range of vision with minimal compromise on distance vision. It's a very satisfying option, although it's not suitable for every patient."

Managing Appointments and Treatments

While the LAL technology opens up the possibilities for a host of patients to reach their vision potential, there are some scheduling and logistical hurdles to overcome within the clinic.

Introducing this lens to your staff should be gradual, and everyone should expect adjustments to be made as it's rolled out to more patients, surgeons tell us.

"Implementing significant changes in workflow begins with bringing everyone together in the practice to explain why we're adopting this new process," explains Dr. Hovanesian. "It's crucial to get everyone on board, as they're more willing to work through the steps when they understand the rationale. Many practices overlook this essential step, assuming that everyone will simply fall in line with new procedures. We approach this very deliberately."

The scheduling and management of postoperative visits for patients with the LAL has the potential to be quite intricate and differs from the typical postop cataract visits. "Initially, I'd schedule a standard follow-up plan: a day one visit, possibly with a co-managing optometrist, followed by a visit with me three to four weeks later," Dr. Khandelwal says. "However, with the LAL, we've adjusted this approach to optimize outcomes.

"The LAL really works better if you schedule the second eye surgery one week after the first eye to align with the LAL's requirement for simultaneous adjustments," she continues. "This approach ensures that both eyes are treated together. You don't want to stagger them. After the initial surgery, we schedule follow-up visits for light treatments one week apart."

For patients with a history of hyperopic LASIK or RK, the adjustment schedule will differ. "For post-myopic LASIK or virgin eyes, we recommend the first adjustment about three weeks after the second eye is done, with subsequent adjustments and lock-ins spaced one week apart, usually completed within eight weeks after surgery," Dr. Shamie says. "In contrast, for post-hyperopic or post-RK patients, we start the first adjustment at least six weeks after their second eye, with adjustments spaced two weeks apart. This longer schedule helps ensure that the cornea has stabilized before making further adjustments."

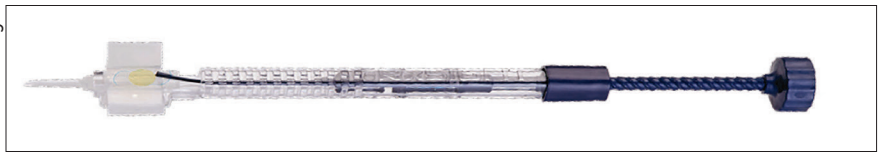
Dr. Hovanesian says there's no denying that the adjustment process is somewhat time-consuming, but it's discussed from the outset. "There can be as many as five visits for light treatments, with two of those being lock-ins," he says. "Each visit includes careful refractions, counseling, dilation and treatment, along with any waiting time. Therefore, each adjustment visit usually takes at least 45 minutes to an hour, often longer."

The adjustment itself is relatively quick, taking about 10 minutes, says Dr. Khandelwal. "However, the entire visit usually lasts about an hour and a half. Patients undergo a refraction with our optometrist, followed by dilation. If the goal is to achieve distance vision only, the process takes about an hour, but if the patient seeks additional near vision, we might conduct a monovision trial and have them walk around to gauge their vision. This extra step can extend the duration of the visit," she says.

Considering the scheduling challenges associated with the LAL, practitioners using the lens have adopted their own *modus operandi* that suits their particular clinic. Some surgeons choose to perform the adjustments and lock-ins themselves, and others rely on the skills of an optometrist (whether internal or external) to see the patient through these appointments.

"In our practice, managing patients with the Light-Adjustable Lens involves a dedicated team approach," Dr. Khandelwal says. "Initially, when we started using the LAL, we had several technicians help with refractions

RxSight



Surgeons say to enlarge the cataract incision to 2.8 mm to accommodate the Light-Adjustable Lens insertion device. They recommend careful loading of the lens to avoid scratching the optic.

and trained them to assist with the treatments. However, we have since found it beneficial to have one or two primary staff members responsible for performing refractions and conducting monovision trials and patient counseling during each visit. In our office, we have an optometrist who does this for multiple surgeons. This setup allows for a collective experience."

Dr. Khandelwal prefers to personally handle her patients' adjustments of the LAL. "Although some practices may have optometrists or even retired ophthalmologists perform these final adjustments, we find that having our optometrists involved in the refraction and counseling process, while I handle the adjustments, works effectively," she says. "This arrangement works well because the refraction, the monovision trials, and counseling all fall within the optometrist skillset. Then I come in and verify everything with the patient before doing the treatment with the optometrist by my side. It doesn't take me out of the clinic for very long."

She adds that each surgeon at her center has designated days for surgeries and treatments, and patients are aware of the schedule from the start to manage patient expectations.

When Dr. Shamie began working with the LAL, she initially performed light adjustments in order to gain a thorough understanding of the process before training their staff optometrists. "Now, our optometrists, who are specially trained in light adjustments, handle this aspect," she says. "They perform initial postop light-adjustment exams, including trial frames and contact lens trials if necessary, to determine the best refractive target."

Dr. Hovanesian says everyone on his staff was trained for the LAL, and they developed a special process, including electronic paperwork and a patient flow protocol. "Our optometrists play an integral role in this process; they handle everything except the light treatments," he says. "During appointments, optometrists dilate the patients and then send them to us on the same visit for light treatment, with the surgeons performing the actual light treatments. Given the number of visits required, it's vital to have a well-organized system in place."

In the process of making adjustments, Dr. Khandelwal says patient psychology is still in play. "For example, if I know they were a monovision patient, but they didn't tolerate driving at nighttime with monovision contact lenses, I'm not going to push the monovision right away," she says. "I'll go slow with the monovision, whereas, if they were a rock star monovision patient, we can go a little bit more near on that first eye treatment. If the patient used to be a -3 and now I've made them distance in both eyes, I know that patient is going to want to push the envelope on the near vision. I make sure to discuss compromises with them."

These surgeons warn others to be careful not to keep moving those visual goalposts.

"It's important to get a clear commitment from the patient to the refractive target prior to initiating the first adjustment to avoid confusion and ensure a smooth process," Dr. Shamie advises. "If the patient is given the impression that they can change their mind at every adjustment, it would cause a serious workflow challenge. We made that mistake in the beginning. Now, the optometrists handle subsequent adjustments, focusing on moving towards the target without revisiting the target at each visit."

Remember that the ultimate goal is patient happiness, Dr. Hovanesian adds. "Sometimes we may feel tempted to pursue a sharper target, but it's important to avoid pushing the goal too far, which could lead to a worse outcome," he says.

One final word of caution from Dr. Khandelwal: Occasionally, patients may experience early posterior capsule opacification. "In such cases, we address this issue with an early YAG capsulotomy before proceeding with any adjustment treatments," she says.

Weighing the Return on Investment

The vast array of IOL options on the market leaves some cataract surgeons wondering where the LAL fits into their everyday practice. These surgeons say it's a worthwhile investment.

"For those considering adopting the LAL in their practice, I recommend viewing it as an opportunity to expand premium offerings rather than as a replacement for existing lens options," says Dr. Khandelwal. "I don't think it cannibalizes the current lenses out there."

More often than not, patients are seeking advanced IOL technology, but are limited by their own pathology. "Having the LAL expands the offerings to those patients who would otherwise have gotten standard lenses," Dr. Shamie says. "There are patients in every practice who desire freedom from glasses or want customized vision, but for one reason or another, they're not a great candidate for the other presbyopia-correcting lenses. Unfortunately, if the surgeon doesn't have access to the LAL, this patient can only fall back onto a standard lens when they may have been willing—more than willing—to invest in optimized, advanced lens technology."

"By offering this technology, you may find that it can be used for more patients than you initially thought, extending beyond just post-refractive patients," Dr. Hovanesian concludes. "It allows for greater patient control over their outcomes. ◀

HOW TO FIND AND RETAIN SKILLED PHYSICIANS AND STAFF

Practical tips on how to distinguish your ophthalmology practice in a crowded labor market.

LEANNE SPIEGLE
ASSOCIATE EDITOR

The field of ophthalmology is facing a significant challenge: a shrinking workforce. A recent study on ophthalmology workforce projections in the United States found that while the number of full-time ophthalmologists will decline by 2,650 between 2020 and 2035, the demand for these doctors will jump to 5,150, representing a supply and demand mismatch of 30 percent.[1] For practices, this shortage means stiffer competition for recruiting the available talent.

It's also getting more difficult to find reliable support staff for ophthalmology clinics, such as administrators, receptionists and technicians. A recent report by the U.S. Bureau of Labor Statistics showed that over the last 20 years, the labor participation rate has declined steadily.[2] Staff turnover rates have also increased among health-care workers since the COVID-19 pandemic.[3]

To navigate these current challenges, practices need innovative recruitment and retention strategies. Below, several practice managers and ophthalmologists share their secrets on locking in good physicians and staff and creating a positive environment that nurtures employee retention.

Hunting Down Doctors

When looking for ophthalmologists or optometrists to join your practice, you have to cast your net far and wide to find the person who will be the best fit.

"You've got to look everywhere," says John Pinto, president and founder of J. Pinto & Associates, an ophthalmic practice management firm based in San Diego. "It's not just one call to a recruiting company and you're done; to boost the candidate pool, you have to search on the academy website, send letters out to schools, make calls to your friends in the industry," and so on, he says.

Numerous websites allow you to post job openings and/or search for potential candidates (sometimes for a fee), two examples being Indeed and ZipRecruiter. There are also several online resources specific to MD and OD hiring, such as The Eye Group, ETS Vision and PracticeLink. Saralee Esau, COA, CPSS, practice manager of Empire Eye and Laser Center in Bakersfield, California, says they exhaust all of these resources when hunting for doctors to hire.

"The Eye Group and ETS Vision are physician recruiters, while PracticeLink is a platform we use to post jobs when looking for providers," she notes. "We've seen success using all of these platforms, as well as Indeed."

Another way to find doctors to hire is by taking advantage of local optometry schools and residency programs. Consider posting directly on local school websites around graduation time, Mrs. Esau suggests. "There have been times where we've attended specialty-specific job fairs; some of the national boards and organizations will have gatherings for new grads, and it's a great opportunity to network with doctors looking for new positions," she says.

Colleen Halfpenny, MD, a managing partner at Valley Eye Professionals in Huntington Valley, Pennsylvania, and clinical instructor at the cataract and primary eye care clinic at Wills Eye, says that they've found most of their physicians through the network of residents and fellows that she or her colleagues already knew or personally trained. "If you live in an area with a lot of residency programs, it's a great resource," she says, "especially when

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you're involved in teaching them and can recruit them at an early stage, if they're interested in staying in the area."

Finding Support Staff

A solid team of support staff is just as integral as skilled physicians to the health and success of a practice. "Patients come to the practice to see the doctors, but their experience starts from the minute they make a phone call to the clinic," says Dr. Halfpenny.

Leverage the available resources to attract eager candidates as you would when recruiting physicians. These include online job posting and recruiting platforms, local staffing agencies (especially those that are health-oriented), crowdsourcing to colleagues and friends or, Mr. Pinto adds, even "turning to your own staff and offering a finder's fee of $1,000 or so for information leading to a successful hire."

Ms. Esau says that in her experience, the most useful job posting site for finding support staff is ZipRecuiter, which "uses AI support to target candidates and help you identify people that haven't applied for your position but have characteristics that match what you're looking for."

Ensuring Candidates Fit

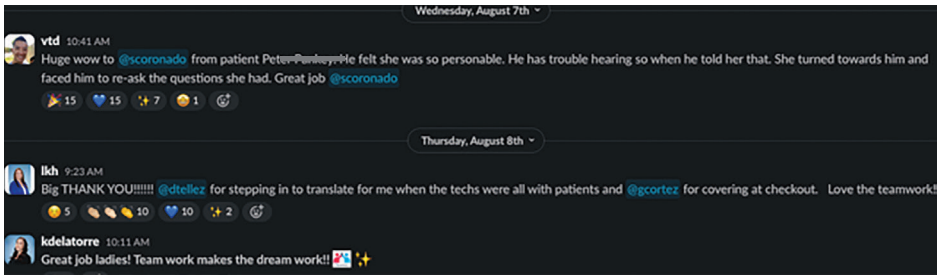
When entertaining any potential candidate, it's important to remember not to hire too quickly; you first have to ensure the person will work well with your existing team and can offer a level of patient care consistent with what patients expect from your practice. Holding multiple phone calls and bringing candidates into the office for at least one physical interview can help you get a better feel for their personality and demeanor, as well as how they interact with the other staff.

Mary Siegman, who works with Dr. Halfpenny at Valley Eye Professionals as the practice administrator, points out that for some people, job interviews stir up a great deal of anxiety, potentially obscuring their true personality. In these instances, she suggests pausing the interview and redirecting the conversation to one that's more casual to give them a chance to let their guard down.

"People often get more comfortable when you let them talk about themselves," she says. "You can't ask if they have kids or anything like that, because that could be considered discrimination," she cautions, "but you can ask if they had a nice weekend, or talk about the weather that day; any topic that isn't related to the interview."

Another tip is to ask about a candidate's long-term goals to differentiate people who are solely focused on a paycheck from those trying to build a career—and, according to Ms. Siegman, there's a tangible difference between the two in terms of work ethic. "People who want a career are the ones who really work hard and work really well with the doctors," she says.

To get a feel for a candidate's work ethic and experience, Mr. Pinto asks about their first job. "You want someone who has a long work history," he says. "Take people who run successful businesses, who work hard, enjoy work and have a sense of commitment to their organization. If you ask about their first paying job, they'll typically say, 'I was babysitting at 12,' or, 'I cut all the neighbors' lawns when I was 14;' the people with this drive have typically been working since they were quite young."



Empire Eye and Laser Center

Staff at Empire Eye and Laser Center in Bakersfield, California, have a group chat where they share affirmations and congratulate one another, for example, when someone goes above and beyond for a patient.

How to Stand Out

To attract and retain the best candidates, you have to offer unique value and opportunities to your employees that they can't just find at any other practice in your area. While competitive salaries are undoubtedly attractive to prospective physicians and staff, other factors play into one's decision to work—and continue working—at a particular practice, such as a positive office culture, performance-based incentives, certain benefits and schedule flexibility.

Here are some insights on fostering a work environment that distinguishes your practice and reduces staff turnover:

• ***Build staff morale***. Encouraging good relationships among staff not only boosts job satisfaction and makes it easier to retain quality employees; it can also positively impact the overall efficiency and success of a practice.

"Something that we focus a lot of energy into is maintaining our staff morale, because it does reflect onto patient care," says Ms. Esau. "Patients feel the difference if staff genuinely get along and if the overall feeling of the environment is positive."

Having a group chat with your employees through text or a communication app like Slack or WhatsApp can help encourage interaction between staff beyond the daily few-minute chats by the lunchroom microwave. For Ms. Esau's practice, their group chat serves as a place to celebrate and connect with one another, as well as exchange compliments and positive feedback on each other's performance.

"If it's someone's birthday, anniversary, baby shower, etc., we make a 'thing' out of it; we get on Slack to post memes and congratulate each other," she says. On the Slack app, you can create various "channels" to communicate only about specific topics; Ms. Esau says they use this feature by dedicating a channel solely for giving kudos and affirmations to each other. "If a patient compli-

Advertorial

Giddy Up: OSRX Says 'There's a New Sheriff in Town'

The Montana-based pharmacy has achieved 503B status and is gunning to become the top compounder – not just out West – but in all of ophthalmology.

OSRX® Pharmaceuticals recently achieved its new status as a 503B outsourcing facility, marking a significant leap toward becoming the top ophthalmic compounder nationwide. Guided by Founder and CEO Anthony Sampietro, OSRX is set to expand its services to allow doctors to bulk order OMNI by OSRX® ophthalmic formulations to their private practices, hospitals, and ambulatory surgery centers.

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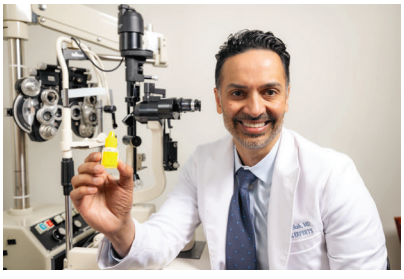
"We are applying OSRX's expertise, talent, and commitment to quality to ensure our 503B business meets CGMP standards and align with the FDA's requirements for outsourcing facilities," says Chief Pharmacy Officer Amy Frost, another key leader in this exciting venture for OSRX. "It's been a challenging, but very rewarding journey. Instead of only being able to ship patient-specific prescriptions, we can now transport in bulk directly to medical facilities. It's a win-win for prescribers and their patients."

Great News for High-volume Practices

Chirag Shah, MD, is a board certified ophthalmologist and the founder of LASIK Experts in New Jersey and Pennsylvania. Having trusted OSRX post-op eye drops for his high-volume practice, he is excited about the 503B announcement. "With this new status, OSRX bulk ordering will help remove barriers, making quality medications more accessible to patients. The drops we receive from OSRX are predictable with consistent high-quality medications in each bottle."



Quality is Top Priority

"Since 2017, our company has been predicated on providing simple, affordable and quality solutions for pre- and post-op care with white-glove treatment," says Sampietro. "We will continue our long-standing service model. OSRX as a 503B is an expansion of services, not a change. We are not altering what made us who we are."

About OSRX

OSRX is an FDA-registered 503B outsourcing facility committed to transforming ophthalmic care through quality compounded solutions. The Missoula, MT-based company is on a mission to redefine the landscape of the corrective eye care market with a focus on simplicity, affordability and patient-centric care. Trusted by more than 5,500 prescribers across the U.S., OSRX is providing A New View of Medicine®. Learn more at www.osrxpharmaceuticals.com.

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Valley Eye Professionals

Valley Eye Professionals in Huntington Valley, Pennsylvania, treated its staff to an evening at the Philadelphia Phillies game last spring.

Empire Eye and Laser Center

At Empire Eye and Laser Center, the favorite quarterly staff event is an afternoon at the movies.

ments someone, if we get a good review online about someone or if a doctor or manager observes something exceptional, we share it there. It really helps to build connections and rapport with the team. It also opens the door for people to show their personality and make connections based on common interests."

Scheduling social events outside of the office for doctors and staff is another great way to deepen personal relationships between colleagues. Some outings that Ms. Siegman and Dr. Halfpenny have arranged for their employees include a baseball game, bowling party and potluck lunches. At Ms. Esau's practice, staff events happen quarterly: "This can be a game-filled afternoon or offsite activities, like going to a wine safari, having a paint and sip or, our favorite, an afternoon at the movies."

• ***Make it fun.*** Ms. Esau remarks, "The job market is changing; if we can't be both fun and productive, we're behind."

Some ways to switch up the typical nine-to-five hustle, while also helping your employees to feel more valued and connected, include celebrating employee birthdays and holidays in the office, treating staff to lunch or even weaving fun activities into the clinic day such as quizzes or office scavenger hunts.

Dr. Halfpenny and Ms. Siegman say that at their practice, everyone's birthday gets celebrated. Each month, they get a cake with everyone's name on it who has a birthday coming up. "We also give employees a birthday card and small gift on their day," Dr. Halfpenny adds.

Holidays are another opportunity to sprinkle some fun into the daily grind. "For Chinese New Year, we decorated our kitchen with Chinese lanterns and ordered Chinese food for the day; for Cinco de Mayo, we'll decorate with sombreros and bring in Mexican food for the staff," Ms. Siegman says.

At Ms. Esau's practice, her assistant consults the National Day Calendar and selects a few days to celebrate each month. "For instance, on National Ice Cream Day, which we had in July, we brought in stuff to make sundaes," she notes. They also celebrate national and international events: "During the Olympics, we put little flags up everywhere, and during the Super Bowl, everyone wore their favorite team's jersey. These things don't have to be huge, but they help keep it interesting."

Another thing Ms. Esau's clinic does to break up the day is pop quizzes—on the office's SOPs, for example—where staff can win prizes. "We'll ask everyone, 'What is our no-show fee if someone doesn't show up for a cataract consult?' Then, the first person to answer correctly receives a $5 Amazon gift card or something small like that," she says.

• ***Reward your employees.*** It's important to express your appreciation for your employees both verbally and financially and to recognize and reward them when they go the extra mile.

One non-financial way to let staff know you recognize their hard work is to hand out thank you cards when you witness them doing an exceptional job, Ms. Siegman suggests. "I will also send an email to our team to congratulate the whole staff when we receive positive feedback from a patient," she adds.

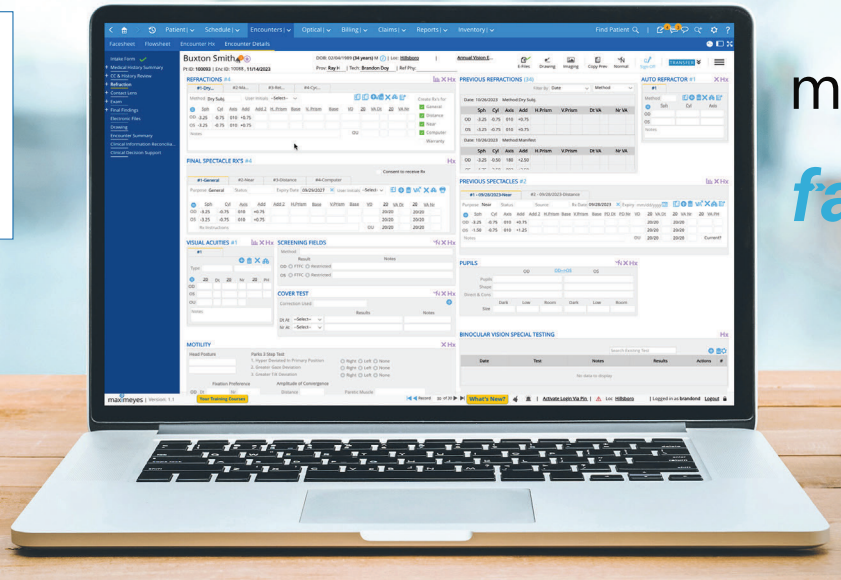
Rather than giving employees a standard 3-percent raise each year, consider basing their annual salary increase on the quality of their performance that year; having employees know that they are working towards a bigger paycheck is a great way to encourage and reward a strong work ethic.

Ms. Esau says their employees are eligible for a merit increase every year "based on a percentage of their current earnings, and what they receive is based on the score from their performance review; it's weighted," she explains. "The better they perform, the more they make. It gives employees something to look forward to, a feeling of growth and

Empire Eye and Laser Center

Celebrating your employees' personal milestones in the office, such as by decorating for birthdays or throwing small baby showers, can help them feel seen and appreciated.

Schedule a Demo



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Valley Eye Professionals

Ms. Siegman gives thank-you notes to staff who do an exceptional job to let them know their hard work is being recognized.

an opportunity to build. Rather than passively hoping they'll get a raise each year, employees will know that one is expected, but that the size of that raise depends on the effort they put in." This approach also removes subjective variables, such as personal bias or favoritism, from the equation when it comes to measuring performance and calculating wage increases.

• ***Cater to the increasing demand for work-life balance***. Especially since the COVID-19 pandemic, more workers are seeking jobs that offer better work-life balance, with policies that promote scheduling flexibility and overall employee well-being. This is something Ms. Esau has observed while interviewing candidates over the last few years.

"It seems peoples' values are shifting more towards personal growth and development and self-care; things like being able to take time off without guilt and making sure that lunch breaks are actual lunch breaks are more important to people today," she says.

Some strategies to help accommodate those individuals who desire a more flexible schedule and better work-life balance include revisiting vacation and sick time allotments, offering a paid or longer lunch, staggering employees' shifts or allowing employees to have compressed work weeks, where they work longer hours some days in exchange for shorter days or a day off in the same week.

Dr. Halfpenny points out, "Lots of people have children at home or need time off for different reasons, and if they know we're willing to work with them in those situations, it leads to a more comfortable working environment."

• ***Review your employee benefits package***. If you're having trouble finding or retaining employees, revisit the benefits your practice offers. Mr. Pinto suggests polling your staff to learn which benefits are most important to them.

One unique benefit employers are offering more frequently is pet insurance. "I got it priced out for our practice, and it's not that expensive to add," Ms. Siegman notes. "Not everyone has a pet, but for those that do, this could be a special thing that sells us vs. the practice down the street," she notes.

Employee Check-ins

It's a good idea to perform "temperature checks" with your employees every few months. These one-on-one discussions serve multiple purposes:

• It opens the door for employees to vocalize any concerns promptly, rather than let them fester until the annual performance review.

• It allows practice owners to affirm staff's good performance, as well as offer constructive feedback to address any areas of concern that may be hindering performance or efficiency.

• It's a great time to discuss potential promotion opportunities to key staff in on what they're working towards.

"Set that time aside to meet one-on-one and discuss areas for improvement, as well as identify those areas of success where the employee did the right thing, made the right call and used those critical thinking skills," says Ms. Esau. These meetings don't have to be long, she adds; in her experience, biweekly talks lasting 15 to 20 minutes are ample.

Keeping these open lines of communication can help discourage "quiet quitting," a more recent phenomenon where employees disengage from their roles by doing the minimum required work, often as a response to burnout, lack of recognition, insufficient compensation or a perceived imbalance between effort and reward.

"If that door is open for communication, you can usually tell by a person's body language if they are happy or not, because oftentimes they don't come right out and say it," Ms. Esau points out. "If you're perceptive enough, you can identify someone who may be on their way out, and hopefully be able to mitigate that by pinpointing the areas where they're struggling."

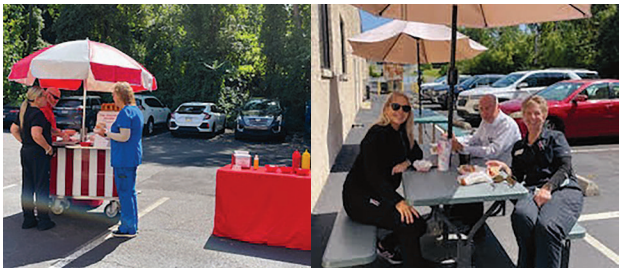
Hire Slow, Fire Fast

Retaining a toxic or unmotivated employee can cost you by damaging team morale, overall productivity and company culture.

"So many practices will hold onto staff members much longer than they should, whether it's out of kindness or desperation," says Mr. Pinto. "The decision of whether an employee is going to make it at your practice should be made rather briskly," he advises.

At Ms. Esau's practice, they have zero tolerance for toxicity or negativity. "It can be easy to let behaviors slide, but by doing this, we may not realize that one person may be responsible for the turnover of three or four," she says. "We have to look at the value of creating that positive environment, and sometimes that means eliminating people who are taking the culture down." While this can be difficult and feel like more work at first, Ms. Esau assures, "It's always for the greater good." ◀

Valley Eye Professionals



Valley Eye Professionals organized a hot dog vendor to come provide lunch to its staff just to switch up the daily routine.

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SECONDARY IOL: BEST PRACTICES

Key pearls and tips for fixating lenses in the anterior and posterior chambers.

CHRISTINE YUE LEONARD
SENIOR ASSOCIATE EDITOR

Secondary lens implantation can remedy a variety of scenarios, from the wrong power lens having been implanted to a lens that's creating problems within the eye such as UGH syndrome or one that's decentered or dislocated. However, the ideal place for a lens—the capsular bag—is usually off the table in a reoperation. Instead, surgeons must identify a different space for the replacement lens, and that new location depends on the eye's anatomy after the first lens is removed. It also influences the choice of fixation technique.

Here, experts share the approaches they use, along with pearls for completing successful cases.

Active vs. Passive Fixation

There are two general categories of IOL fixation—passive fixation and active fixation.

Passive fixation is possible in the capsular bag, provided there's enough capsular support; the ciliary sulcus; and the anterior chamber with a typical anterior chamber lens. "It's rare to have enough good capsular support to put a lens in the ciliary sulcus with passive fixation," says Kevin M. Miller, MD, chief of the Cataract and Refractive Surgery Division and director of the Anterior Segment Diagnostic Laboratory at UCLA. "Usually, the capsule and zonules are damaged. In an ideal situation, passive implantation in the sulcus with optic capture could work, if the capsulorhexis is the right size. If the capsule and zonules are damaged or completely gone, then you need to find another way of fixating the lens."

> **As a field, we have more and more patients returning a decade after having flawless cataract surgery with dislocations due to trauma, the effects of retinal detachment repair, and diseases such as pseudoexfoliation.**
>
> ***—Kevin M. Miller, MD***

Active fixation involves securing the IOL haptics to part of the eye. In the United States, suturing a lens to the back of the iris in the ciliary space is an option. In other parts of the world, iris clip or iris claw lenses are available. These lenses attach to the posterior or anterior surface of the iris.

There are three types of active fixation to the sclera: inner scleral; intrascleral; and transscleral fixation. "With inner scleral fixation, the haptics are secured to the sclera with sutures, either 9-0 Prolene or CV-8 Gore-Tex." Dr. Miller says. "Intrascleral fixation involves creating a tunnel in the sclera, as initially described by Gabor Scharioth and modified in Amar Agarwal's glued IOL technique. Transscleral fixation was popularized by Shin Yamane and many others after him, and it involves taking the haptics all the way through the sclera from the inside of the eye to the outside and melting the distal haptic to create a bulb, which is pulled back into the sclera."

Retina Specialist Support

For some dislocated lens cases, partnering with a retina colleague may be necessary. "If the lens implant is in the anterior half of the vitreous cavity, I do those cases alone," says Dr. Miller.

This article has no commercial sponsorship.

Dr. Safran is a consultant for Johnson & Johnson Vision. **Dr. Miller** is a consultant for Alcon and Johnson & Johnson Vision. **Dr. Xu** has no related financial disclosures.

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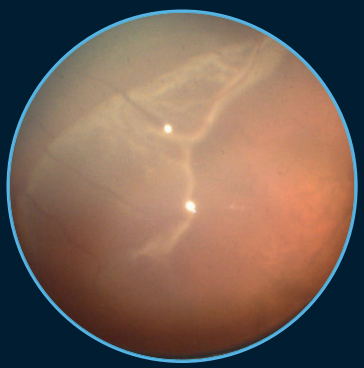

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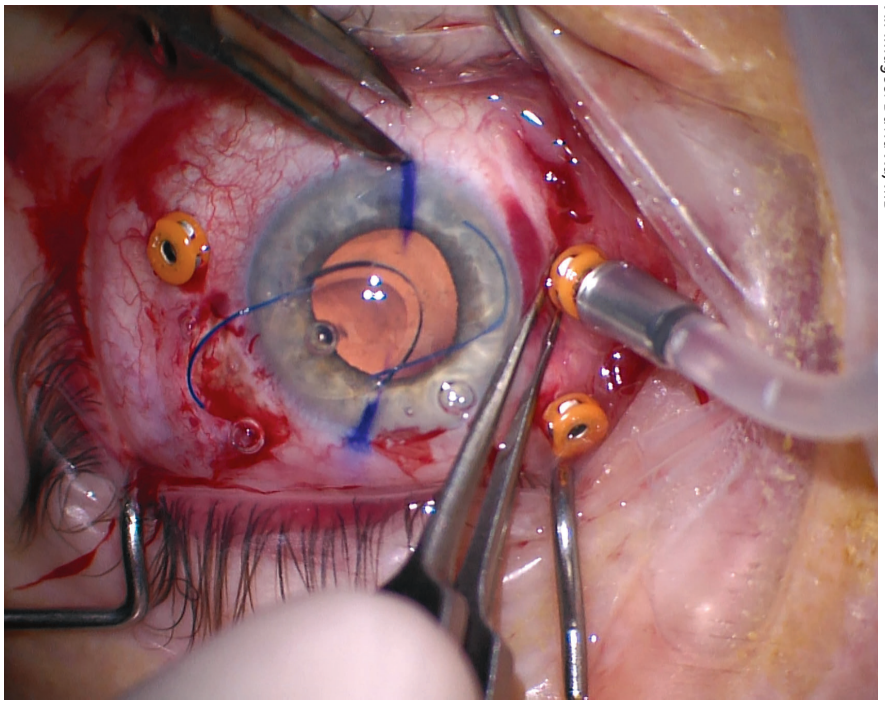


All images: David Xu, MD

Figure 1. In the Yamane technique, the new IOL for scleral fixation is inserted into the anterior chamber and a toric marker is used to mark the 6 and 12 o'clock meridians where the haptics will be externalized.

"But if it's sitting on the retina, it's often best to have a retina specialist there to do a good vitrectomy, lift the lens off the retina and then perform a check of the peripheral retina to ensure there are no tears or breaks and treat any that are there."

The Anterior Chamber

Anterior chamber IOLs are often a source of contention among surgeons. Proponents of AC IOLs emphasize the importance of patient selection when using these implants, since anterior chamber anatomy and corneal health play a major role in determining the long-term success of the lens. "These lenses aren't for every eye," says Dr. Miller. "They get a bad rap because they're often put into eyes with compromised corneas to begin with. However, I have patients who I implanted with an AC IOL 30 years ago, and their corneas are healthy and their vision is still good."

Still, many surgeons avoid AC IOLs altogether, pointing out that these implants may lead to scarring, irritation, glaucoma, CME and corneal edema. "I'd much rather deal with the complications of a dislocated posterior chamber lens than the complications of an anterior chamber lens," says Steven G. Safran, MD, who's in private practice in Lawrenceville, New Jersey, who adds he's never used anterior chamber lenses in his practice, though he's removed quite a few. "The problems [they cause] are very difficult to fix. There's often high astigmatism, glaucoma, scarring and fibrosis in the angle. They're difficult to take out."

For AC IOL candidacy, Dr. Miller offers the example of a patient with Marfan's syndrome who already had problems with a lens implant dislocating in the posterior chamber. "In the prior surgery, the ophthalmologist sutured a capsular tension ring to the sclera," he says. "Now the sutures have loosened, there's a wobbly capsular bag, and the posterior capsule is open. How might you salvage this, given the difficulty of re-suturing the lens?

"In this case, I would take out the current PC IOL and put an in AC IOL," he continues. "In a Marfan's patient, the concern is that they're already at high risk for retinal detachment, so the more time you spend behind the iris with needles, the greater the chance of a detachment later."

Every case is unique, and the anatomy and prior eye history will help determine what type of secondary IOL technique will work best in a given eye. Dr. Miller shares the following tips for selecting eyes for potential AC IOL placement:

• ***Avoid distorted pupils.*** "The most commonly used AC IOL lens's optic measures 5.5 mm, so if the pupil is deformed in such a way that it exceeds the diameter of that 5.5-mm optic centered in the eye, then this lens isn't a good choice," he says.

• ***Avoid anterior synechiae.*** "Adhesions between the iris and cornea leave little room for positioning an AC IOL," he says. "Breaking those synechiae often results in iris defects, and you can't have a lot of iris defects and expect a lens to fit well in the anterior chamber."

• ***Avoid eye rubbers.*** Selecting patients who aren't eye rubbers is vital. "I've noticed in past years doing AC IOLs that I'd slip them in through the incision and close it up," Dr. Miller says. "Some patients would rub their eye, and then return later with irritation, and I'd find the haptic in the incision. So, I learned to put the lens in and rotate the haptics 90 degrees from the incision. If you make a temporal incision, rotate the haptics to 6 and 12 o'clock. Then, if the patient rubs their eye, the haptics aren't going to spin into the incision. It's also important to take care to protect the cornea when implanting these lenses. Use a dispersive viscoelastic if needed to avoid additional corneal trauma during the surgery."

Appropriate sizing also contributes to the longevity of an AC IOL. "The haptics must be sized correctly," says Dr. Miller. "Oversized, and you'll get corneal decompensation; undersized, and the lens will rattle around inside the eye with eye movements and rotate. It's a Goldilocks situation where it has to be just right."

Initial lens sizing is usually based on the horizontal corneal white-to-white

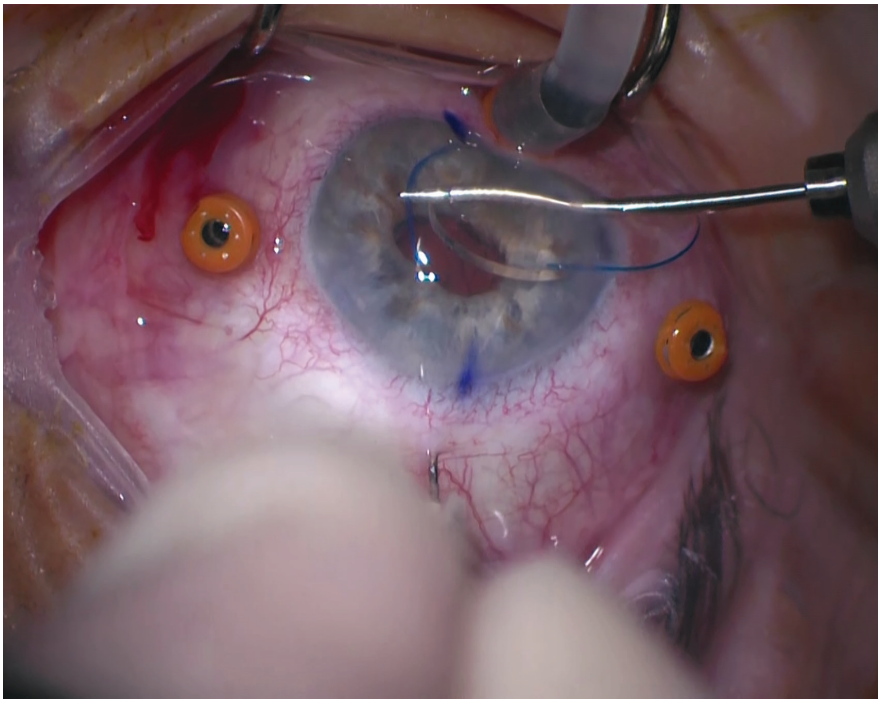


Figure 2. The leading haptic is introduced into the lumen of a thin wall 30-gauge needle which has been tunneled through the sclera.

dimension. Dr. Miller adds 1 mm to this measurement. "I recently had a patient whose horizontal corneal white-to-white diameter was 11.5 mm," he says. "I added a millimeter to get 12.5 mm and put in an AC IOL with a haptic dimension of 12.5 mm, and it fit very nicely. Proper sizing is important. If you put a lens in, sized initially, and it's too big or too small, take it out and use a larger or smaller lens."

The Iris

As with AC IOLs, iris-fixated lenses can work well in the right patients, surgeons say. However, surgeon experience and patient selection factor in heavily, as these lenses are attached to the delicate, vascularized uveal tract tissue.

"Suturing a lens to the iris may induce UGH syndrome and inflammation or cause cat-eyeing and other forms of pupil irregularity," notes David Xu, MD, an assistant professor at Sidney Kimmel Medical College at Thomas Jefferson University and member of the Wills Eye Hospital Retina Service in Philadelphia. "Iridodonesis and phacodonesis may result. Pigment dispersion and secondary glaucoma are another potential complication. Additionally, the polypropylene sutures used for fixation have a long-term risk of breakage."

"Iris suture fixation is fraught with more issues than other fixation approaches," Dr. Miller says. "If there's a lot of capsule behind the iris to stabilize it, you won't have iridodonesis and you can suture lens haptics to the iris and get a pretty decent long-term result. But if there's no capsular support, the iris tends to be floppy, and if you stick a lens on it, it'll wiggle quite a bit when the eye moves. These patients often experience chronic iritis, which can lead to macular edema and other problems.

"When suturing a lens to the iris, ensure the suture passes are distal on the haptics to avoid creating an ovalized pupil," he adds. "It's difficult suturing so far out, but it's necessary."

Dr. Miller says he reserves iris suture fixation for the older patient whose lens is already in the ciliary sulcus, just decentered. "With older patients, I'm not worried about them having a lens sutured to the iris for 50 years," he says, noting that for five or 10 years, it may be a reasonable option. "The other option would be to take out the decentered lens and replace it with a different lens and do more surgery. There's a lot more trauma when doing a lens exchange—the operation tends to take longer. You have to consider the immediate effect of that longer surgery and the potential of its damage versus the long-term potential damage of sutures in the iris and lens jiggling around forever. There are many aspects to weigh. For a young patient, I don't generally suture-fixate lenses to the iris. I'd rather suture-fixate the lens to the sclera."

The Sclera

Scleral fixation has gained popularity over the last several years, with the Yamane technique at the forefront. "Scleral fixation is a very technique-dependent procedure," explains Dr. Safran. "It depends on the surgeon skillset quite a bit. I used to suture lenses to the sclera using Prolene or Gore-Tex through the eyelets of a lens like CZ70BD. Then from about 2012 to 2016 I'd externalize the haptics and tuck them into a scleral groove and cover it with a flap and do glued IOL. Once the Yamane procedure came out, I transitioned to that. Now I mostly do all Yamane.

"The Yamane is a nice procedure because you don't have to touch the conjunctiva or damage the ocular surface," he continues. "You can do it through a 2.75-mm clear corneal incision, though it must be done with a proper vitrectomy or else you'll be engaging vitreous."

"I've done a range of [scleral fixation techniques] in patients with complete aphakia and no capsular support," Dr. Xu says. "These days, I prefer to do the Yamane technique. It's a sutureless, flanged scleral haptic fixation technique. In the past, I did Gore-Tex fixation."

Dr. Xu says the Yamane technique has a steep learning curve, but once you get it and you're comfortable with it, it's a very efficient procedure. "Two

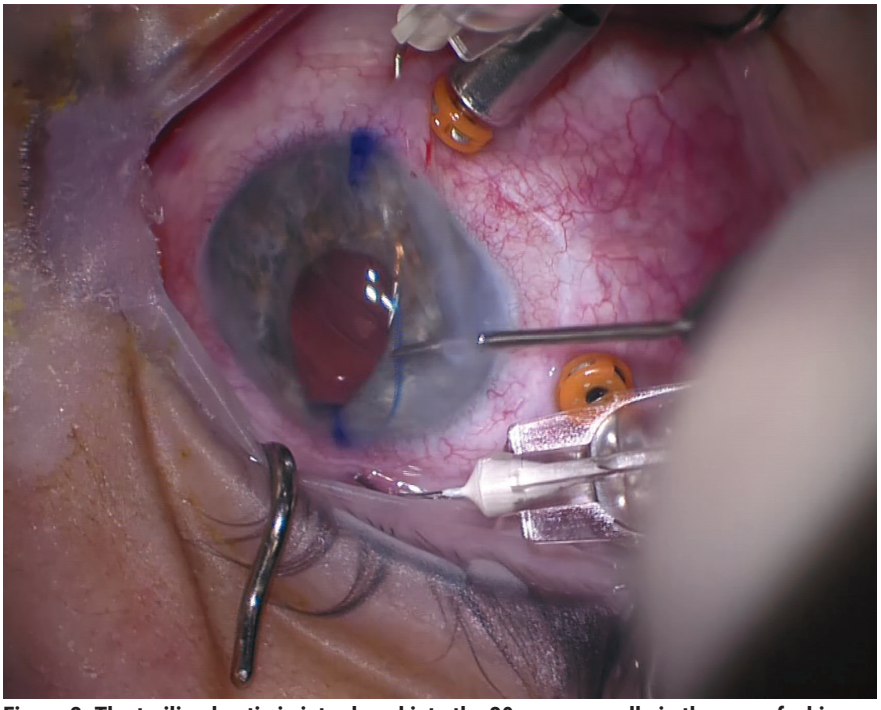


Figure 3. The trailing haptic is introduced into the 30-gauge needle in the same fashion as shown in Figure 2. This allows the haptics to be externalized out of the scleral tunnels.

important factors to keep in mind when doing the Yamane technique are making sure that the corneal incisions and where you're planning to externalize the haptics are all set up exactly," he says. "Precision is key, otherwise it's a big struggle on the inside of the eye to get everything lined up.

"The second thing that makes a difference is the angle at which you insert the needles to do the fixation. If you're not exact in the angle and direction that you're inserting those needles during Yamane, then the IOL will come out tilted. Intraoperatively, if you see that, you can repass the needles. If you don't catch it intraoperatively, there's not much you can do except take the patient back to the OR.

"When doing the Yamane technique, I make a corneal incision temporally and fixate the haptics at six and 12 o'clock," he continues (*Figure 1*). "Always do the leading haptic on the left-hand side of the eye, regardless of whether it's the right eye or left eye. When you grab the haptic, grab at the midpoint and flex it a little so that it slides smoothly into the needle (*Figures 2-3*). The bevel of the needle and where you orient it is also important. It needs to be beveled in such a way that it catches the natural curve of the haptic going in towards the movement of the needle. This is true for both sides of the eye. The second haptic, the trailing haptic, is more challenging because there's less space within the temporal part of the anterior chamber you're working in. Making sure you have enough space there and setting up your grab points for where you're holding the haptic is incredibly important."

Hypotony is a potential danger with scleral fixation techniques. "For Yamane, I recommend suturing the main corneal wound, hydrating all corneal wounds and checking to ensure they're water-tight," says Dr. Xu. "I also suture all sclerotomies in. For four-point fixation, ensure the exit sites for all the sclerotomies are reasonably water-tight. If they look like they're still gaping open, another suture can be placed to close it up."

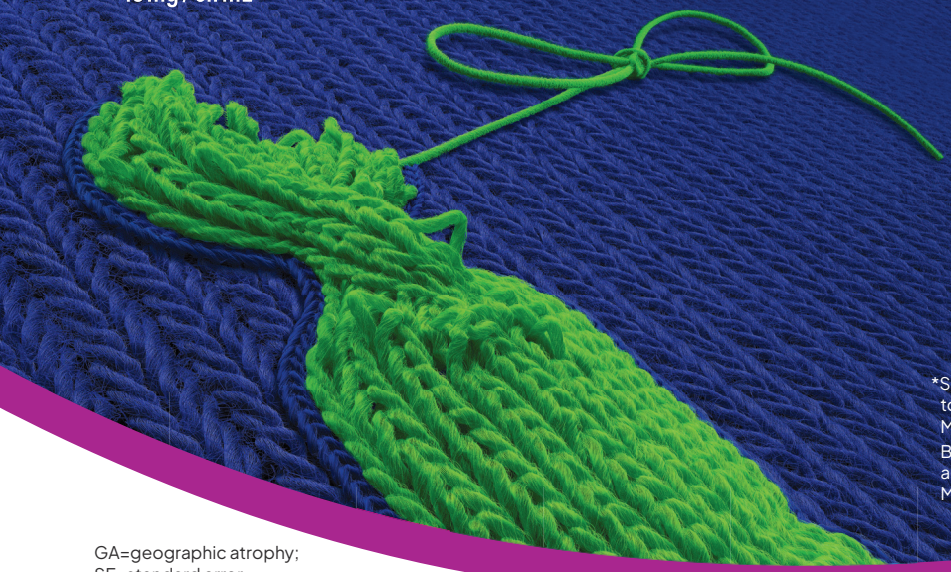
There are several IOL designs used for the Yamane technique, but Dr. Xu cautions that some of these IOLs have different haptic angulations, which will affect IOL calculations. "The popular CT Lucia 602 and ZA9003 lenses and most others have an IOL haptic angulation of five degrees, but there are others, for example the MA60AC, that have a haptic angulation of 10 degrees. This difference changes the effective lens position by about half a millimeter or sometimes more, which could be refractively significant. So, if surgeons stick with one IOL design then they'll be fine, but if they are switching between the various IOL designs, I encourage surgeons to look at the haptic angulation and make sure their postop refractions are within the range they desire and make corrections on IOL power as needed."

Dr. Safran has used both the CT Lucia 602 and AR40 lens for the Yamane technique. "The CT Lucia 602 is ideal for scleral fixation because of its robust polyvinylidene fluoride haptics, which don't kink and have very good memory," Dr. Safran says. "You can twist them, and they go right back to their original shape, whereas if you twist the PMMA haptics of an AR40, they'll kink or even break. However, the AR40 has a 6-mm functional optic, which makes it a bit more forgiving in terms of centration."

To use the AR40 requires some technique modification. "The flanges of the CT Lucia 602 produce a mushroom shape [when melted using low-temperature cautery]," Dr. Safran says (*Figure 4*). "If you melt the PMMA haptics on an AR40, you get a light-bulb shape which isn't quite as secure. However, if you hold the AR40 haptic about 1 to 2 mm from the tip and melt it into the forceps, this will produce a more mushroom-shaped flange."

He also notes that the AR40 haptics are thicker, which may require using a different gauge needle or modifying your approach. "The needle we use to capture the haptic is a TSK 30-gauge needle, and its lumen is 192 µm on average," he says. "The CT Lucia 602

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

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

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Active Intraocular Inflammation
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Increased Intraocular Pressure
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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:
Apellis Pharmaceuticals, Inc.
100 Fifth Avenue
Waltham, MA 02451

SYF-PI-30NOV2023-2.0

12/23 US-PEGGA-2200163 v4.0

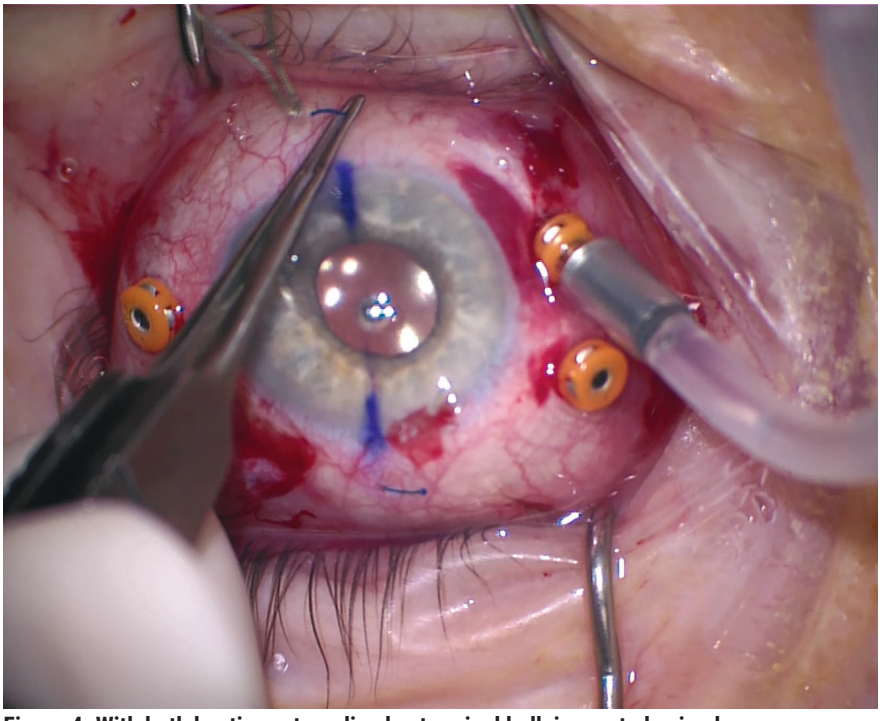


Figure 4. With both haptics externalized, a terminal bulb is created using low temperature cautery.

haptic is about 147 µm thick and the AR40 is 180 µm thick, so it's a little harder to put the 180-µm haptic into the 192-µm lumen of the needle. Some surgeons use a 27-gauge needle for this. It's important to match the angle of the needle and the haptic. Any off-axis attempts to get the haptic in the lumen won't work and you'll end up damaging the haptic."

Here are several pearls for performing other scleral fixation techniques:

• ***Take care to keep sutures organized.*** "For the Gore-Tex procedure, surgical efficiency can be improved by ensuring the sutures aren't getting tangled outside and inside the eye," says Dr. Xu. "Sometimes the sutures can become looped inside of the eye. Be sure you have clear visualization to check that the IOL is in the right place.

"When doing Gore-Tex four-point fixation, I like to thread two of the Gore-Tex sutures through the eye while the IOL is still outside of the eye," Dr. Xu continues. "Then, I introduce the IOL into the anterior vitreous plane and then externalize the remaining two sutures. I prefer using the MX60 lens for four-point fixation. It creates a pseudo four-point fixation using one eyelet on each side. Another suitable IOL is the Akreos AO60 lens. This lens is easier to use because it has four fixation points, which reduces the risk for inappropriately looping sutures. However, it has the chance of opacification with gas and is incompatible with silicone oil."

When would you choose four-point fixation over Yamane? "If a patient has a dislocated IOL and it's a PMMA IOL," Dr. Xu says. "In those cases, a large scleral tunnel incision needs to be made and you often run out of room within the limbus of the eye to put the Yamane lenses in, between the large scleral incision and all the trocars. With the Gore-Tex procedure, it's a bit more facile because the sutures exit at the same place where the trocars are, thus saving more real estate around the eye."

• ***Sutures should exit on the top of the IOL.*** "No matter which IOL design you're using, the sutures should exit the IOL flanges on the top of the IOL," Dr. Xu says. "This will prevent any iris-IOL chafe."

• ***For inner scleral fixation, ensure sutures bisect the pupil precisely.*** This helps avoid having a decentered lens. "Even if it's perfectly centered, the lens can still be torqued or tilted, inducing cylinder as a result," says Dr. Miller. "You have to make sure your suture passes are appropriate."

• ***Don't pull sutures too tightly.*** "Some lenses have fixation eyelets and some just have haptics," he says. "You have to be careful that the sutures don't pull off the end of the haptics as you're tightening them. Additionally, if using Prolene, ensure that the sutures' ends and knots are buried well by sclera. We often use Prolene inside a Hoffman pocket. If using Gore-Tex, make sure the knots aren't exposed on the sclera because they'll erode right through the Tenon's capsule and conjunctiva. Bury Gore-Tex knots inside the sclerotomy."

• ***Tunnel carefully when performing intrascleral fixation.*** "When performing intrascleral fixation, make sure your tunnels are nice and long," Dr. Miller advises. "Use haptics that aren't going to kink or break when you insert them into the tunnels. It's also key to construct your tunnels in such a way that the lens isn't tilted or decentered."

• ***Caution patients against eye rubbing.*** "Warn patients that if they start rubbing their eye postoperatively, they could end up backing the haptics out of the tunnels, causing a dislocation just from eye rubbing," says Dr. Miller.

Expanding Skillsets

The bulk of lens exchanges are done by only a handful of surgeons, says Dr. Miller. "Many surgeons just aren't comfortable with these secondary IOL procedures, but they need to become comfortable because there will be a lot more of them in the future. As a field, we have more and more patients returning a decade after having flawless cataract surgery with dislocations due to trauma, the effects of retinal detachment repair, and diseases such as pseudoexfoliation." ◀

DIAGNOSIS AND MANAGEMENT OF OPTIC NEURITIS

Experts go over the various causes of optic neuritis and the diagnostic clues to look for when a possible ON patient presents.

CHRISTINE BAHLS
CONTRIBUTING EDITOR

The optic nerve, all 1.75 inches of it, has long challenged science to find the reasons it can become inflamed. In 1890, 40 years after the ophthalmoscope arrived on the diagnostic scene, physician A.A. Hubbell observed in the *Buffalo Medical Journal* that "[Optic] neuritis, as a rule, presents nothing which distinguishes its cause."[1]

And while technologies now exist to help pinpoint why a patient has optic neuritis, physicians are still vexed by the nerve's diagnostic one upmanship. In small anatomic regions, "Pathology is more difficult to visualize, such as the optic nerve and the brainstem," noted one paper in 2019.[2]

Today, the spectrum of optic neuritis subtypes includes other co-associated inflammatory disorders of the central system, besides multiple sclerosis. The use of OCT and MRI and the discovery of serum biomarkers have helped to provide accurate diagnoses of other causes of optic neuritis, including myelin oligodendrocyte glycoprotein associated antibody (MOGAD) and neuromyelitis optica spectrum disorders (NMOSD). Treatments are now available for these disorders.

But most good news has a price tag.

In interviews with prominent neuro-ophthalmologists, who discuss these recent diagnostic and treatment successes, they interject a poignant caveat: Therapeutic success for optic neuritis requires rapid diagnosis and treatment—days, not months—to save the patient's sight.[3] Here, they share their tips for ferreting out the cause.

A Primer

Optic neuritis is a syndrome, not a disease. It's a common diagnosis; the prevalence is 115 per 100,000 persons in both the United States and the United Kingdom. The optic neuritis associated with multiple sclerosis appears more in women, Caucasians and those who live at high altitudes.[4,5]

The ON associated with idiopathic and multiple sclerosis usually involves:

- subacute vision loss;
- just one eye;
- pain that often worsens with eye movement;
- a relative afferent pupillary defect in cases of unilateral or asymmetric optic nerve involvement; and
- dyschromatopsia from the affected eye.

Optic neuritis can manifest in autoimmune conditions of the central nervous system, infections and systemic diseases, such as:

- Multiple sclerosis;
- MOGAD;
- NMOSD;
- CRION, or chronic relapsing inflammatory optic neuritis;
- GFAP, or glial fibrillary acidic protein antibody-associated astrocytopathy;
- Tuberculosis, syphilis and cat-scratch fever;
- Sarcoidosis, Sjögren's syndrome, granulomatosis with polyangiitis.

The optic nerve bridges the outside world to the brain, and in doing so places its diagnostic and clinical jurisdiction, from the vantage point of specialty medical training, into the hands of the neuro-ophthalmologist. But, because it is the eye that becomes symptomatic,

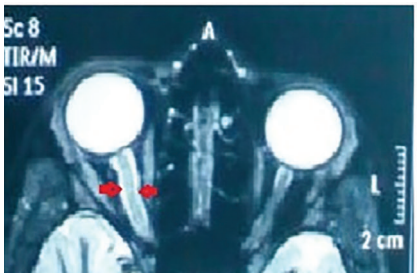
This article has no commercial sponsorship.

Dr. Bennett reports fees from Alexion AstraZeneca Rare Disease, Antigenomycs, BeiGene, Chugai, Clene Nanomedicine, Genentech, Genzyme, Reistone Bio, Roche, Imcyse, Mitsubishi-Tanabe, and TG; speaker fees from Alexion; grants from Alexion and the NIH and the National MS Society. Dr. Bennett has a patent 'Compositions and methods for the treatment of neuromyelitis optica.' **Dr. Costello** has received speaker fees or advisory board honoraria from Alexion, Sanofi, Amgen and Novartis. **Dr. Newman** reports no relevant disclosures. **Dr. Sergott** consults for Amgen, Mallinckrodt, Roche and Novartis.

first-line health-care providers are those whom a patient generally sees. "A person presents with pain in the eye and loss of acuity," says Robert C. Sergott, MD, chief of the Neuro-Ophthalmology Service at Wills Eye Hospital. And the place of presentation is often in the emergency department, says Nancy J. Newman, MD, the LeoDelle Jolley Chair of Ophthalmology at Emory University School of Medicine.

Unfortunately, the ER may lack diagnostic tools, such as OCT, to identify optic neuritis or exclude other causes of vision loss, says Fiona Costello, MD, FRCPC, a professor at the Cumming School of Medicine Department of Clinical Neurosciences at the University of Calgary.

A patient with NMOSD might develop rare symptoms such as inappropriate sodium control or protracted hiccups, nausea or vomiting before the optic neuritis, says Jeffrey Bennett, MD, PhD, the Gertrude Gilden professor for Neurodegenerative Disease Research at the University of Colorado School of Medicine. "You can imagine if someone shows up with nausea and vomiting in the ED, they will call gastroenterology. And, unless someone is knowledgeable, the next attack [of NMOSD] could be devastating," he says.



Axial T 2 MRI scan showing swelling of retrobulbar intraorbital segment of optic nerve of the right eye. *(Gupta A. A Case of Unilateral Optic Neuritis in a 13Year Old Boy. J Ophthalmic Clin Res 2019;6:055.)*

So, yes, misdiagnosed cases of optic neuritis exist.[6] Referrals are important. But to get a referral in time to save a patient's sight, should the cause of the optic nerve's inflammation be vision robbing? Not easy, says Dr. Newman: There are just not enough neuro-ophthalmologists out there. At last count: fewer than 700, nationwide[7]—which increases the urgency to get the diagnosis right on the patient's initial visit.

Background

In the late 1980s and early 1990s, the Optic Neuritis Treatment Trial compared patients with newly developed optic neuritis treated with either oral prednisone, IV methylprednisolone or placebo. They found no long-term benefits to visual outcomes and that those with optic neuritis recovered their sight, with or without medication.[8]

"We used to say that there's no urgency to treat," says Dr. Sergott. "Ophthalmologists and neuro-ophthalmologists assumed ON was synonymous with MS. MS is a very serious disease, but for patients with ON and MS, their vision will improve quite well without steroids."

That all changed when biomarkers for two CNS-attacking autoimmune diseases were discovered in the mid-2000s.

In NMOSD, patients with this dis-

TABLE 1. THE DETAILED FINDINGS OF DEMOGRAPHIC, CLINICAL FEATURES AND TREATMENT IN MOGAD, MS AND NMOSD PATIENTS

	MOGAD	MS	NMOSD
Male/Female, *n/n* (% female)	11/15 (57.7)		7/19 (73.1)
Age at onset, mean (SD)	29.8 (16.1)		41.8 (16.3)
Disease duration, years, median (IQR)	2.4 (0.4-7.3)		1.0 (0.1-4.0)
Status at time of blood draw, *n*			
Onset	4		3
Relapse	19		21
Remission	3		2
Clinical symptom, *n*			
ON	13		8
Myelitis	11		25
Encephalopathy	24		8
Immunotherapy, *n*	Steroids (19)	Steroids (20)	Steroids (18)
	Intravenous immunoglobulins (3)	Intravenous immunoglobulins (4)	Rituximab (3)
	Plasma exchange (2)	Teriflunomide (1)	Tocilizumab (1)
	Mycophenolate mofetil (3)	Siponimod (9)	No information (4)
	Rituximab (12)	Fingolimod (2)	
	Tocilizumab (1)	Rituximab (5)	
Concomitant autoimmune disease, *n*	IgA nephropathy (1)	0	Systemic lupus erythematosus (1)
	Anaphylactic purpura (1)		Sicca syndrome (1)
Thyroid disease, *n*	Thyroid nodules (1)	Thyroid nodules (2)	Thyroid nodules (3)

(Source: Wang Y, Danzeng Q, Jiang W, Han B, Zhu X, Liu Z, Sun J, Chen K and Zhang G. A retrospective study of myelin oligodendrocyte glycoprotein antibody-associated disease from a clinical laboratory perspective. Front. Neurol 2023;14:1187824.)

ease are anti-aquaporin-4 antibody-positive. The disease moves quickly. These patients don't have "a lot of time to wait [for treatment]," Dr. Sergott says. "They will get irreversible damage that they can't repair." In MOGAD, the immune system attacks a protein called the myelin oligodendrocyte glycoprotein, found on the CNS' sheath. MOGAD also affects the optic nerves and brain. These patients also require treatment within a week after symptom onset to limit the severity of the attack.

NMOSD may cause irreversible injury to the optic nerves and spinal cord. According to Dr. Sergott, NMOSD is "the real big one" with a "devastating natural history." A quarter of patients have lasting disability after the initial attack, and one-third of patients given steroids show improvement, but in time "these patients may have paralysis from the neck down."

"What experts know now is that ON is an optic emergency," says Dr. Bennett. And the point, says Dr. Sergott, is to let all other health-care providers know it too.

From Specific to Idiopathic

The signs and symptoms of ON's causes often overlap with each other. One recent study found that, due to the poor specificity of the clinical manifestations of MOGAD, it can easily be misdiagnosed as MS, NMOSD or other demyelinating diseases.[9]

Moreover, the known disorders or diseases affecting the optic nerve only comprise about 60 percent of actual diagnoses. In the United States "MS accounts for half of what will come through the door, the other two [MOGAD and NMOSD] are 6 percent," says Dr. Bennett. The "dreaded idiopathic" diagnosis eludes cause but often has significant effects.

That 50-percent figure represents the patients who are referred by ophthalmologists, primary care physicians and ED visits. A study published in 2018, based on blood samples of 177 patients enrolled in the 1992 Optic Neuritis Treatment Trial, found three patients were positive for MOG-IgG and none had NMOSD.[10] The trial's design likely impacted these findings: It was U.S.-based, restricted age to those 18 through 46, and excluded those with bilateral optic neuritis, which is a characteristic of NMOSD and MOGAD.[11]

The discovery of NMOSD and MOGAD led researchers to think they could learn more about differentiating MS, but that didn't happen, Dr. Bennett says. At this time, it's likely some patients are under the MS umbrella because they mimic a pattern of distribution and progression of activity that fulfills current MS criteria. But, "the risk of MS is heightened by a whole lot of individual mutations and genes. With about 250 genes implicated in that risk, "the [odds of the] impact of one gene remain rather low."

History

Dr. Costello says the keys to diagnosis

More MOGAD, NMOSD comparisons

- Vision loss can be severe with both; with MS it's milder.
- MOGAD can present with "strange things like seizures and generalized acute encephalopathy," Dr. Bennett says.
- MOGAD worsens over a period of hours and involves central vision. Patients are less likely to have more than one attack, unlike NMOSD.
- Worrisome symptoms: The patient says he has gotten better since initial onset, but the opposite is happening.
- Bilateral optic neuritis is most commonly seen in MOGAD, although it may also be seen in NMOSD.

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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,
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are listening to your patient and knowing what to ask. In the case of optic neuritis, she considers who the patient is, how the patient lost vision, what co-associated medical issues they may harbor, and where they live to determine what subtype she may be treating.

Other questions:

• How did the patient notice vision loss? Was it sudden, gradual, did it progress over hours to days?

• What is the pain like? Did it worsen with eye movement? Has the patient felt such pain before?

• Is the vision loss monocular or binocular? What was the patient doing or looking at when the vision loss was noted?

Optic neuritis tends to cause new eye pain over a week or so, generally with demonstrable vision loss in the affected eye. Recurrent pain with transient positive visual phenomena—have the patient alternately cover each eye to check—could be migraine, Dr. Costello says.

Also, females are more prone to optic neuritis and autoimmune disease. For NMOSD, the female to male ratio is almost 10:1.[12]

Beware the Mimics

Dr. Newman also discussed the following optic neuritis mimics:

• ***Macular causes of vision loss***. These entities can imitate ON, and include such conditions as central serous retinopathy, which is more male prevalent. Other clinical differences: Central serous retinopathy doesn't cause pain nor is there an afferent pupillary defect. An OCT scan will pick up subtle central serous retinopathy more acutely. Without an OCT, Dr. Newman says, "If you have someone with central vision loss, you might make a mistake, especially if they already have a diagnosis of MS, [because] fingolimod, for example, can affect central vision with macular edema."

• ***Nonarteritic anterior ischemic optic neuropathy***. NAION is unilateral, painless and causes sudden vision loss, due to a lack of blood flow to the front of the optic nerve. Disc swelling is always present, Dr. Newman says, adding that NAION is the most common misdiagnosis for ON.

• ***Compressive infiltrative optic neuropathy***. Here, there could be sudden awareness of vision loss, like a person covers the affected eye and realizes he can't see. If a compressive lesion is causing the vision loss, she says, an orbital MRI with contrast and fat saturation sequences will identify it.

• ***Leber's hereditary optic neuropathy***. People with LHON have mitochondrial DNA point mutations. LHON is often mistaken as ON, says Dr. Newman, but LHON differs from optic neuritis as it is most often found in men, is painless and often presents as bilateral, or becomes so within months.

MRI scans with contrast, specifically of the patient's orbits, are very helpful with diagnosis, she says. At least 90 percent of all acute cases of optic neuritis "will have enhancement of the optic nerve, but you won't see that in Leber's or with a maculopathy."

• ***Lyme***. Dr. Sergott adds that it can be prudent to also consider Lyme disease, because the optic nerve can have infectious inflammation.

Adverse events

Some drugs for certain diseases can affect the optic nerve, such as:

• Arrhythmia: Amiodarone or digoxin;

• Immune check point inhibitors;

• Tumor necrosis factor alpha inhibitors;

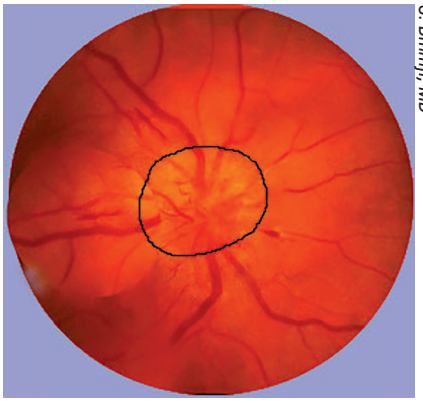
• Cancer: Methotrexate, vincristine, and tamoxifen;

• Malaria: Chloroquine and hydroxychloroquine;

• Infections: Ethambutol, chloramphenicol, isoniazid and sulfa-type antibiotics; and

• Others: Isotretinoin, linezolid, sildenafil, disulfiram.[13]

A word about misdiagnoses: The Stunkel paper found that 60 percent of the 122 patients referred to neuro-ophthalmology for possible ON were overdiagnosed. Migraine was misdiagnosed in 22 percent of these patients. "The most common diagnostic error,



S. Bhimji, MD

Optic neuritis can be visualized through fundoscopy, which may indicate the presence of multiple sclerosis. *(Guier C, Stokkermans T. Optic neuritis. StatPearls 2024 [internet].)*

seen in 33 percent of cases, [was in] eliciting or interpreting the history"; the second, at 32 percent, was "not generating an appropriate differential diagnosis with alternative diagnoses."[2]

Treatments

Steroids have been the mainstay of treatment for ON for decades, and they primarily still are. "MOGAD responds briskly to steroids, and there's a high risk of recurrence if steroids are taken away too fast," says Dr. Bennett. Most cases of NMOSD don't respond to steroids at all, adds Dr. Bennett, but have a more complete response to plasma exchanges, or PLEX.

IVIG, along with intravenous methylprednisolone, can be somewhat effective in preventing NMOSD relapses and extending the time period between attacks—as long as it's given within days of onset.[14]

Three prescription medications are now approved for patients with AQP4 antibody-positive NMOSD, namely eculizumab, inebilizumab and satralizumab.

Referrals

As to referrals, Dr. Newman says, "You will only need to send those who make you uncomfortable or the diagnosis doesn't seem right."

Discerning what is going on with the optic nerve isn't especially easy even with the tools in the ophthalmologist's

office, says Dr. Costello. Seeing inflammation behind the globe is tricky and in the areas around the retina and nerve itself, there's less to see in cases of retrobulbar ON.

Diagnosis isn't always apparent, even using those specialized tools in eye clinics, says Dr. Costello. It takes experience, she says, to appreciate an OCT's pitfalls to properly interpret it. An experiment trying to connect ED physicians with more knowledgeable eye specialists—albeit for central retinal artery occlusion—for the purpose of remote consultations, cut treatment time down significantly. [15]

Advances in artificial intelligence could aid with more rapid, accurate diagnoses. Using 1,599 fundus photographs, Dr. Costello and colleagues trained an AI algorithm to distinguish optic neuritis associated with MS from non-MS subtypes; the model was 76.2 percent accurate.[16] While AI won't replace a good history and examination to localize ON, she says tools like AI could help flag a patient who needs a quick evaluation for a non-MS optic neuritis subtype, like NMOSD.

Says Dr. Sergott: "Our job is to make as rapid a diagnosis as we can, to treat as quickly as possible." Or forgo a definitive diagnosis, and just start treating, based on presentation, history and any other available information.

Dr. Bennett agrees. In lectures, he "points out certain features that would bias [the diagnosis] towards a rare disease." In these situations, he advises "plasma exchange from the start." As for risk vs benefit, he says overtreatment is preferable to the time lost "fiddling around to figure it out." ◀

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(Continued from p. 24)

Surgeons should take extra care during the patient evaluation. "Most people are seropositive for HSV, but testing isn't universally recommended unless they demonstrate signs of ocular HSV," says Dr. Warren. "It's also important to review the patient's medication list. For instance, patients may be on acyclovir or Valtrex and that's a red flag. You want to further tease out why they're on that medication.

"One thing that's not normally done in other patients but should be done in HSV patients is checking corneal sensitivity," she continues. "If a patient has had an HSV episode or has latent infection, they could have neurotrophic keratitis. If they're already neurotrophic, performing LASIK could exacerbate the problem, as cutting the flap transects nerves and can further reduce corneal sensation. This can impair healing even if PRK is performed. Ensuring that the corneal epithelium is healthy and the tear film is in good condition is vital."

Most surgeons avoid these procedures due to the high risk of reactivation, however, if the patient's HSV is well-controlled and there have been no recent flare-ups, others may consider proceeding with caution, says Dr. Warren. A narrative review[2] that examined corneal refractive surgery in patients with a history of herpes simplex keratitis concluded that surgery is appropriate provided the patient has no history of multiple recurrences and no evidence of disease for at least one year. It also recommended patients begin 400 mg twice daily of oral acyclovir or valacyclovir 500 mg once daily for two weeks prior to surgery, to be continued for two weeks postop or for as long as the patient is on topical steroids.

"It's important to educate patients thoroughly about the potential risks and ensure they understand the possibility of future reactivations," says Dr. Warren.

"For those who can't proceed with surgery, I discuss alternative options such as contact lenses or glasses," notes Dr. Feldman. "If someone has dry eye and HSV in an eye, they can do well with a scleral lens. Although these alternatives may not offer a permanent solution like LASIK, they can still meet patients' needs. Patients are often appreciative of the detailed explanation of the potential risks and the focus on their safety. There's very little pushback when I tell them they aren't candidates for laser vision correction." ◀

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DISCLOSURES

Dr. Chu, Dr. Feldman and **Dr. Warren** report no related financial disclosures.

WHEN IS IT SAFE TO YAG FOR PCO?

Early YAG laser capsulotomy following cataract surgery can have its benefits, but some complications may arise if done prematurely.

ANDREW BEERS
ASSOCIATE EDITOR

Posterior capsule opacification can threaten vision postoperatively, but this can be avoided simply with a YAG capsulotomy. What's challenging, however, is that PCO can develop over a long period of time and the severity levels may not increase for years. So, when's the best time to YAG for PCO? Here, surgeons weigh in.

When to YAG

There are many arguments for why surgeons should perform an Nd:YAG laser capsulotomy early after cataract surgery because the risk of PCO fluctuates over time.

"There are almost four million cataract surgeries done in the U.S. every year, and the estimates are that roughly 10 to 30 percent of cataract surgery patients will develop PCO," shares J. Kevin McKinney, MD, an ophthalmologist practicing at Eye Health Northwest in Oregon City, Oregon. "It depends on the type of implant and the surgical technique used, but it does become more common with time. So, it's something we see almost every day." One large population study[1] showed that the incidence of PCO after three years following surgery ranged between 4.7 and 18.6 percent, which increased to between 7.1 and 22.6 percent after five years. Also, the incidence of Nd:YAG capsulotomy increased at three and five years. So we know how prevalent PCO is following cataract surgery, and the rate at which it develops. Knowing this, should physicians employ YAG earlier?

> **There are some who advocate doing YAG laser right away, and as soon as the cornea is clear and the wound is stable, it's okay to do it after cataract surgery. My own personal reasoning is that I like to wait for the blood-aqueous barrier to reestablish.**
>
> ***– Nick Mamalis, MD***

"Technically you could do a posterior capsulotomy very quickly after surgery as long as the capsule has become tight," explains Dr. McKinney. "When that happens, it becomes tight and it's easier to cut. So as soon as it's become tight, you could do the laser." This occurrence has been studied before and physicians are aware that it can take some time for patients' capsules to reach complete contact with their lens implants. It was discovered that silicone IOLs following implantation take approximately eight days to gain full contact with the capsule and 11 days for acrylic IOLs to hit the same mark.[2] By these metrics, ophthalmologists could perform an Nd:YAG capsulotomy within the first two weeks post-cataract surgery. But some physicians argue that this may be too soon to employ an Nd:YAG capsulotomy.

"I like to wait to do a YAG laser capsulotomy after cataract surgery until the blood-aqueous barrier has reestablished, meaning until any chance of postoperative inflammation following that cataract surgery goes

This article has no commercial sponsorship.

Drs. McKinney and **Mamalis** have no related financial disclosures.

away," says Nick Mamalis, MD, the director of the Ophthalmic Pathology Laboratory and a professor of ophthalmology & visual sciences at the University of Utah School of Medicine. "And so, depending on the patient and depending on what you read in the literature for reestablishment of the blood-aqueous barrier after cataract surgery could be on the order of six, eight, even 12 weeks following surgery. So, I'm not one to do a really early YAG laser capsulotomy. I want to make sure everything is completely healed and reestablished before jumping in and doing a capsulotomy."

As Dr. Mamalis suggested, depending on the literature, the rate at which the blood-aqueous barrier can fully heal differs. Earlier studies[3,4] found that the blood-aqueous barrier reached normalcy at approximately three months following surgery, and those investigators employed extracapsular cataract extraction. However, one study[5] compared phacoemulsification to ECCE and discovered that a significant number of their cohort that underwent phaco regained a healthy blood-aqueous barrier within two to five weeks, while it took four to six weeks for ECCE patients to meet the study's endpoint.

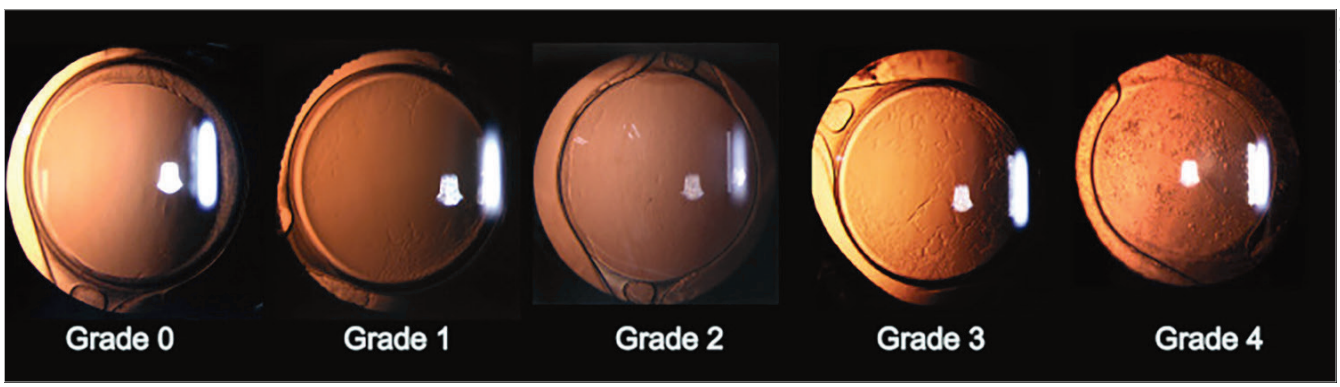
"Just like with cataract surgery, the main determinant of when it's time to do YAG capsulotomy is the patient's visual function," adds Dr. McKinney. "So not just that their vision is reduced, but that they have a functional complaint—difficulty reading or driving at night, for example. When that develops, as long as enough time has passed after surgery, it's a reasonable time to do the laser. It's true, just like with a regular cataract, if you let it get super thick, then it's harder to open and complications can be more likely. So, there's an essence of timeliness, but it's not like you have to jump on it as soon as it develops. You really want to wait until a patient has a functional visual deficit."

One point that Dr. McKinney made was that PCO could become "super thick," or severe. Earlier in this article, a study was presented looking at the incidence rates of PCO over a three- and five-year period, but this study failed to observe early-onset PCO and severity levels in their study's population. Early-onset PCO can develop in about three months following cataract surgery, and if it's not treated properly, then it can cause light scattering and reduce visual performance over time. Approximately 3 percent of patients may experience severe levels of PCO during early development of the condition.[6] The severity levels can be graded from 0 to 4, where grades 3 and 4 are defined as having PCO with a visual impact.[7] This can alter the timeframe in which an Nd:YAG capsulotomy is performed, since the severity of PCO may not have as much of an impact on a patient's visual function early on. But don't wait too long.

"If you have a really significant PCO, especially what we call a fibrotic PCO where the lens capsule has become very stiff and very fibrotic, or if you have PCO caused by a large amount of proliferation of cortical material, then the denser the material and the denser the PCO, and the more difficult it is to perform the YAG laser capsulotomy," shares Dr. Mamalis. "And so, you always want to try to do the capsulotomy as soon as necessary without waiting an inordinate amount of time until the capsulotomy itself becomes more difficult to do."

Complications of an Early YAG

"If you do the laser too soon, there are studies to show that there's an increased risk of retinal tear or retinal detachment," says Dr. McKinney. "There are certain risk factors that



Gu X et al.

Posterior capsule opacification at different severity levels based on a research study.[7] Grade 0 indicates no opacity, or opacification was found only on the peripheral capsule. Grade 1 indicates that the posterior polar retina can be clearly viewed, but some capsular wrinkling or opacity was found centrally and peripherally. Grade 2 indicates opacification worse than Grade 1, but the cup-to-disc ratio isn't affected and can still be observed. Grade 3 indicates the first stage of PCO with a visual impact. Patients with Grade 3 PCO have worse opacification than Grade 2, and the cup-to-disc ratio is difficult to observe. Grade 4 is the most severe case of PCO. Although Grade 4 opacification is similar to Grade 3, fundus observation is far more difficult, and in some cases, impossible. *(Creative Commons License: https://creativecommons.org/licenses/by-nc/4.0/.)*

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(varenicline solution)
nasal spray 0.03 mg

FOR THE SIGNS & SYMPTOMS OF DRY EYE DISEASE

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IT'S THE OCULAR SURFACE-SPARING NASAL SPRAY FOR DRY EYE[1]

Tyrvaya is believed to work by activating the trigeminal parasympathetic pathway via the nose to help increase the production of patients' own basal tears. The exact mechanism of action is unknown.[1]

Indication

Tyrvaya® (varenicline solution) nasal spray is indicated for the treatment of the signs and symptoms of dry eye disease.

Important Safety Information

The most common adverse reaction reported in 82% of patients was sneezing. Events that were reported in 5-16% of patients were cough, throat irritation, and instillation-site (nose) irritation.

Please see Brief Summary of Prescribing Information on the next page and the full Prescribing Information at Tyrvaya-pro.com.

Reference: 1. Tyrvaya. Prescribing Information. Oyster Point Pharma.

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tyrvaya®
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nasal spray 0.03 mg

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INDICATIONS AND USAGE

TYRVAYA® (varenicline solution) nasal spray is a cholinergic agonist indicated for the treatment of the signs and symptoms of dry eye disease.

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.

In three clinical trials of dry eye disease conducted with varenicline solution nasal spray, 349 patients received at least 1 dose of TYRVAYA. The majority of patients had 31 days of treatment exposure, with a maximum exposure of 105 days.

The most common adverse reactions reported in 82% of TYRVAYA treated patients was sneezing. Other common adverse reactions that were reported in >5% of patients include cough (16%), throat irritation (13%), and instillation-site (nose) irritation (8%).

USE IN SPECIFIC POPULATIONS

Pregnancy: Risk Summary: There are no available data on TYRVAYA use in pregnant women to inform any drug associated risks. In animal reproduction studies, varenicline did not produce malformations at clinically relevant doses.

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

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.

The lack of clinical data during lactation precludes a clear determination of the risk of TYRVAYA to an infant during lactation; however, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TYRVAYA and any potential adverse effects on the breastfed child from TYRVAYA.

Pediatric Use: Safety and efficacy of TYRVAYA in pediatric patients have not been established.

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

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make that more common, such as in a young patient or someone who hasn't had a posterior vitreous detachment yet. So yes, you can do it [early], but it's generally accepted practice that you should attempt to wait a few months to perform the laser to reduce those complications."

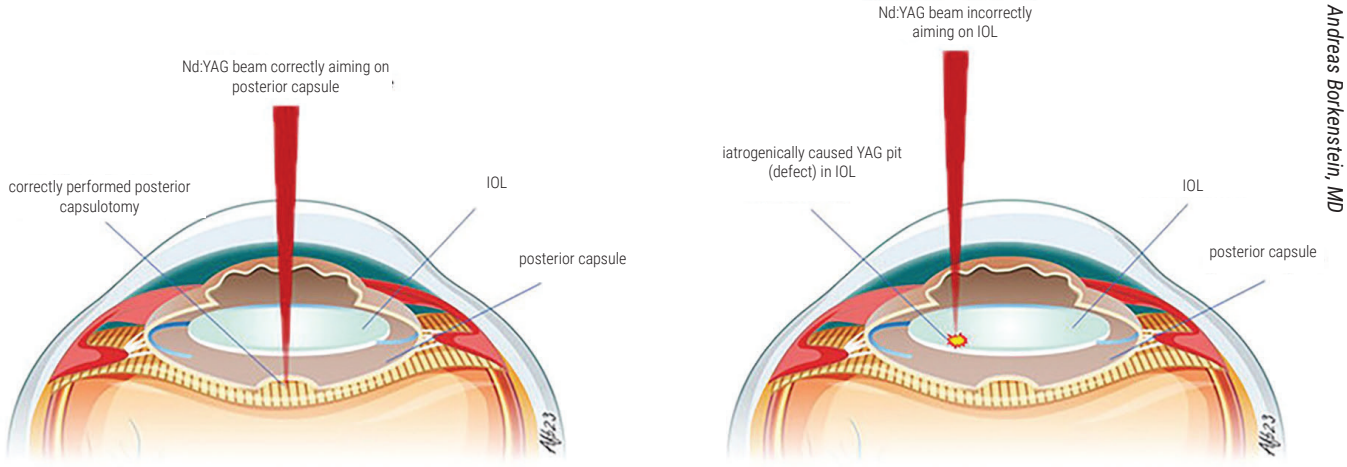
There are studies that look at the rate at which retinal tears and detachments occur following an Nd:YAG capsulotomy, but none has fully assessed the risk of these conditions developing. Of course, there's literature that could bolster the argument that the procedure increases the risk of developing vitreoretinal diseases, but these studies have varying population sizes and patient demographics as well as subjects with comorbidities that could contribute to retinal tears and detachment. One study reviewed literature on the subject but couldn't find conclusive evidence that the laser increases these risk factors, but they do believe that the laser's energy should be as low as possible to reduce the chance of anterior hyaloid damage, which may increase the chance of developing vitreoretinal diseases.[8]

Dr. Mamalis says he uses the re-establishment of the blood-aqueous barrier as a gauge for the timing of an Nd:YAG capsulotomy, because he notes that complications could arise for the patient if treated prematurely. "There may be a rebound of inflammation, or the laser and vaporizing of the capsule along with liberating the material that's in the capsule could at least theoretically trigger more inflammation or a rebound of inflammation after the cataract surgery," he explains. "There are some who advocate doing YAG laser right away, and as soon as the cornea is clear and the wound is stable, it's okay to do it after cataract surgery. My own personal reasoning is that I like to wait for the blood-aqueous barrier to reestablish."

There's the possibility that an Nd:YAG capsulotomy could be detriment to the ocular surface and patient's vision if done too early. Two studies from investigators in Taiwan examined refractive[9] and corneal endothelial[10] changes of two groups of patients—one group underwent a capsulotomy early on, within one year; one group underwent a capsulotomy later on, after one year.

Results from the refractive study[9] showed that patients who underwent Nd:YAG capsulotomy within one year post-cataract surgery showed a similar significant improvement to CDVA compared to the later surgical group. However, earlier surgical patients revealed more significant hyperopic changes compared to the later surgical group, which correlated with a deeper axial chamber depth. Therefore, the investigators believe surgeons should wait more than a year before performing a capsulotomy.

Similarly, the results from the corneal endothelial study proved that waiting longer to perform an Nd:YAG capsulotomy can mitigate the reduction of endothelial cell density following surgery.[10] Although their cell density levels recovered over time, the earlier surgical group showed a significant reduction after one week postop. However, their recovered status was still lower than the postoperative baseline results. Endothelial cell density in the earlier surgical group was recorded at 2,441.55 ±321.80 mm^2 postoperatively, 2,221.50 ±327.73 mm^2 at one week, and 2,369.95 ±341.53 mm^2 at four weeks after laser capsulotomy. The later surgical group maintained their baseline parameters without a significant change throughout the four-week follow-up period (2,584.57 ±274.51 mm^2 postoperatively, 2,565.14 ±304.66 mm^2 at one week, and 2,557.32 ±317.87 mm^2 at four weeks).



Andreas Borkenstein, MD

Graphic depicting an Nd:YAG laser beam being applied to an eye with an IOL implanted. Precise focus of the laser allows for safe and effective treatment (left), while incorrectly positioning the laser can pit the IOL (right). *(Creative Commons License: https://creativecommons.org/licenses/by-nc/3.0/.)*

Surgical Pearls

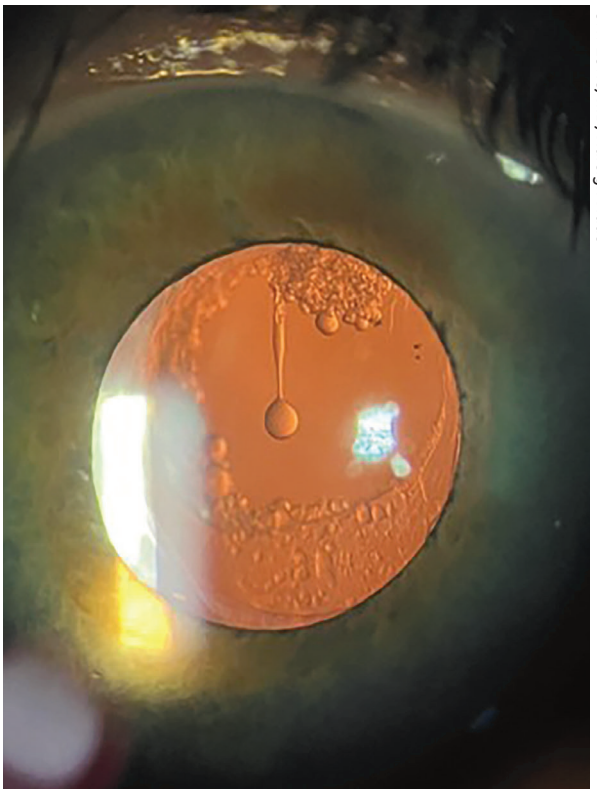
Physicians beginning their first steps towards treating PCO should be aware of all possible outcomes that may arise during surgery. Many experienced surgeons tout that using an Nd:YAG laser to perform a capsulotomy is quick and easy, but there's a learning curve young ophthalmologists should be aware of before handling the laser.

"Firing the laser is easy … you just need to push a button," boasts Dr. McKinney. "But the challenge is that the YAG laser throws off shockwaves that can damage the eye and can pit or even crack an intraocular lens. So, you want that energy to cut the cloudy capsule to clear the visual axis, but you want to avoid collateral damage to the eye. It's critical to be able to aim it very precisely. On average, the distance between the capsule and the implant lens is only 130 µm. That's the length of a particle of dust. Sometimes the capsule lies right on the implant, so that increases the risk that you can damage the IOL when you do the laser.

"You also need to know where to put the laser spots," he continues. "Depending on the nature of the cloudiness, there may be a pattern of laser spots that would be most effective at opening the capsule. In addition, you want to know how big to make the capsulotomy. If you make it too small, you may not remedy the patient's visual complaints. If you make it too big, you may let vitreous come forward into the anterior chamber, or you may actually cause the implant to be unstable. It's rare to have complications with a YAG laser if you're an experienced surgeon, but those complications can be sight threatening. So, it's essential to be able to recognize and manage complications, and that requires extensive training and experience."

In addition to Dr. McKinney's advice on how to properly perform an Nd:YAG capsulotomy, Dr. Mamalis mentioned that ocular abrasions and irregularities can reduce the effectiveness of the laser, as it won't allow the ophthalmologist to properly focus the laser spots.

"If there's any significant scarring in the cornea, then you're not getting a clear view," Dr. Mamalis adds. "That can make the YAG laser more difficult. If the patient has severe dry eyes where there are irregularities on the surface of the eye, that can also make it more difficult to do the laser. If you're going to be doing YAG capsulotomy, you want to dilate the pupil as widely as you can, because doing a YAG capsulotomy through a smaller pupil or a pupil that is scarred down with synechiae makes it more difficult to do."



C.Y. Lewis, MD; Kaleigh Haus

Elschnig pearls can be found hanging in the posterior capsule. If an Nd:YAG laser is unavailable, peeling and aspiration of the pearls can be a safe and effective method to employ. *(Ophthalmic Atlas Images by EyeRounds.org, The University of Iowa are licensed under a Creative Commons Attribution-NonCommercial-NoDerivs 3.0 Unported License.)*

Also, be aware of when not to employ an Nd:YAG capsulotomy. Yes, this procedure is the current mainstay for treating PCO, but sometimes patients' complaints may have arisen from some other ocular complication.

"There are patients who've received multifocal IOLs who have significant dysphotopsias or other issues with their vision, and there are those in our profession out there who tout a very early immediate YAG laser capsulotomy to clear the visual access and get rid of these potential issues," shares Dr. Mamalis. "I take the opposite tack. I say you definitely shouldn't do a YAG laser capsulotomy in a patient who's got visual aberrations and dysphotopsias from a multifocal lens because the reason for that is actually from the lens itself, not the posterior capsule.

"Once you've opened a posterior capsule, if you have to do a subsequent IOL exchange, that exchange becomes much more difficult to do," he continues. "And so, if you've got a patient who's having issues postoperatively, but they've had cataract surgery, their implant looks fine, yet they're having issues with glare, photophobia, dysphotopsia, other things like that, then you better make sure that that is coming from the capsule, not the lens itself before you do a YAG. So that's the one time I would advocate taking a step back and saying, 'Hey, wait a minute, should we really be doing a YAG capsulotomy and trying to improve this patient's symptoms, or should we be looking at the lens itself as the culprit rather than the posterior capsule?'"

Although uncommon, Dr. McKinney noted that epithelial cells can regrow as either fibrous membrane on the back of the IOL

or as Elschnig pearls. He explained that this is caused by the capsule being opened during the procedure. Membranous PCO doesn't always have to be treated with an Nd:YAG laser, and peeling and aspiration of Elschnig pearls has been cited as an effective alternative to capsulotomy.[11] However, this requires taking the patient into the operating room "A time when you might not want to use YAG would be if the zonules are very weak or missing," adds Dr. McKinney. "For example, in a post trauma patient, sometimes you might actually dislocate the lens by doing the laser. In that setting, it may be better for a vitreoretinal colleague to do a pars plana vitrectomy and remove the back of the capsule. If the lens becomes unstable in that setting, they're already in the eye and they can take the lens out and sew in a secondary implant lens." (*See Secondary IOL: Best Practices on pg. 50*)

Additionally, physicians can attempt to prevent PCO by implanting specific IOLs following cataract surgery. Make sure to talk with the patient before making this choice for them, because they're looking for comfort and improvement to their vision and may not want the IOLs that could potentially mitigate the development of PCO in terms of how they're implanted.

"In terms of trying to prevent PCO, there are some different things that we can do with an IOL," says Dr. Mamalis. "One of the things that's been studied the most is to put what we call a sharp edge on the posterior optic of the IOL. And so, if you can put a sharp edge on there—it's a right-angle band—then you can sometimes get the lens capsule to almost shrink wrap around the posterior surface of the IOL postoperatively.

"Anything you can do that creates a barrier where the capsule meets the edge of the lens optic can help to slow down PCO and maybe prevent it," he continues. "I do think that a lot of IOL manufacturers have provided lenses that have that very sharp, right angle of the posterior optic edge on the IOL, and that can help to prevent or slow down PCO."

Maybe the addition of a sharp edge on an IOL can help, but this all circles back to a point that Dr. McKinney made earlier. If these IOLs can make the lens capsule "shrink wrap" around the posterior capsule, as Dr. Mamalis suggested, then these lenses give you a better chance of success with an earlier Nd:YAG capsulotomy, alluded to by Dr. McKinney. In the end, the IOL of choice will have some impact over how PCO is developed and when a capsulotomy can be performed.

Though YAG capsulotomy has become a time-honored skill, surgeons say it still should be approached with care. "However, while YAG capsulotomy can be performed in a fairly short period of time by a skilled ophthalmologist, it's not easy and it's not risk-free," Dr. McKinney notes. "It has the potential to do permanent damage to the eye if it's done incorrectly. So, for that reason, it should only be performed by ophthalmologists who've had hundreds of hours of surgical training in the care of actual patients."◀

The Invaluable YAG Laser

The YAG is so ubiquitous and useful, it's easy to forget that, prior to its invention, cases of PCO had to be treated in the operating room using meticulous techniques.

"I'm old enough now to remember before YAG was available, and in those patients who developed significant PCO, you would have to take them back to the operating room, and you'd have to go behind the lens optic with a sharp needle and actually open the posterior capsule manually, which was very tricky to do," shares the Moran Eye Center's Nick Mamalis, MD. "Once the YAG laser was approved, I think that was a marked advance because you didn't have to take patients back to the operating room anymore. I think the YAG has been one of the great inventions of my 40-year ophthalmic career."

Will there ever be a better way to treat PCO? Oregon City, Oregon's, J. Kevin McKinney is skeptical since this treatment consistently provides positive results for most patients.

"It's essential," says Dr. McKinney. "There's no good alternative. While it requires a great deal of skill on the surgeon's part, from the patient's perspective it seems easy. It doesn't take very long to do and it's an instant fix for the vast majority of patients. So, it's an essential tool in the toolbox."

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An Open Letter to Ophthalmologists:

I would like to issue a correction regarding my previous comments related to Eyeleve® MGD that appeared in a press release from Bruder Healthcare and Hilco Vision. The comments that appeared in this press release from Bruder Healthcare and Hilco Vision ascribed to me were made several years ago in an approved OCuSOFT® press release regarding **Retaine® MGD®** when the formulation was under the oversight of OCuSOFT Inc. OCuSOFT Inc. remains the owner of the trademark **Retaine® MGD®** and has recently introduced an advanced formulation, **Retaine® MGD® Advanced.**

At the time of my statements in the Bruder Healthcare and Hilco Vision press release, I was under the impression that the formulation in question was still associated with OCuSOFT Inc.'s product, **Retaine® MGD®**. To make the record crystal clear, it is my understanding that while the old formulation has transitioned to a new brand under Eyeleve® MGD, **Retaine® MGD®** remains the property of OCuSOFT Inc. OCuSOFT®'s newest technology formulation, branded as **Retaine® MGD® Advanced**, is also the sole property of OCuSOFT Inc.

The recommendations and endorsements I have provided over the years were not solely based on the formulation itself but were rooted in my/our extensive experience with the product, the study data, and the trust built through our collaboration with OCuSOFT Inc. Given that the new Eyeleve® MGD product does not share this history with me and that it has not been evaluated within the context of previous research, it is important to clarify that my endorsement is not extended to this new product, Eyeleve®, or any formulation of Eyeleve®.

My comments were not intended to misrepresent the ownership of the trademark or to imply any ongoing association with the Eyeleve® MGD brand. I apologize for any confusion this may have caused and appreciate the opportunity to clarify this matter. My intention is to always provide accurate information to support the best interests of patients and the eye care community.

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Paul Karpecki

Dr. Paul Karpecki

OCuSOFT

Getting Started With GATT

A glaucoma specialist shares pearls for patient selection and how to perform the suture technique.

AMY D. ZHANG, MD
ANN ARBOR, MICH.

Gonioscopy-assisted transluminal trabeculotomy is a MIGS procedure that increases aqueous outflow by removing the trabecular meshwork and the inner wall of Schlemm's canal. In moderate to advanced open-angle glaucoma, it has a reported success rate of 83.7 percent.[1] One of the biggest benefits of GATT is that it's a cost-effective option when using Prolene suture and other equipment that's already in the OR.

Here, I'll describe how to perform GATT using the suture technique and share pearls for success.

Patient Selection

Adults and children[2] with open-angle glaucomas are ideal candidates for the GATT procedure, though GATT is safe and effective for both primary and secondary open-angle and angle-closure glaucomas as well.[3] GATT can be employed in all stages of glaucoma since it treats the entire collector system. Studies have also shown that GATT is an option for patients who've already undergone filtering procedures such as trabeculectomy and tube shunt implantation, with reported success rates ranging from 60 to 70 percent.[4] GATT is contraindicated in patients with unidentifiable angle structures, intraocular lens instability, those who can't stop anticoagulant medication and those with corneal endothelial disease.

> **Before attempting GATT, it's a good idea to have some experience with other angle-based surgeries that might not involve cannulating the entire canal, such as iStent or Kahook dual blade goniotomy, in order to get familiar with working in the angle.**

For surgeons who are new to GATT, selecting the right patients for the first few procedures will set you up for success. Those who have secondary open-angle glaucomas such as pseudoexfoliation, pigment dispersion or pigmentary glaucoma are good options. The reason for this is that when you're first working in the angle, it can be difficult to visualize the structures, so having some of the pigment present as a landmark for identifying the trabecular meshwork is helpful. Using trypan blue to stain the trabecular meshwork can also aid visualization and identification of the angle layers.

Before attempting GATT, it's a good idea to have some experience with other angle-based surgeries that might not involve cannulating the entire canal, such as iStent or Kahook dual blade goniotomy, in order to get familiar with working in the angle. Try performing intraoperative goniotomy on all your cataract patients to get used to using the gonioprism and obtaining an en face view of the angle.

Surgical Technique

I perform GATT using 5-0 Prolene most of the time because it's cost effective. If using Prolene suture, it must first be prepared using low-temperature cautery to blunt the ends of the suture. The microcatheter technique is very similar, though these devices don't require priming and have an illuminated, blinking tip to help the surgeon track its progress through the canal (*Figure 1*). The canaloplasty device iTrack is often used off-label for GATT.

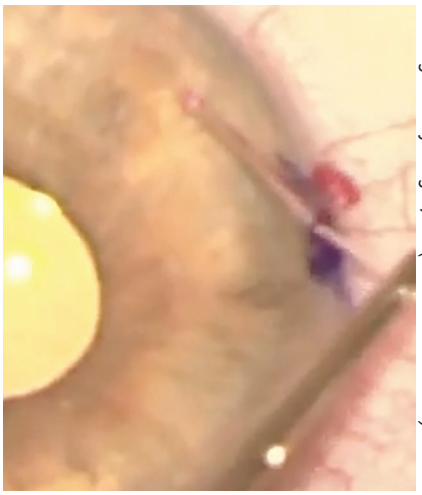
Begin by making a clear corneal paracentesis directly across from the nasal meshwork. Fill the anterior chamber with viscoelastic such as Healon GV and rotate the eye on the gonioprism to visualize the angle. Direct visualization is one of the first steps in any angle-based surgery. So, if you don't have a clear en face view—stop and try to get better visualization. Don't press too hard on the gonio prism to avoid creating corneal striae.

I use a 25-gauge MVR blade to make a 1- to 2-mm goniotomy in the nasal quadrant. Before inserting the prepared suture, I inject a little more viscoelastic at the goniotomy site to further open up the area so that the suture has an easier point of entry.

At the goniotomy site, insert the suture at a 10- to 15-degree angle to

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.



All Images: Uday Devgan, MD (CataractCoach.com)

Figure 1. In this combined GATT-phaco case performed by Ali Al-Beshri, MD, phaco is performed first, followed by GATT. A microcatheter is placed using an *ab interno* approach to unroof Schlemm's canal for a full 360 degrees.

ease entry into the lumen of Schlemm's canal (*Figure 2A*). It's important to confirm that you're in the correct space before starting to cannulate, especially when using suture because even though it's blue, it's often more difficult to see than a microcatheter. You certainly don't want to be in the ciliary body or create a cyclodialysis cleft for 360 degrees. Advance the suture slowly, about one clock hour at a time, in a counterclockwise direction for right eyes; clockwise for left eyes.

When the distal end of the suture returns to the initial goniotomy site (*Figure 2B*), grasp it together with the proximal end using microforceps and pull to unroof the trabecular meshwork (*Figure 2C*). As you tear through the trabecular meshwork, there will be some blood reflux. At the end of the case, leave some Healon in the eye to tamponade the bleeding (*Figure 2D*). The amount left will depend on the amount of blood reflux from the episcleral veins. If I see a lot of blood reflux, I'll leave as much as half of the Healon in the eye, and the pressure may be closer to 20 or 30 mmHg at that time. If there's minimal blood reflux, I leave less viscoelastic. The target pressures on the first day after surgery may range from 15 to 18 mmHg.

Around the Globe

A 360-degree GATT is considered ideal since it treats the entire collector system; currently, we can't easily identify the key areas where the collector channels are most robust. However, it's not always possible to achieve a 360-degree GATT. If you meet considerable resistance, rather than attempting to shove the suture or microcatheter, cannulate what you can and tear through. A 200- to 270-degree GATT is often sufficient.

Hemi-GATT paired with cataract surgery has also been described in the literature. In one study, 180-degree cannulation of the inferior hemisphere was performed in 112 eyes of 112 patients with moderate to severe primary open-angle glaucoma, resulting in an IOP reduction of 37.9 percent (13.6 ±3.9 mmHg at 24

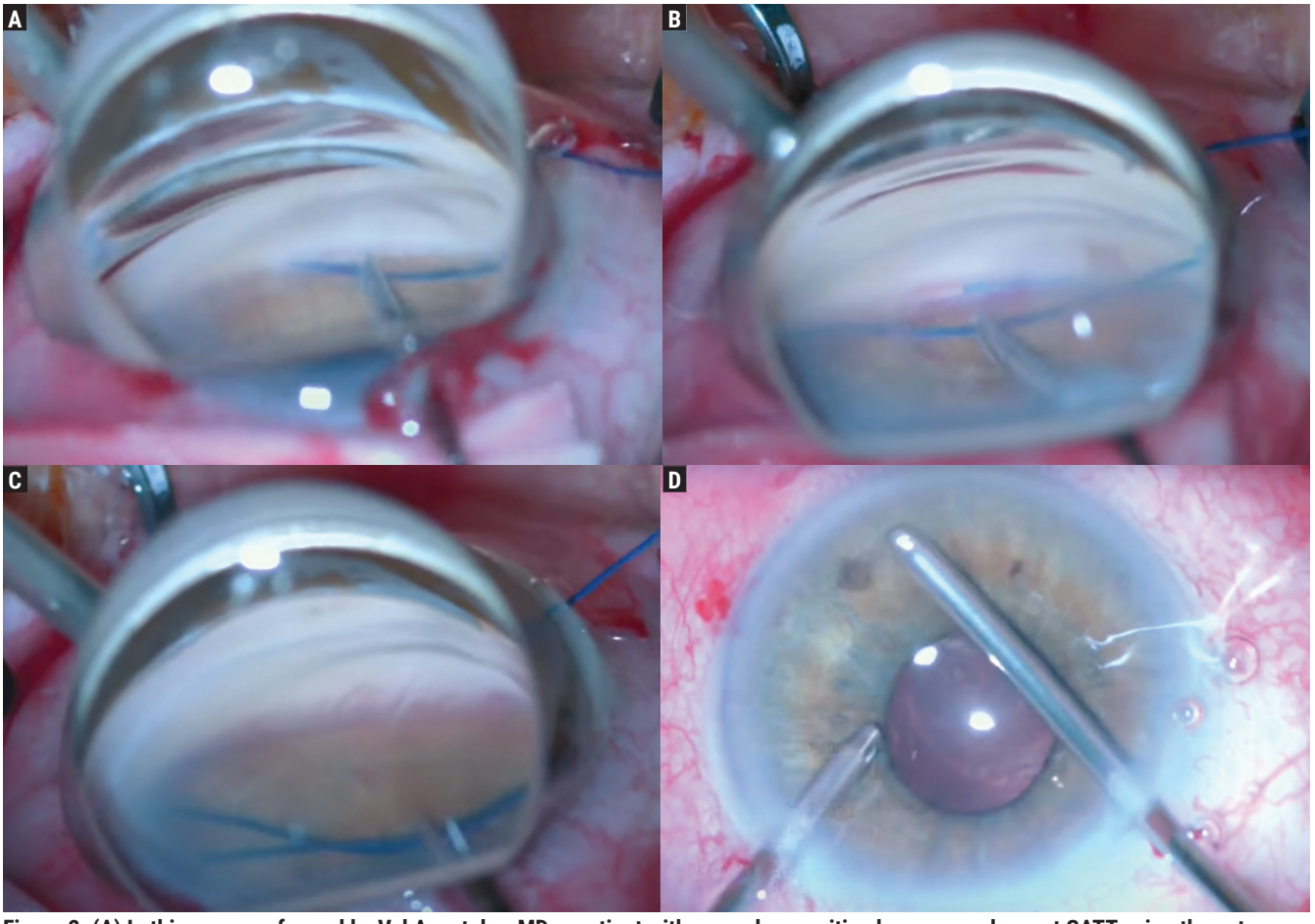


Figure 2. (A) In this case, performed by Val Apostolov, MD, a patient with secondary uveitic glaucoma underwent GATT using the suture technique, followed by phacoemulsification. Combining phaco with GATT helps to provide additional pressure lowering, since crystalline lens removal opens the angle. Here, the blunted 5-0 polypropylene suture is inserted gently into the goniotomy incision at a slightly upward angle. (B) The suture is passed through Schlemm's canal for a full 360 degrees, advancing slowly by about one clock hour at a time. (C) Using microforceps, both ends of the suture are grasped and pulled to unroof the trabecular meshwork. (D) Some viscoelastic is aspirated out of the anterior chamber. Leave a fill of 25 to 50 percent as a tamponade, depending on the amount of blood reflux present.

months) from a baseline of 21.9 ±5.8 mmHg.[5]

Postoperative Pressures

Pressure reduction after GATT is best evaluated about one week postoperatively. Take the initial IOP drop the day after the case with a grain of salt. On postop day one, patients may have good eye pressures because their glaucoma medications may not have washed out of their systems. It's closer to the one-week mark where you can assess whether or not the procedure was successful. Certainly, for those times when the pressure is higher than expected, perform gonioscopy at the slit lamp to see the areas that have been cannulated and check whether there's a clot or something else prohibiting the pressure from dropping more.

Intraocular pressure spikes are common after GATT and are most likely to occur within the first two weeks.[6] Though they resolve with topical and systemic pressure-lowering treatments, pressure spikes are a risk factor for GATT failure. If IOP spikes occur due to postoperative topical steroid use, steroids should be discontinued in favor of an NSAID. ◀

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Stargardt's: The State of The Art in 2024

An in-depth review of the pathophysiology and diagnostic clues, as well as potential therapies on the horizon.

MUHAMAD FESTOK, MD, AND MICHAEL A. KLUFAS, MD
PHILADELPHIA

Stargardt disease was first described by German ophthalmologist Karl Stargardt in 1909 and remains the most common juvenile macular dystrophy, with an incidence of ~1/10,000 individuals worldwide. Clinically, patients typically present with central vision loss in childhood or early adulthood, central scotomata and irregular yellow-white outer retinal flecks, and an atrophic maculopathy which may be progressive throughout life. Choroidal neovascularization can rarely also develop in some cases. As our knowledge of the disorder has evolved, there's been recognition of significant heterogeneity in the clinical findings, presentation, severity and course of STGD phenotypes among families with the disorder, even in patients with similar genotypes. Even though the previous term "Stargardt macular dystrophy" may describe the early posterior pole findings of the disease, in the past decade numerous studies have suggested it's characterized by generalized retinal dysfunction as evidenced by ultra-widefield imaging and electrophysiologic testing.

Here, we'll focus on the key aspects of Stargardt disease, from the pathophysiology to the most up-to-date diagnostic and treatment strategies in 2024.

Pathophysiology

The vast majority (>90 percent) of STGD cases are due to mutations in the *ABCA4* gene, and are inherited in an autosomal-recessive manner. Additionally, Stargardt-like phenotypes may be inherited in an autosomal-dominant manner with mutations in *PROM1* and *ELOVL4*.

The *ABCA4* gene encodes the ATP-binding cassette (ABC) transporter protein in both rods and cones, which plays a crucial role in the transport of retinaldehyde across the retinal pigment epithelium and the photoreceptor cells. Dysfunction of the ABCA4 protein results in an accumulation of toxic products from the visual pathway within the photoreceptor outer segments which are then shed and phagocytized by the RPE, forming a major component of lipofuscin. The lipofuscin buildup leads to degeneration of the RPE and ultimately to the loss of photoreceptor cells.

One barrier to classifying and predicting STGD cases is there is substantial heterogeneity and over 800 mutations in *ABCA4* autosomal recessive STGD with a wide range of effects on the protein function and expression. Therefore the phenotypes of *ABCA4* STGD often exhibit large variability due to the underlying genetic heterogeneity. Additionally, certain types of mutations (truncating, severe misfolding, and intronic or splice variant mutations) may result in severe functional loss of ABC transport protein and severe disease.

Clinical Features and Diagnostic Testing

The clinical presentation will vary based on age of onset, presenting symptoms, fundus appearance and the severity of the underlying mutation, which can create some clinical uncertainty for a physician. As discussed above, the differences are most often explained by the severity of the mutations in the *ABCA4* gene, the sensitivity of the foveal cones and RPE to these genomic differences.

The most common presenting complaint is usually a loss of central VA, which can range from 20/30 to 20/400. This loss of VA can occur as early as 5 years of age (i.e., the time of a potential failed vision screen) or in late adulthood (40 years or later). Usually the earlier and more severe conditions correlate to a severe *ABCA4* genotype and more sensitive cones and RPE. Another reason why a patient presents to an ophthalmologist or retina specialist is due to an incidentally abnormal fundus exam during routine evaluation.

The fundus exam often demonstrates lightly colored flecks at the level of the RPE. They may be differentiated from drusen as they're usually more elongated, often in contact with each other and commonly extend beyond the macula. The flecks often meet, creating a fishtail appearance, hence the name pisciform flecks *(Figure 1)*. Some patients will have a cluster of flecks two to three disc diameters

This article has no commercial sponsorship.

Dr. Regillo is the director of the Retina Service of Wills Eye Hospital, a professor of ophthalmology at Thomas Jefferson University School of Medicine and the principle investigator for numerous major international clinical trials.
Dr. Yonekawa is an assistant professor of ophthalmology at Sidney Kimmel Medical College at Thomas Jefferson University. He serves on the Education Committee of the American Society of Retina Specialists and on the Executive Committee for the Vit Buckle Society, where he is also the vice president for academic programming.

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around the fovea, while in others the flecks extend beyond the temporal vascular arcades up to or even beyond the equator. These flecks can also differ in several ways, but most notably in the amount and extent (preequatorial or extending anterior to the equator) to which they're present. It's possible some patients will exhibit minimal to no flecks, while others will have too many to count.

The fovea, on clinical exam, is often described as having a beaten-bronze appearance. This appearance is usually caused by the retention of bisretinoids (specifically A2E) intracellularly, resulting in a uniform light brown color that obscures choroidal details on ophthalmoscopy. This obscuration also contributes to the "dark or silent choroid" observed during fluorescein angiography, which is present in greater than 60 percent of patients *(Figure 2)*. On FA, retinal blood vessels will hyperfluoresce against a hypofluorescent choroid. Flecks may appear hypofluorescent, or hyperfluorescent if associated with atrophy.

Fluorescein angiography, along with ophthalmoscopy, will demonstrate relative sparing of the peripapillary RPE, which is diagnostic for Stargardt disease. Fundus autofluorescence is an excellent non-invasive alternative to FA and can further highlight flecks. Figure 3 demonstrates an SD-OCT image, which is a useful adjunct for illustrating the extent of outer retinal loss and RPE atrophy and can often detect early changes. The flecks appear as subretinal and intraretinal hyperreflective deposits. A sub-foveal optical gap, along with thickening of the external limiting membrane, hyperreflectivity at the base of the outer nuclear layer and disruption of the ellipsoid zone are also evident on OCT. Electrophysiology studies are typically normal or subnormal in full-field ERGs early in the disease stage but, over time, will show reduced responses secondary to photoreceptor degeneration. ERG can also be used to classify the severity and can be useful in tracking progression. Visual field testing may also accomplish a similar goal.

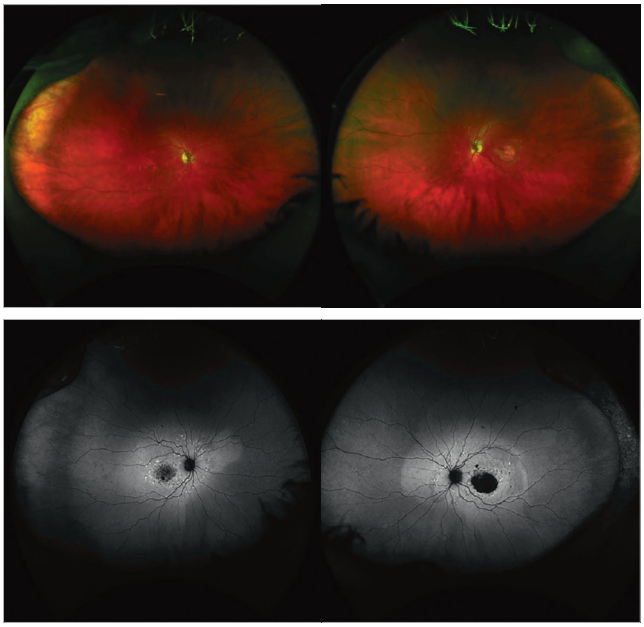

Figure 1. Fundus photo and fundus autofluoresence of a young male with *ABC4A* (c2588GC)-confirmed Stargardt disease.

Though a choroidal neovascular membrane is a rare, late complication of STGD, it has the potential for severe visual impairment, if present. The CNVM can be treated with anti-VEGF if it occurs.

Genetic Testing

In cases of diagnostic uncertainty, and even in cases of confirmed STGD on clinical appearance, genetic testing should be performed, which offers several clinical benefits.

With inherited retinal degenerations in general, there can be significant phenotypic variability, and genetic testing can help conclusively determine the underlying molecular variant and provide more certainty to both physician and patient alike of the underlying mutation and clinical disease. Likewise, most clinical trials, as discussed below, will require genetic confirmation prior to entry into a trial. It's important to involve a genetic counselor, because while most *ABC4A* STGD don't have other non-ocular manifestations, there may be other relevant issues to address, such as prenatal counseling and family planning.

It's important to remember that, in general, a causative mutation can be identified in up to 60 to 80 percent of patients with IRD. Often a saliva sample (2 mL) is sufficient for initial panel testing. For STGD, *ABC4A* mutations are relatively well-characterized. However, if panel testing doesn't identify a variant, I'll consider repeating the panel test in two to four years, as more loci and mutations are added yearly.

Furthermore, it bears mentioning that panel testing of a single individual doesn't identify whether two mutations identified are in cis- or trans-configuration. Segregation analysis with a familial pedigree can often identify the inheritance pattern with greater precision, as well as if they're on the same or different chromosomes. This can have important implications when a family is considering additional children or for their children's reproductive future.

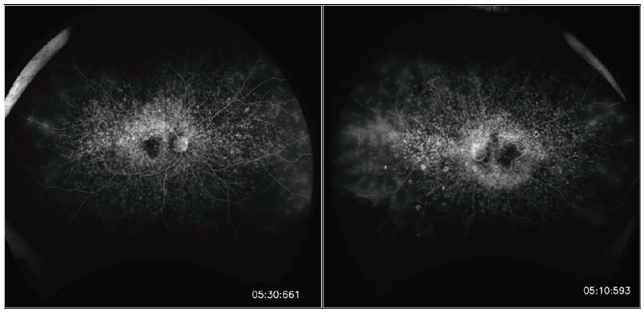

Figure 2. Dark choroid on fluorescein angiography.

Management of Stargardt Disease

At this time, there are no proven treatments for Star-

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ABOUT RICK

Rick Bay served as the publisher of *The Review Group* for more than 20 years.
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gardt disease. Clinical trials may be an option depending on genetic testing results, age and risk/benefits of an investigational therapy (ongoing trials are discussed in greater detail below). Currently, there's extensive research taking place in genetics, gene therapy and cell replacement therapy as possible therapeutic strategies. Given our knowledge of the underlying genetic derangement with the ABCA4 transmembrane protein, vitamin A is poorly processed and vitamin A byproducts are toxic. There's some limited evidence that lower levels of vitamin A may be linked to a better visual outcome in STGD, but this also must be balanced against the need for vitamin A in other bodily functions, and patients should be counseled that vitamin A shouldn't be completely cut out. Clinically, patients can be bothered by transitioning from one lighting environment to the next due to this particular dysfunction.

Other reasonable recommendations—though not well-studied—would be lutein supplementation (AREDS2 vitamins contain this), a diet rich with tomatoes (lycopene) and corn (zeaxanthin), as well as sunglasses/sun protection and avoidance of smoking. Lutein, lycopene and zeaxanthin accumulate on the inner surface of the retina and diminish the amount of blue light that's transmitted to the photoreceptors. Involvement of a low-vision specialist or low-vision aids may be of use to patients for activities of daily living and should be proposed when necessary by a physician.

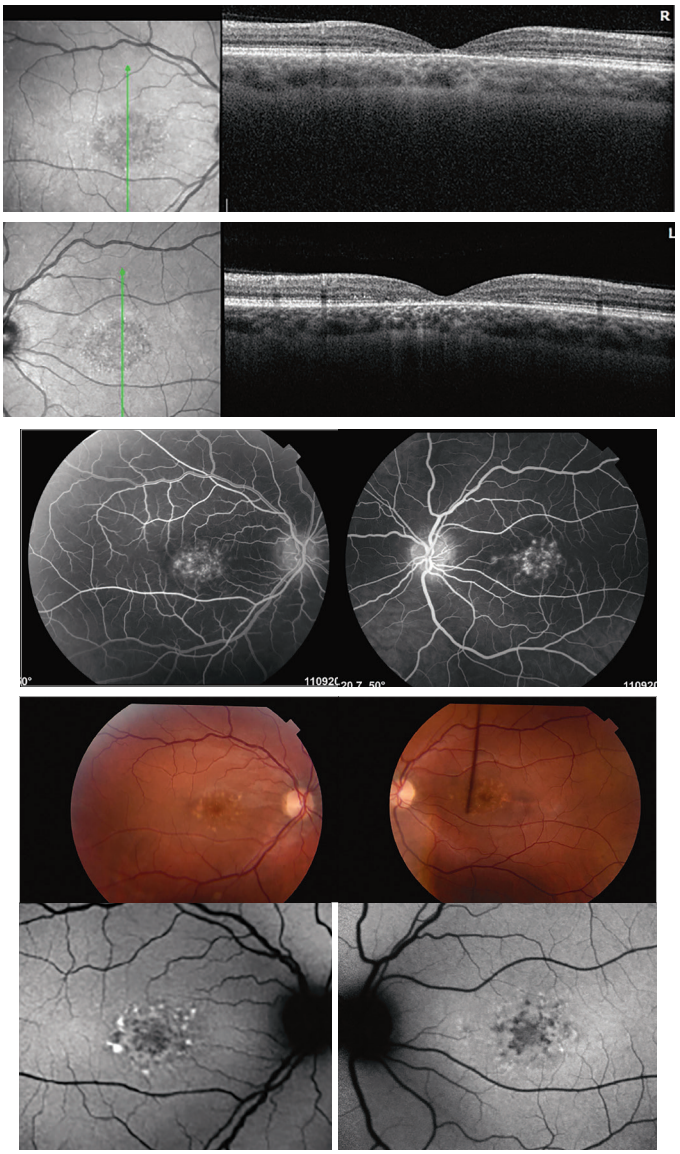

Figure 3. Multimodal imaging, including OCT, demonstrating foveal thinning and central loss of RPE and outer retinal layer in *ABC4A* STGD.

Clinical Trials And Potential Treatments

Given there are no current effective treatments for STGD, there's great interest in cell, gene and pharmacologic therapies to potentially cure or slow this progressive disorder.

Cell therapy was initially explored in 2010, a Phase I/II safety and tolerability assessment for the use of hESC-derived RPE cells (named ASP7316 or MA09-hRPE) in STGD sponsored by Advanced Cell Technology, which has since been acquired by Astellas Pharma. In the U.S. trial arm, the subretinal delivery of stem cells via pars plana vitrectomy was safe and well-tolerated in 13 patients without failure or rejection. The most common postoperative complication was cataract progression following vitrectomy. Though visual acuity outcomes showed improvements in some patients, there was no control group. In 2024, the cell lines have undergone extension revision and Astellas plans ongoing trials in geographic atrophy secondary to age-related macular degeneration, and with hopes of expansion to STGD as well.

Pharmacologic intravitreal anti-complement agents that have gained FDA approval for geographic atrophy secondary to AMD have also completed trial enrollment and we eagerly await the results. A Phase IIB, randomized, double-masked, sham-controlled trial of the complement C5 inhibitor Zimura (Astellas) in subjects with autosomal recessive Stargardt disease has been fully enrolled and nears completion. The hypothesis is that reducing the inflammatory milieu with intravitreal complement inhibition may reduce the rate of atrophy progression as measured by *en face* OCT and fundus autofluorescence. Given good tolerability in the atrophic AMD population, we look forward to the results of this late-stage trial in the STGD population.

One downside of complement inhibition is that it doesn't target the underlying cause of STGD, as a gene therapy would. However, there are limitations to gene therapy in *ABC4A* STGD given the size of the *ABC4A* gene. Well-established adenovirus vectors aren't able to accommodate the size of the *ABC4A* gene, and therefore other viral vectors such as lentiviral

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vectors are under investigation. However, these other vectors require much preclinical and early clinical trial work.

In terms of gene therapy in the pipeline, Ocugen recently announced that dosing is complete in the third cohort of its Phase I/II GARDian clinical trial for OCU410ST (AAV-*h*RORA)—a modifier gene therapy candidate being developed for STGD. Three subjects received a single subretinal injection of the highest dose (2.25×1011 vg/mL) being tested.

Given the limitations of viral vectors, other methods, such as nanoparticles, offer an alternative transport method for larger transgenes. Another approach in early stages may be modulation of RNA via anti-sense oligonucleotides. Clustered regularly interspaced short palindrome repeat (CRISPR)-based technology is also under investigation for STGD as well as other IRDs.

Less-invasive approaches which may be favorable, especially in younger patients, are also under investigation and tend to focus on visual cycle inhibition to slow the progression and accumulation of toxic biproducts. For instance, emixustat hydrochloride from Acucela is being investigated in STGD. Emixustat is a potent visual cycle inhibitor of RPE65 isomerization activity and reduces visual chromophore (11-cis-retinal) production in a dose-dependent and reversible manner. One side effect of this type of therapy, however, is delayed dark adaptation due to the drug's mechanism of action. Another oral visual cycle inhibitor, Tinlarebant (BeliteBio), is currently undergoing a Phase III clinical trial (DRAGON) in adolescent patients with Stargardt disease in hopes of slowing disease progression. Also, Nanoscope is currently developing a gene therapy that's now in Phase II (STARLIGHT).

One other promising approach is oral administration of deuterated vitamin A (ALK-001/Gildeuretinol, Alkeus Pharmaceuticals). This drug has the C20 hydrogen atoms replaced with deuterium atoms, an isotope of hydrogen with a neutron in the nucleus; this impedes the dimerization of vitamin A and therefore reduces the opportunity for production of A2E. The hypothesis is that reducing levels of vitamin A will limit the production of all-trans-retinal and subsequently A2E. This compound is the subject of four clinical studies known as the TEASE trials, the initial results of which suggest good safety and tolerability and perhaps some encouraging early efficacy with regard to reducing the growth of atrophic lesions.

It's important to note that, though several different therapeutic approaches have been discussed above, that list isn't exhaustive. Other dietary supplementation approaches are being considered with various supplements, including docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) and alpha-linolenic acid (ALA) which are all omega-3 fatty acids and may support photoreceptor cells.

In conclusion, though Stargardt disease is one of the most common "juvenile macular dystrophies," it remains a complex condition, and the search for therapeutic approaches is challenging. Genetic testing has become widely available in 2024, and is low cost, non-invasive and continues to expand our understanding, especially with the most common *ABC4A* STGD. Though there are currently no FDA-approved therapies or interventions for STGD, there are promising cell therapies, gene therapies and pharmacologic approaches, including intravitreal and oral methods, under investigation. At this time, once the diagnosis is established and genetic testing agrees, I tell patients there's very likely to be some type of therapy in their lifetime. For now, supportive care with patient education, clinical trial referral when appropriate, low-vision services and monitoring by a retina or IRD specialist remain the mainstays of care. ◀

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Uveitis and Vision Issues In Herpes Zoster

A recent analysis found that uveitis developed in about half of individuals with herpes zoster ophthalmicus, with diagnosis occurring most often in the second week after the rash appeared. This research, published in the *American Journal of Ophthalmology*, also showed that eyes affected by uveitis were more likely to experience additional ocular complications and vision loss.

In this retrospective, cohort study, which included individuals with acute herpes zoster ophthalmicus, investigators sought to determine the timing of uveitis onset as well as the frequency of associated complications.

The primary outcomes measures included the proportion of individuals who developed uveitis and the time to uveitis diagnosis after HZO onset. Secondary outcome measures were the complications associated with HZO-related uveitis and the impact of early antiviral treatment (within 72 hours) on outcomes.

Of the 869 study participants, 413 (47.6 percent) developed uveitis. Data showed that the median time from onset of rash to uveitis diagnosis was 10 days. Among the 658 patients examined within the first week following rash appearance, 17.6 percent (116/658) were diagnosed at that initial presenting exam and an additional 24.9 percent (164/658) received a diagnosis at a subsequent visit.

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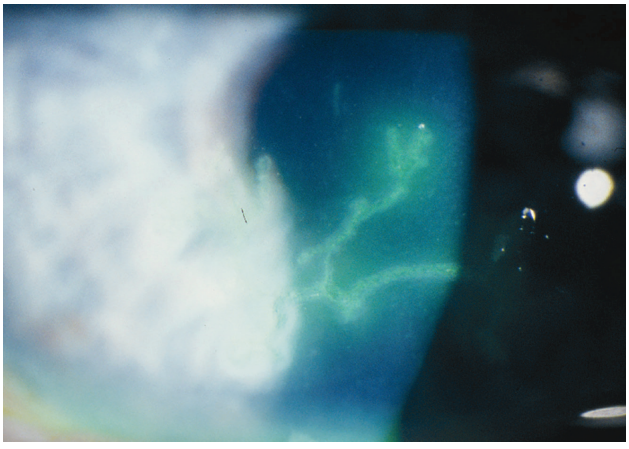
Complications, including moderate or severe vision loss, corneal scarring, neurotrophic keratitis, band keratopathy, corneal melt, elevated intraocular pressure, glaucoma and cataract, were higher in eyes with uveitis. Prompt



antiviral treatment was correlated with a lower rate of moderate vision loss among patients with the condition, according to the researchers.

"In summary, uveitis is a common complication of herpes zoster ophthalmicus and is associated with other ocular complications. Prompt antiviral treatment did not appear to prevent onset of uveitis in this cohort but was associated with a lower risk of vision loss in those that did develop uveitis. The diagnosis of uveitis was most frequently made during the second week following the rash onset," the study authors noted in the *AJO* paper.

"Individuals examined during the first week after onset of HZO rash may still develop uveitis after that visit, and a follow-up examination within the first month should be considered or they should be warned of the symptoms of uveitis that would prompt a repeat examination," they concluded.

Am J Ophthalmol. September 19, 2024 [Epub ahead of print].
J Meyer JJ, Liu K, Danesh-Meyer HV, et al.

Risk for RD with ARN Studied

Recently published research showed that retinal detachment is a frequent and serious complication of acute retinal necrosis (ARN), influenced by several risk factors such as the extent of initial retinitis involvement and the initial intraocular viral load.

"Active local antiviral therapy may reduce the risk of late-onset RD. The antiviral medication should be adjusted according to the inflammatory state," the study authors noted. "Therefore, timely detection of causative viruses and intensive systemic and local antiviral therapy is crucial for preserving visual function in acute retinal necrosis patients."

This retrospective, observational analysis, which examined the risk and prognostic factors that impact the long-term clinical outcomes of ARN, included patients with the condition who underwent treatment and completed follow-up from 2011 to 2021.

Researchers enrolled 59 ARN patients (65 eyes) with an average follow-up of 48.9 months. During the follow-up period, retinal detachment was reported in 34 eyes (52.3 percent). The risk factors for RD included the quadrants of involved retinal necrosis and the initial intraocular viral load. The analysis revealed an independent association between early intravitreal antiviral treatment and a reduced risk of late-onset retinal detachment.

Factors independently linked to an

increased risk of final vision loss included poor initial visual acuity and late-onset RD, according to the investigators, who also measured the viral load reduction ratio following the first intravitreal antiviral injection (IAI) and found it strongly correlated with initial intraocular IL-8 concentration and moderately correlated with the initial degree of aqueous flare.

Discussing their research in *BMC Ophthalmology*, the study authors reiterated that these findings indicated that the initial viral load and the early extent of retinitis were linked to an increased risk of retinal detachment. These factors, they noted, may reflect the severity and progression of the infection, which can lead to retinal necrosis and detachment.

"Our study also showed that late-onset RD may increase the risk of final vision loss related to other factors, such as low initial vision," the research team wrote. "Therefore, timely detection of viral type and aggressive systemic and local antiviral therapy are crucial for preserving visual function. The shorter interval of IAI application was associated with a reduced risk of late-onset retinal detachment, which suggests that IAI can effectively suppress viral replication and inflammation in the vitreous cavity and prevent further damage to the retina.

"Therefore, eyes with low initial vision and more extensive retinitis or initial viral load at high risk of RD may require closer monitoring for final vision loss," the study authors concluded. "In addition, early combined systemic and local antiviral therapy in these high-risk patients may reduce the risk of late-onset retinal detachment and final vision loss."

BMC Ophthalmol. September 15, 2024 [Epub ahead of print].
Li Y, Chen L, Li P, et al.

The Dermatitis/Keratoconus Connection

The literature on atopic dermatitis explains how this condition is sometimes associated with risk of keratoconus, and that higher incidence rates of keratoconus have been reported in patients with eczema. However, not enough has been reported on potential causal relationships between the two diseases. To further investigate this association, researchers from China recently conducted a Mendelian randomization study.

What is a Mendelian randomization study? According to the researchers, this unique statistical method uses single nucleotide polymorphisms, the most common type of genetic variation in people, to estimate whether there's a causal relationship between the exposure (atopic dermatitis) and the outcome (keratoconus). This allows investigators to limit the influence of confounders and/or reverse causation that may happen regularly in more common observational studies.

After identifying a total of 22,474 cases for their dataset, the researchers began their analysis. Basically, the researchers plugged their data into a statistical analysis package designed for such purposes. This program made all causal inferences for the relationship between the exposure and outcome, and further strengthened the study by using a host of Mendelian randomization study methods in a two-sample approach. The

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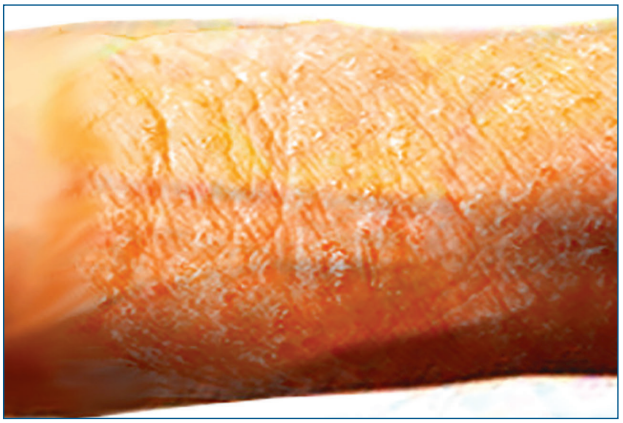
analysis revealed significant evidence that atopic dermatitis has a causal effect on keratoconus and displayed consistent results to that effect throughout the study. Only after performing a reverse Mendelian randomization analysis did the researchers discover that keratoconus does not have a causal effect on eczema.

"We recommend that individuals with atopic dermatitis undergo regular ophthalmic examinations, such as corneal thickness and cornea topography, to detect any early signs of keratoconus," suggested the researchers in their study, published recently in *Translational Vision Science & Technology*. "Especially for young patients, receiving ophthalmic examinations and treatment upon the diagnosis of atopic dermatitis can help to prevent permanent ocular damage threatening vision."



O.Chaigasame, MD

Researchers say that atopic dermatitis may have a causal relationship with keratoconus. *(From: Atopic Dermatitis. Copyright 2024, StatPearls Publishing, Used under the Creative Commons License)*

In their paper, the researchers cite evidence in previous studies suggesting that some combination of eye rubbing, systemic inflammation and genetic factors present in those with atopy conspire to induce corneal shape changes characteristic of keratoconus.

There were some limitations that may have skewed the results in this study. The researchers cited that their dataset didn't have a diverse population, and that all participants were of European decent. Further genetic data will need to be analyzed in future studies. Additionally, this investigation ruled out possible pleiotropic effects even though they are important to recognize in a clinical setting. They were removed by the Mendelian randomization program during analysis.

"In conclusion, using a two-sample Mendelian randomization approach, our study strongly supported previous observational studies suggesting that atopic dermatitis has unidirectional causal effects on keratoconus," concluded the researchers in their paper on the study. ◀

Ophthalmol Retina 2024; Apr 24. [Epub ahead of print].
Abbasgholizadeh R, Habibi A, Emamverdi M, et al.

ADVERTISER INDEX

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PRODUCT NEWS

New items on the market to improve clinical care and strengthen your practice.

IMAGING AND DIAGNOSIS

AI for Dry Eye

If certain dry-eye patients have been a challenge to diagnose in the past, a new device from Lumibird may be able to assist.

The company recently launched Omnicad, an ocular surface imaging system that integrates multiple exams such as transillumination meibography and an autofocus HD camera for sharp image quality and automatic, accurate and reproducible results, Lumibird says. To help display the health of the meibomian glands, the device uses an eyelid everter with transillumination infrared light to get two images in one click, notes the company.

The Omnicad also incorporates artificial intelligence, based on algorithms derived from more than one million clinically validated images. For more information, visit lumibirdmedical.com.

Easyfield VR Headset Upgrade Available

Earlier this year, Oculus introduced its Easyfield virtual reality headset for assessing patients' visual field, color vision and stereopsis. The original device uses standard automated perimetry (SAP) for VF testing; now, an optional update announced recently by the company also gives it the capability to perform frequency doubling perimetry (FDP).

Compared to SAP, FDP—which uses a series of flickering white and black bands—has been shown to evaluate the extent and pattern of VF loss with high precision and specificity. Particularly in glaucoma or ocular hypertensive patients, FDP may offer the benefit of sooner detection of functional damage.

The company says that practitioners can configure the Easyfield VR with one testing strategy, then upgrade to a dual configuration combining FDP and SAP as needed down the road. The headset can also be used in a fully lit room, with no internet connection required.
For more information, visit oculususa.com/easyfield-vr.

Streamlined Fundus Imaging

A new automated fundus camera on the market aims to help streamline retinal exams for physicians and staff. Launched by Visionix USA, the VX 610 non-mydriatic fundus camera is equipped with automatic functions for alignment, focus and capture to enhance imaging accuracy and consistency, according to the company.

The camera uses technology referred to by Visionix as "cross-polarized light," which developers say enables high-quality imaging clarity without the need for pupil dilation. It offers a 45-degree field of view along with a 90-degree mosaic function for extensive retinal screening capabilities.

Using AI, the company explains that the system is trained to auto-detect early signs of 13 common retinal pathologies. Visionix notes that the AI technology correctly flags a positive result 93 percent of the time, while negative results are properly identified at a rate of 90.6 percent. The VX 610 device employs a touch-screen interface and occupies a compact space, making it easy to integrate into various practice settings, says Visionix.

For more information, visit visionix.com/product/visionix-vx-610.

New Functionality for Maestro2

For clinicians familiar with the Maestro2 OCT device from Topcon, the company recently announced a new upgrade: Now, the color fundus camera is also available with OCT angiography, an imaging modality increasingly being employed in eye care to help identify and assess various vascular and retinal conditions.

The device, featuring single-touch automated image capture, offers 3×3, 4.5×4.5 and 6x6 mm OCTA scans to evaluate macular disorders such as age-related macular degeneration, Topcon says. Additionally, a 12x9 mm 3D widefield scan can be used to analyze more peripheral areas of the eye affected by conditions like diabetic retinopathy and vein and artery occlusions.

Other features now integrated into the Maestro2 with OCTA system include one the company calls "pinpoint registration," which enables comparison of subclinical OCT and OCTA findings with related areas on a color fundus photograph, as well as an eye-tracking feature that helps to improve image quality and reduce motion artifacts. The combined system also offers en face OCTA imaging and Angio B color-coding to help discern normal and abnormal blood flow in the retina and choroid.

The Maestro2 OCT can be purchased with or without OCTA. For doctors who already own a Maestro2 device, Topcon says most will have the option to purchase an OCTA upgrade.
For more information on the Maestro2, visit topconhealthcare.com/maestro2. ◀

EDITED BY ERIK MASSENZIO, MD

WILLS EYE RESIDENT CASE REPORT

A 71-year-old man presents to the Wills Emergency Room with worsening vision and intermittently elevated IOP.

BAILEY M. HARRISON, MD, KARINE SHEBACLO, MD, AND TATYANA MILMAN, MD
PHILADELPHIA

Presentation

A 71-year-old male was referred to the Wills Emergency Room with a concern for markedly elevated intraocular pressure in the right eye. The patient had been seen multiple times at outside optometry and ophthalmology practices for intermittent elevated IOP as high as 36 mmHg and 42 mmHg in his right eye. One month prior, he'd been treated for an unspecified unilateral keratitis with prednisolone acetate eye drops, and initially his elevated IOP was thought to be related to a steroid response. The patient also reported progressively worsening vision over this time, with his initial visual acuity at 20/40 OD one month prior then progressing to 20/100 OD over the month prior to presentation. He denied pain or pressure sensation. He also reported some swelling of the right upper and lower eyelids but was unsure how long this was present. He specifically denied eye redness, photophobia or diplopia.

History

The patient had a medical history notable for coronary artery disease and prior myocardial infarction, deep venous thrombosis, aortic valve disease, peripheral vascular disease, hyperlipidemia, hypertension and atrial fibrillation on dual-antiplatelet therapy. His prior surgical history included coronary artery stenting and aortic valve replacement. He reported a prior smoking history of 15 pack years and occasional alcohol use. His family history included ovarian cancer in his mother and colon cancer in his father. The patient had no known prior ocular history.

Examination

At presentation the best-corrected visual acuity was 20/100 OD and 20/25 OS. His pupils were round and reactive. There was no evidence of a relative afferent pupillary defect OU, though he did report light desaturation in the right eye. Intraocular pressures were 12 mmHg OU. The patient was able to identify zero out of eight Ishihara color plates OD and eight out of eight OS.

External examination disclosed a palpable, non-tender mass in the lower right orbit which was nonmobile. There was marked proptosis of 4 mm and resistance to retropulsion OD. Extraocular motility was restricted in all directions of gaze in the right eye; there was only 10 percent inferoduction, 10 percent superoduction, 50 percent adduction, and 40 percent abduction. He had no visible skin lesions of the periorbital region or on the face.

Anterior segment examination demonstrated mild ptosis OD (MRD1 2 mm OD, 3.5 mm OS) and bilateral mild nuclear sclerosis cataracts, but was otherwise unremarkable. Posterior segment examination was unremarkable, including normal bilateral optic nerves without pallor, hyperemia or cupping.

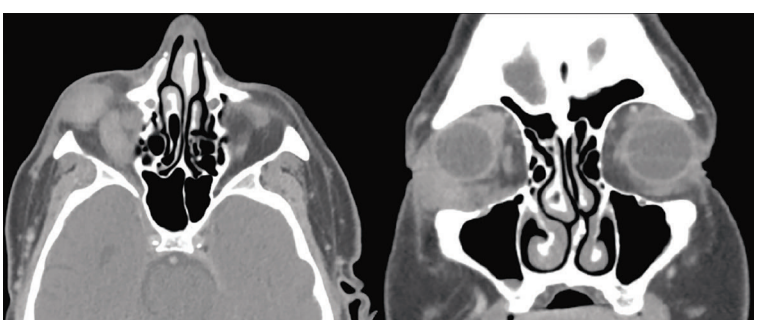

Figure 1. Right orbital soft tissue mass and right extraocular muscle enlargement. CT scan of the orbits with contrast, axial and coronal sections.

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

Work-up, diagnosis and treatment

A CT scan of the orbits with contrast was obtained, which again highlighted right eye proptosis. A right inferolateral homogeneously enhancing soft tissue mass infiltrating between the insertions of the lateral and inferior recti measuring 1.5 cm x 2.3 cm x 1.1 cm was discovered. This study also disclosed an enlarged and centrally hypoattenuating right inferior rectus muscle, as well as enlarged superior, lateral, and medial recti and superior oblique muscles. There was crowding of the right orbital apex due to enlarged musculature. The left orbit was within normal limits. Representative sections from this CT scan are shown in figure 1.

Laboratory studies were also obtained at the initial visit. Labs were notable for an elevated sedimentation rate of 60, mildly elevated LDH of 282 and an elevated monoclonal IgM lambda of 0.11 g/dL. Thyroid function and thyroid immunoglobulin studies, complete blood count, basic metabolic panel, hemoglobin A1C, QuantiFERON gold, ACE, ANA, ANCA and IgG4 were all within normal limits.

A biopsy was obtained of the mass in the right inferolateral orbit. Histopathology disclosed fibroadipose tissue with a mixed infiltrate largely composed of histiocytes, plasma cells, lymphocytes and rare lymphoid follicles in a background of intense fibrosis *(Figure 2)*. Numerous multinucleated giant cells, mostly foreign body and Langerhans-type were present focally arranged around necrobiotic collagen. Immunohistochemical stains highlighted a mixed population of CD20+ B cells, CD3+ T cells, and CD138+ plasma cells, which were polytypic with a balanced kappa and lambda light chain expression. Although there was no xanthogranulomatous process seen, the combined pathologic and laboratory findings indicated possible necrobiotic xanthogranulomatous disease. The patient was referred to rheumatology and oncology given concern for Erdheim-Chester disease versus necrobiotic xanthogranuloma versus given the predominance of histiocytes and paraproteinemia.

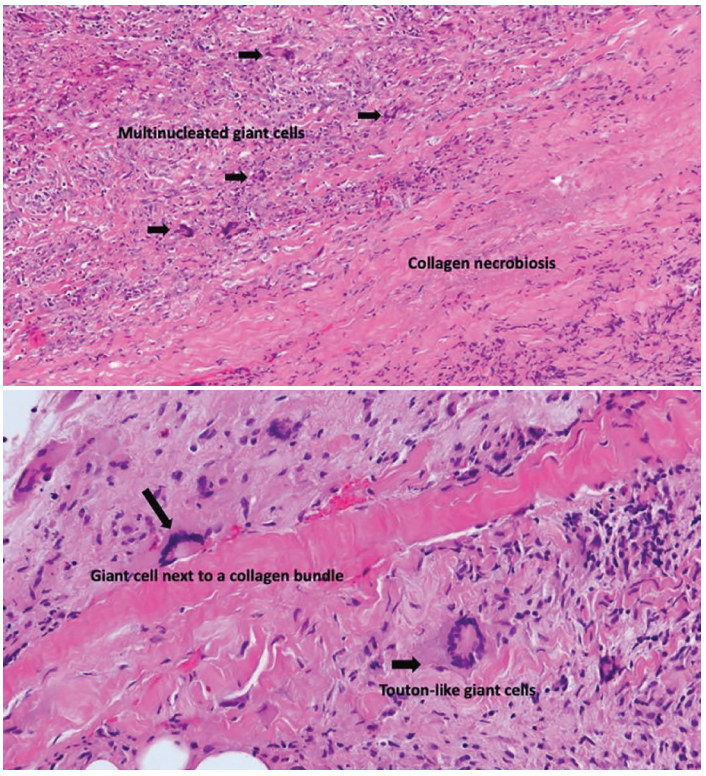

Figure 2. Histopathology of right orbit mass highlighting giant cells and collagen necrobiosis using hematoxylin and eosin staining.

Two months following initial referral, the patient underwent repeat laboratory workup. A significant drop in renal function was discovered, with creatinine of 2.18 from an initial 0.91, with associated hypernatremia. He has thus been referred to nephrology for further workup. He will undergo PET scan and MRI of the brain and orbits for further systemic assessment of his disease burden.

Discussion

The term "orbital xanthogranulomatous disease" describes conditions in which there is orbital proliferation of non-Langerhans histiocytes. This encompasses four main disease categories: necrobiotic xanthogranuloma (NXG); adult-onset asthma with periocular xanthogranuloma, Erdheim-Chester disease; and adult-onset xanthogranuloma.[1]

This patient's presentation is most concerning for Erdheim-Chester disease (ECD). In this patient, tissue biopsy wasn't ultimately diagnostic but was able to elucidate a final diagnosis within the spectrum of histiocytic disease. The pattern of histiocytosis, paraproteinemia, orbital infiltration into the posterior orbit and apex, history of valvular disease, and worsening renal function is consistent with a presumed diagnosis of ECD. This is a xanthogranulomatous disease in which there is a proliferation and accumulation of histiocytes in adults, often occurring in several areas of the body. Most often ECD is seen in the long bones, but has been seen in the periorbital skin and the orbit.[2,3] Orbital disease typically presents with exophthalmos, extraocular movement abnormalities, and/or vision loss related to infiltration surrounding and within the extraocular muscles.[4] Patients may also present with eyelid xanthelasma, chemosis and sequela of compressive infiltration of the posterior orbit including compressive optic neuropathy, as seen in the patient described in this case report.[5] ECD typically affects the posterior orbit and can infiltrate further posterior into the cavernous sinus. ECD can

also affect the central nervous system, notably with infiltration of the pituitary gland and hypothalamus.[5]

Other manifestations of ECD include those in the cardiovascular system. It's estimated that roughly 17 percent of patients with ECD develop symptomatic valvular disease. This patient had recently undergone aortic valve replacement for aortic valvular disease, which may have been related to his presentation described above.[6] Patients with ECD can also develop renal dysfunction and ultimately even renal failure, similar to our patient.[3] It's important to note that this patient has been referred to nephrology for characterization of renal failure, but his differential for renal failure is highly concerning for ECD-related infiltrative disease versus deposition from known paraproteinemia.

Tissue biopsy is typically required to make the diagnosis of ECD, most often in conjunction with imaging of affected sites and to rule out other infiltration. Laboratory studies are recommended at diagnosis to assess for endocrinopathies, blood count abnormalities, systemic immunologic/inflammatory conditions, and renal or hepatic disease.[4] Treatment of ECD involves observation for asymptomatic patients, or systemic therapy for symptomatic patients depending on system involvement. Therapies for ECD can involve BRAF inhibitors, systemic cytotoxic therapies, and immunomodulatory medications, including glucocorticoids. Surgery is typically not involved in treatment.[2]

Another consideration for this patient's diagnosis is necrobiotic xanthogranuloma. NXG specifically involves proliferation of histiocytes with associated lymphocytes, giant cells and varying degrees of fibrosis as well as necrobiosis, which is the degeneration of collagen.[1] The pathogenesis of this condition isn't well-understood, but is thought to be caused by reaction and proliferation of macrophages in the tissue.[1] NXG proliferation of macrophages has been postulated to be associated with viral infection, immunoglobulin deposition, and paraproteinemia, among other potential causes.[7]

NXG often presents with cutaneous lesions that are typically firm and yellow-orange in color. These lesions can be seen anywhere on the body, but most commonly are found in the periorbital region.[7] The most commonly reported ocular findings include these periorbital skin findings, as well as proptosis, ptosis, palpable anterior orbit lesions and restricted eye movements.[8] The patient in this case study presented with an anterior orbital lesion and eye muscle enlargement but no skin findings. Radiographic studies have shown extraocular muscle involvement in this disease process. Laboratory studies most commonly disclose elevated sedimentation rate and IgG kappa monoclonal gammopathy, similar to this patient.[9]

Data is mixed regarding specific diagnosis of systemic proliferative disease in light of the frequency of associated monoclonal gammopathy. Patients diagnosed with NXG have been reported in association with multiple myeloma, plasmacytosis and lymphoproliferative disorders.[6] This disease entity should be considered in this patient given his elevated inflammatory markers and paraproteinemia.

NXG tends to be a progressive and chronic condition.[8] Its treatment includes multiple modalities, all with inconsistent and mixed results when reviewing the literature. Alkylating agents are the most commonly reported treatment, with varied responses to treatment reported, either alone or in conjunction with systemic corticosteroids.[8,9,10] Other treatment modalities involve both intralesional and systemic corticosteroids, again with mixed reported results in the literature.[11] Excision has been shown to have a possibly favorable response,[10] though previous literature reviews have shown recurrence with excision.[4,9] Interestingly, it's been shown that the NXG lesions often don't resolve in patients with monoclonal gammopathy even after the systemic disease has been adequately treated.[12]

In conclusion, this patient presented with one month of intermittent intraocular pressure elevation and progressive vision loss in the right eye. On examination, a right orbital mass was discovered as well as proptosis limitation of extraocular motility of the right eye. Further investigation including imaging, serologic studies and incisional biopsy disclosed paraproteinemia as well as histiocyte proliferation and necrobiosis of collagen consistent with possible Erdheim-Chester disease versus necrobiotic xanthogranuloma. This infiltration of the orbit and extraocular muscles has precipitated the above orbital signs and optic neuropathy. The patient is currently being referred to rheumatology and oncology for further assessment for possible treatment, which may include systemic immunomodulatory versus cytotoxic medication. ◀

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Ryzumvi™
(phentolamine ophthalmic solution) 0.75%

BRIEF SUMMARY: Consult the full Prescribing Information for complete product information available at www.RYZUMVI.com

INDICATIONS AND USAGE: RYZUMVI is indicated for the treatment of pharmacologically-induced mydriasis produced by adrenergic agonists (e.g., phenylephrine) or parasympatholytic (e.g., tropicamide) agents.

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS
- **Uveitis:** RYZUMVI is not recommended when active ocular inflammation (e.g., iritis) is present because adhesions (synechiae) may form between the iris and the lens.
- **Potential for Eye Injury or Contamination:** To avoid the potential for eye injury or contamination, care should be taken to avoid touching the vial tip to the eye or to any other surface.
- **Use with Contact Lenses:** Contact lens wearers should be advised to remove their lenses prior to the instillation of RYZUMVI and wait 10 minutes after dosing before reinserting their contact lenses.

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.

RYZUMVI was evaluated in 642 subjects in clinical trials across various subject populations. The most common ocular adverse reactions reported in >5% of subjects were instillation site discomfort including pain, stinging, and burning (16%) and conjunctival hyperemia (12%). The only non-ocular adverse reaction reported in >5% of subjects was dysgeusia (6%).

USE IN SPECIFIC POPULATIONS
Pregnancy: Risk Summary: There are no available data with RYZUMVI administration in pregnant women to inform a drug-associated risk. In animal toxicology studies, when phentolamine was administered orally to pregnant mice and rats during the period of organogenesis skeletal immaturity and decreased growth was observed in the offspring at doses at least 24-times the recommended clinical dose. Additionally, a lower rate of implantation was seen in pregnant rats treated with phentolamine administered at least 60-times the recommended clinical dose. No malformations or embryofetal deaths were observed in the offspring of pregnant mice, rats, and rabbits administered phentolamine during the period of organogenesis at doses of at least 24-, 60-, and 20-times, respectively, the recommended clinical dose (see Data). RYZUMVI should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.

Data *Animal Data* Oral administration of phentolamine to pregnant rats and mice at doses at least 24-times the recommended clinical dose (based on a body weight per surface area (mg/m^2) comparison with a 60-kg human) resulted in slightly decreased growth and slight skeletal immaturity of the fetuses. Immaturity was manifested by increased incidence of incomplete or unossified calcanei and phalangeal nuclei of the hind limb and of incompletely ossified sternebrae. At oral phentolamine doses at least 60-times the recommended clinical dose (based on a mg/m^2 comparison with a 60-kg human), a slightly lower rate of implantation was found in rats. Phentolamine did not affect embryonic or fetal development in rabbits at oral doses at least 20-times the recommended dose (based on a mg/m^2 comparison with a 60-kg human). No malformations or embryofetal deaths were observed in the rat, mouse or rabbit studies.
Lactation: Risk Summary: There is no information regarding the presence of phentolamine in human milk, the effects on the breastfed infants, or the effects on milk production during lactation to inform risk of phentolamine ophthalmic solution 0.75% to an infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RYZUMVI and any potential adverse effects on the breastfed child from RYZUMVI.
Pediatric Use: The safety and effectiveness of RYZUMVI have been established in pediatric patients aged 3 to 17 years. No overall differences have been observed between pediatric and adult subjects.
Geriatric Use: No overall differences in safety and effectiveness have been observed between elderly and younger adult subjects.

OVERDOSAGE
No deaths due to acute poisoning with phentolamine have been reported. Overdosage with parenterally administered phentolamine is characterized chiefly by cardiovascular disturbances, such as arrhythmias, tachycardia, hypotension, and possibly shock. In addition, the following might occur: excitation, headache, sweating, visual disturbances, nausea, vomiting, diarrhea, or hypoglycemia. There is no specific antidote; treatment consists of appropriate monitoring and supportive care. Substantial decreases in blood pressure or other evidence of shock-like conditions should be treated vigorously and promptly.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY
Carcinogenesis: Carcinogenicity studies with RYZUMVI have not been conducted.
Mutagenesis: Phentolamine was not mutagenic in the in-vitro bacterial reverse mutation (Ames) assay. In the in-vitro chromosomal aberration study in Chinese hamster ovary cells, numerical aberrations were slightly increased after a 4-hour exposure to phentolamine without metabolic activation, and structural aberrations were slightly increased after a 4-hour exposure to phentolamine with metabolic activation only at the highest concentrations tested, but neither numerical nor structural aberrations were increased after a 20-hour exposure without metabolic activation. Phentolamine was not clastogenic in two in-vivo mouse micronucleus assays.
Impairment of Fertility: The effect of phentolamine on female fertility has not been studied. Male rats treated with oral phentolamine for nine weeks (four weeks prior to mating, 3 weeks during the mating period and 2 weeks after mating) were mated with untreated females. At doses up to 648-times human therapeutic exposure levels at the C_{max}, no adverse effects on male fertility parameters or on reproductive parameters in the untreated females mated with the treated males were observed.

Marketed by: Oyster Point Pharma, Inc., a Viatris company

References: 1. RYZUMVI (phentolamine ophthalmic solution). Prescribing Information. Ocuphire. **2.** Boyd K. Mendoza O. What are dilating eye drops? American Academy of Ophthalmology. Available at: https://www.aao.org/eye-health/drugs/dilating-eyedrops. Accessed February 8, 2024.

VIATRIS™

EXPERIENCE

THE RYZUMVI™ DIFFERENCE

Reverse dilation and reimagine the post-dilation experience for patients.[1,2]

REDEFINE the PATIENT EXPERIENCE POST-DILATION

Ryzumvi™
(phentolamine ophthalmic solution) 0.75%

1

RYZUMVI is the first and only relatively non-selective alpha-1 and alpha-2 adrenergic antagonist approved to reverse pharmacologically-induced mydriasis.[1]

RYZUMVI reversibly binds to alpha-1 adrenergic receptors on the radial iris dilator muscle, thereby reducing pupil diameter, and indirectly reverses mydriasis induced by muscarinic antagonist effects on the iris sphincter muscle.[1]

30

The onset of action after administration of RYZUMVI generally occurs in 30 minutes, with the maximal effect seen in 60 to 90 minutes, and the effect lasting at least 24 hours.[1]

INDICATION

RYZUMVI™ (phentolamine ophthalmic solution) 0.75% is indicated for the treatment of pharmacologically-induced mydriasis produced by adrenergic agonists (e.g., phenylephrine) or parasympatholytic (e.g., tropicamide) agents.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- **Uveitis:** RYZUMVI is not recommended to be used in patients with active ocular inflammation (e.g., iritis).
- **Potential for Eye Injury or Contamination:** To avoid the potential for eye injury or contamination, care should be taken to avoid touching the vial tip to the eye or to any other surface.
- **Use with Contact Lenses:** Contact lens wearers should be advised to remove their lenses prior to the instillation of RYZUMVI and wait 10 minutes after dosing before reinserting their contact lenses.

Adverse Reactions

The most common adverse reactions that have been reported are instillation site discomfort (16%), conjunctival hyperemia (12%), and dysgeusia (6%).

Please see Brief Summary of Prescribing Information on the adjacent page and the full Prescribing Information at RYZUMVI.com.

Visit RYZUMVI.com

INTERVENTIONAL GLAUCOMA

SHATTERING THE STATUS QUO

Introducing

iDose® *TR*

(travoprost intracameral implant) 75 mcg

The catalyst to advance the interventional glaucoma revolution, helping you and your patients take back control of their treatment journey.

iDose TR is a long duration intracameral procedural pharmaceutical that delivers prostaglandin analog therapy for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.[1]

Actual size
1.8mm x 0.5mm

1. iDose TR (travoprost intracameral implant) 75 mcg Prescribing Information. Glaukos Corporation. 2023.

View full prescribing information at iDoseTRhcp.com

INDICATIONS AND USAGE
iDose TR (travoprost intracameral implant) is indicated for the reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT).

IMPORTANT SAFETY INFORMATION

DOSAGE AND ADMINISTRATION
For ophthalmic intracameral administration. The intracameral administration should be carried out under standard aseptic conditions.

CONTRAINDICATIONS
iDose TR is contraindicated in patients with active or suspected ocular or periocular infections, patients with corneal endothelial cell dystrophy (e.g., Fuch's Dystrophy, corneal guttatae), patients with prior corneal transplantation, or endothelial cell transplants (e.g., Descemet's Stripping Automated Endothelial Keratoplasty [DSAEK]), patients with hypersensitivity to travoprost or to any other components of the product.

WARNINGS AND PRECAUTIONS
iDose TR should be used with caution in patients with narrow angles or other angle abnormalities. Monitor patients routinely to confirm the location of the iDose TR at the site of administration. Increased pigmentation of the iris can occur. Iris pigmentation is likely to be permanent.

ADVERSE REACTIONS
In controlled studies, the most common ocular adverse reactions reported in 2% to 6% of patients were increases in intraocular pressure, iritis, dry eye, visual field defects, eye pain, ocular hyperaemia, and reduced visual acuity.

Please see full Prescribing Information.
You are encouraged to report all side effects to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.
You may also call Glaukos at 1-888-404-1644.

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