Wills Eye Resident Series: A patient presents with ocular pain, redness and decreased vision, *p. 92*

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Start with EYSUVIS® – the first and only FDA-approved corticosteroid for the short-term treatment of dry eye (up to 2 weeks).[4,5]

EYSUVIS®, with proprietary AMPPLIFY Drug Delivery Technology, is designed to deliver loteprednol nanoparticles to the sites of ocular surface inflammation, where dry eye flares start.[2,3]

EYSUVIS® goes to work fast and provides rapid improvement of ocular discomfort, with results as early as Day 4 after starting treatment.[1*]

Go deep to treat dry eye with EYSUVIS®.[2,3]

EYSUVIS
(loteprednol etabonate ophthalmic suspension) 0.25%

*The safety and efficacy of EYSUVIS® was assessed in 4 multicentered, randomized, double masked, placebo-controlled trials in 2,871 patients with documented Dry Eye Disease. Patients received either EYSUVIS® or vehicle 4 times a day for at least 2 weeks. In one Phase 3 study, patients using EYSUVIS® showed significant reduction in the symptoms of dry eye (ocular discomfort) as early as Day 4 after starting treatment (vs. vehicle). Symptom improvement continued up to the end of the treatment period (Day 15, primary endpoint). Patients using EYSUVIS® also showed significant reduction in signs of dry eye (conjunctival hyperemia) at Day 15 vs. vehicle.

INDICATION

EYSUVIS is a corticosteroid indicated for the short-term (up to two weeks) treatment of the signs and symptoms of dry eye disease.

IMPORTANT SAFETY INFORMATION

Contraindication:

EYSUVIS, as with other ophthalmic corticosteroids, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

Warnings and Precautions:

Delayed Healing and Corneal Perforation: Topical corticosteroids have been known to delay healing and cause corneal and scleral thinning. Use of topical corticosteroids in the presence of thin corneal or scleral tissue may lead to perforation. The initial prescription and each renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy, and, where appropriate, fluorescein staining.

Intraocular Pressure (IOP) Increase: Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, as well as defects in visual acuity and fields of vision. Corticosteroids should be used with caution in the presence of glaucoma. Renewal of the medication order should be made by a physician only after examination of the patient and evaluation of the IOP.

Cataracts: Use of corticosteroids may result in posterior subcapsular cataract formation.

Bacterial Infections: Use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, corticosteroids may mask infection or enhance existing infection.

Viral Infections: Use of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular corticosteroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

Fungal Infections: Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local corticosteroid application. Fungus invasion must be considered in any persistent corneal ulceration where a corticosteroid has been used or is in use.

Adverse Reactions:

The most common adverse drug reaction following the use of EYSUVIS for two weeks was instillation site pain, which was reported in 5% of patients.

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

REFERENCES: 1. Holland E, Nichols K, Foulks G, et al. Safety and efficacy of KPI-121 ophthalmic suspension 0.25% for dry eye disease in four randomized controlled trials. Presented at: AAO 2020; November 13-15, 2020; virtual meeting. **2.** Schopf L, Enlow E, Popov A, et al. Ocular pharmacokinetics of a novel loteprednol etabonate 0.4% ophthalmic formulation. Ophthalmol Ther. 2014;3(1-2):63-72. **3.** Popov A. Mucus-penetrating particles and the role of ocular mucus as a barrier to micro- and nanosuspensions. *J Ocul Pharmacol Ther.* 2020;36(6): 366-375. **4.** Alcon Data on File, 2022. **5.** Alcon Data on File, 2022.

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BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE
EYSUVIS is a corticosteroid indicated for the short-term (up to two weeks) treatment of the signs and symptoms of dry eye disease.

CONTRAINDICATIONS
EYSUVIS, as with other ophthalmic corticosteroids, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

WARNINGS AND PRECAUTIONS
Delayed Healing and Corneal Perforation—Topical corticosteroids have been known to delay healing and cause corneal and scleral thinning. Use of topical corticosteroids in the presence of thin corneal or scleral tissue may lead to perforation. The initial prescription and each renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy, and, where appropriate, fluorescein staining. **Intraocular Pressure (IOP) Increase**—Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, as well as defects in visual acuity and fields of vision. Corticosteroids should be used with caution in the presence of glaucoma. Renewal of the medication order should be made by a physician only after examination of the patient and evaluation of the IOP. **Cataracts**—Use of corticosteroids may result in posterior subcapsular cataract formation. **Bacterial Infections**—Use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions of the eye, corticosteroids may mask infection or enhance existing infection. **Viral Infections**—Use of corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular corticosteroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). **Fungal Infections**—Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local corticosteroid application. Fungus invasion must be considered in any persistent corneal ulceration where a corticosteroid has been used or is in use. Fungal cultures should be taken when appropriate. **Risk of Contamination**—Do not to allow the dropper tip to touch any surface, as this may contaminate the suspension. **Contact Lens Wear**—The preservative in EYSUVIS may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of EYSUVIS and may be reinserted 15 minutes following administration.

ADVERSE REACTIONS
Adverse reactions associated with ophthalmic corticosteroids include elevated intraocular pressure, which may be associated with infrequent optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, delayed wound healing and secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. **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 most common adverse reaction observed in clinical trials with EYSUVIS was instillation site pain, which was reported in 5% of patients.

USE IN SPECIFIC POPULATIONS
Pregnancy—Risk Summary: There are no adequate and well controlled studies with loteprednol etabonate in pregnant women. Loteprednol etabonate produced teratogenicity at clinically relevant doses in the rabbit and rat when administered orally during pregnancy. Loteprednol etabonate produced malformations when administered orally to pregnant rabbits at doses 1.4 times the recommended human ophthalmic dose (RHOD) and to pregnant rats at doses 34 times the RHOD. In pregnant rats receiving oral doses of loteprednol etabonate during the period equivalent to the last trimester of pregnancy through lactation in humans, survival of offspring was reduced at doses 3.4 times the RHOD. Maternal toxicity was observed in rats at doses 347 times the RHOD, and a maternal no observed adverse effect level (NOAEL) was established at 34 times the RHOD. The background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies. Data: Animal Data. Embryofetal studies were conducted in pregnant rabbits administered loteprednol etabonate by oral gavage on gestation days 6 to 18, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations at 0.1 mg/kg (1.4 times the recommended human ophthalmic dose (RHOD) based on body surface area, assuming 100% absorption). Spina bifida (including meningocele) was observed at 0.1 mg/kg, and exencephaly and craniofacial malformations were observed at 0.4 mg/kg (5.6 times the RHOD). At 3 mg/kg (41 times the RHOD), loteprednol etabonate was associated with increased incidences of abnormal left common carotid artery, limb flexures, umbilical hernia, scoliosis, and delayed ossification. Abortion and embryofetal lethality (resorption) occurred at 6 mg/kg (83 times the RHOD). A NOAEL for developmental toxicity was not established in this study. The NOAEL for maternal toxicity in rabbits was 3 mg/kg/day. Embryofetal studies were conducted in pregnant rats administered loteprednol etabonate by oral gavage on gestation days 6 to 15, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations, including absent innominate artery at 5 mg/kg (34 times the RHOD); and cleft palate, agnathia, cardiovascular defects, umbilical hernia, decreased fetal body weight and decreased skeletal ossification at 50 mg/kg (347 times the RHOD). Embryofetal lethality (resorption) was observed at 100 mg/kg (695 times the RHOD). The NOAEL for developmental toxicity in rats was 0.5 mg/kg (3.4 times the RHOD). Loteprednol etabonate was maternally toxic (reduced body weight gain) at 50 mg/kg/day. The NOAEL for maternal toxicity was 5 mg/kg. A peri-/postnatal study was conducted in rats administered loteprednol etabonate by oral gavage from gestation day 15 (start of fetal period) to postnatal day 21 (the end of lactation period). At 0.5 mg/kg (3.4 times the clinical dose), reduced survival was observed in live-born offspring. Doses ≥ 5 mg/kg (34 times the RHOD) caused umbilical hernia/incomplete gastrointestinal tract. Doses ≥ 50 mg/kg (347 times the RHOD) produced maternal toxicity (reduced body weight gain, death), decreased number of live-born offspring, decreased birth weight, and delays in postnatal development. A developmental NOAEL was not established in this study. The NOAEL for maternal toxicity was 5 mg/kg. **Lactation**—There are no data on the presence of loteprednol etabonate in human milk, the effects on the 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 EYSUVIS and any potential adverse effects on the breastfed infant from EYSUVIS. **Pediatric Use**—Safety and effectiveness in pediatric patients have not been established. **Geriatric Use**—No overall differences in safety and effectiveness have been observed between elderly and younger adult patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility—Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic in vitro in the Ames test, the mouse lymphoma thymidine kinase (tk) assay, in a chromosome aberration test in human lymphocytes, or in vivo in the single dose mouse micronucleus assay. Treatment of male and female rats with 25 mg/kg/day of loteprednol etabonate (174 times the RHOD based on body surface area, assuming 100% absorption) prior to and during mating caused pre-implantation loss and decreased the number of live fetuses/live births. The NOAEL for fertility in rats was 5 mg/kg/day (34 times the RHOD).

For a copy of the Full Prescribing Information, please visit www.eysuvis-ecp.com/

Manufactured for:
Kala Pharmaceuticals, Inc.
Watertown, MA 02472

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PI Version Date: 10/2020

EYSUVIS®
(loteprednol etabonate ophthalmic suspension) 0.25%

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VOLUME XXX • NO. 10

OCTOBER 2023

Study Finds Increased Risk of Cardiovascular Events after RVO

Retinal vein occlusion is associated with cardiovascular risk factors, and it's possible that such incidents may also carry predictive value for a future subsequent vascular event or mortality risk. In a new study, researchers examined rates of stroke, myocardial infarction (MI), deep vein thrombosis, pulmonary embolism and death in patients after RVO and found patients at an increased risk of these vascular events.

A total of 45,303 patients with diagnosis of RVO and a control group of patients with cataract were included. Patients were excluded if they had history of stroke, MI, deep vein thrombosis or pulmonary embolism within two years of diagnosis of RVO or cataract.

Getty

With a closely matched control population to assure parity in age, gender, ethnicity, race and systemic comorbidities of diabetes, hypertension and hyperlipidemia, this study found increased risks of death and subsequent vascular events, including stroke and MI, after RVO.

According to Ehsan Rahimy, MD, an adjunct clinical professor at Stanford University School of Medicine, Palo Alto, California, and a co-author of the study, previous studies exploring this topic were inconsistent. "There have been some well-publicized population studies out of Southeast Asia with mixed findings. One study out of Taiwan that analyzed a national database showed no increased risk of these systemic events (stroke or myocardial infarction) if somebody has a retinal vein occlusion, whereas a separate study from a Korean national database did demonstrate an increased risk," he says. "Prior to our study we had conflicting results in the literature, which makes it challenging to know how to best counsel patients when these events occur."

The study authors were able to evaluate such a large population retrospectively using the TriNetX network (Cambridge, Massachusetts), an electronic health records research network comprising multiple large health organizations within the United States and globally. "There were three unique advantages of our study design to investigate systemic correlations with RVOs over what has been previously published," says Dr. Rahimy. "Number one was the sheer numbers of patients included for analysis even after applying fairly stringent inclusion/exclusion criteria. We ended up with over 45,000 patients with retinal vein occlusions with a propensity-matched control group of 45,000 patients; whereas these previous studies' numbers were in the low single-digit thousands. A second advantage of this TriNetX network that benefited our study design is the patient data was acquired from multiple countries—not just here in the United States. As of the last time I checked, there were 19 countries worldwide participating in the research network. By virtue of that, we're allowed to assess a very diverse and heterogeneous patient population with vein occlusion. Previous studies tended to be very homogenous populations (i.e. Taiwan, Korea), while our study is presenting more of a balanced representation of this condition across different patient populations."

The second advantage of this study was the long-term follow up. "We were able to carry follow-up out to 10 years after the index event (i.e., the time of RVO onset) to better inform patients' systemic risk," continues Dr. Rahimy. "To obtain that degree of longitudinal long-term follow up

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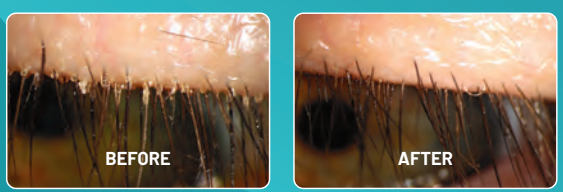

44% and 55% of patients taking XDEMVY in SATURN-1 (N=209) and SATURN-2 (N=193), respectively, achieved a significant improvement in their eyelids (reduction of collarettes to no more than 2 collarettes per upper lid) at Day 43 vs 7% (N=204) and 12% (N=200) of patients taking vehicle ($P<0.01$ in each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

All images are of actual patients who participated in clinical trials for Tarsus Pharmaceuticals.

INDICATIONS AND USAGE

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

IMPORTANT SAFETY INFORMATION:

WARNINGS AND PRECAUTIONS

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

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

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

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

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

*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 (SATURN-1: XDEMVY N=209, vehicle N=204, $P<0.01$; SATURN-2: XDEMVY N=193, vehicle N=200, $P<0.01$).

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tarsus

XDEMVY™ (lotilaner ophthalmic solution) 0.25%, for topical ophthalmic use

BRIEF SUMMARY OF PRESCRIBING INFORMATION
Please see the XDEMVY™ package insert for full Prescribing Information.

INDICATIONS AND USAGE
XDEMVY is indicated for the treatment of *Demodex* blepharitis.

CONTRAINDICATIONS
None.

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

Use with Contact Lenses Contact lenses should be removed prior to instillation of XDEMVY and may be reinserted 15 minutes following its administration.

ADVERSE REACTIONS
Because clinical studies 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.

XDEMVY was evaluated in 833 patients with *Demodex* blepharitis in two randomized, double-masked, vehicle-controlled studies (Saturn-1 and Saturn-2) with 42 days of treatment. The most common ocular adverse reaction observed in controlled clinical studies 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.

USE IN SPECIFIC POPULATIONS
Pregnancy: Risk Summary There are no available data on XDEMVY use in pregnant women to inform any drug associated risk; however, systemic exposure to lotilaner from ocular administration is low. In animal reproduction studies, lotilaner did not produce malformations at clinically relevant doses.

Data *Animal Data* In an oral embryofetal developmental study in pregnant rats dosed during organogenesis from gestation days 6-19, increased post-implantation loss, reduced fetal pup weight, and incomplete skeletal ossification were observed at 50 mg/kg/day (approximately 1390 times the recommended human ophthalmic dose (RHOD) on a body surface area basis) in the presence of maternal toxicity (i.e., decreased body weight and food consumption). A rare malformation of situs inversus of the thoracic and abdominal viscera occurred in 1 fetus from a pregnant rat receiving 50 mg/kg/day; whether this finding was treatment-related could not be excluded. No maternal or embryofetal toxicity was observed at 18 mg/kg/day (approximately 501 times the RHOD on a body surface area basis). In an oral embryofetal development study in pregnant rabbits dosed during organogenesis from gestation days 7-19, no embryofetal toxicity or teratogenic findings were observed at 20 mg/kg/day (approximately 580-times the RHOD on an AUC basis), even in the presence of maternal toxicity (i.e., decreased food consumption and body weight).

In an oral two-generation reproductive toxicity study, F0 male and female rats were administered lotilaner at doses up to 40 mg/kg/day for 10 weeks before pairing and during the 2-week pairing period (3 weeks for males). Dosing for F0 females continued through lactation day 22. F1 male and female rats were administered lotilaner at 1 and 5 mg/kg/day post-weaning from day 23 for 10 weeks before pairing and during the 2-week pairing period (3 weeks for males). Dosing for F1 parenteral females continued through lactation day 22. There were no clear adverse effects on the F1 generation, and a slightly lower mean body weight during lactation was noted for F2 pups at 5 mg/kg/day. The no observed adverse effect level (NOAEL) was determined to be 5 mg/kg/day (approximately 139 times the RHOD on a body surface area basis).

Lactation: Risk Summary There are no data on the presence of XDEMVY in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lotilaner following 6 weeks of topical ocular administration is low and is >99% plasma protein bound, thus it is not known whether measurable levels of lotilaner would be present in maternal milk following topical ocular administration. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XDEMVY and any potential adverse effects on the breast-fed child from XDEMVY.

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

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis Long-term studies in animals have not been performed to evaluate the carcinogenic potential of lotilaner.

Mutagenesis Lotilaner was not genotoxic in the following assays: Ames assay for bacterial gene mutation, *in vitro* chromosomal aberration assay in cultured human peripheral blood lymphocytes, and *in vivo* rat micronucleus test.

Impairment of fertility In a two-generation study of reproductive performance in rats, F0 male and female rats were administered lotilaner at oral doses of 40 mg/kg/day for 80 days reduced to 20 mg/kg/day for 47-50 supplementary days. Reduced pregnancy rates and decreased implantation rates were observed in F0 females at doses 20 mg/kg/day) (approximately 556 times the RHOD on a body surface area basis), which were also associated with maternal toxicity (i.e., decreased body weight and food consumption). No effects on fertility were observed in F0 females at the dose of 5 mg/kg/day (approximately 139 times the MRHOD on a body surface area basis). No effects on fertility were observed in F0 males at the oral dose of 20 mg/kg/day (approximately 556 times the RHOD on a body surface area basis), and no effects on fertility were observed in F1 males and females at the oral dose of 5 mg/kg/day (approximately 139 times the RHOD on a body surface area basis).

PATIENT COUNSELING INFORMATION
Handling the Container Instruct patients to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to minimize contamination of the solution. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

When to Seek Physician Advice Advise patients that if they develop an intercurrent ocular condition (e.g., trauma or infection), have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of XDEMVY.

Use with Contact Lenses Advise patients that 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.

Use with Other Ophthalmic Drugs Advise patients that if more than one topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes between applications.

Missed Dose Advise patients that if one dose is missed, treatment should continue with the next dose.

RX only

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is unique about this TriNetX platform, and was a key strength of our study."

"The key takeaway of the study is that patients who get retinal vein occlusions do carry a higher risk throughout their life, or at least out to the 10 years measured, of experiencing strokes, heart attacks and even death," says Dr. Rahimy. "The two other categories we measured out of interest were other systemic venous occlusive conditions, such as deep vein thrombosis or pulmonary embolism," he continues. "Logically, one may surmise that someone with an RVO may have an elevated risk of other venous occlusive events in the body, too. But interestingly, this didn't turn out to be the case in our study. This may invite some speculation as to what is really going on when a patient presents to you with retinal vein occlusion. Is the underlying pathophysiology more in line with a venous clot, or rather, is this more indicative of broader vascular disease (arterial and venous) in that patient's body (i.e. could this be suggestive of similar microvascular changes within an organ like the brain)?"

Examining central RVO and branch RVO separately may be needed to explore the underlying mechanism, as both showed elevated risk of death when comparing these patients, but no difference in stroke, MI, DVT or PE at the same time points.

"I think most of us would agree that not all retinal vein occlusions are the same," Dr. Rahimy says. "Because of ICD-10 coding we could only break them up by BRVO or CRVO. We didn't find any major signal differences in these sub-types, but in these big-data studies, you're dependent on ICD-10 coding diagnoses to be accurate. However, not all ICD codes capture the different things we see in retina. A great example is that we have ICD codes for CRVO, we have ICD codes for BRVO, but we don't have ICD coding for hemiretinal vein occlusions, and people argue in our field that perhaps HRVOs are a separate subgroup altogether. So, how an HRVO ultimately gets classified depends on a given physician's coding tendencies. Do they classify it as a CRVO or as a BRVO in their EHR? In the data, you probably get a mix of both throughout it."

Overall, ophthalmologists "should be aware of elevated risk of death and vascular events including MI or stroke in patients presenting with RVO," the researchers concluded.

"Ultimately, this study heightens the importance of making sure patients' systemic comorbidities are being optimally controlled and of ommunicating these findings to their core care team when they have a vein occlusion," Dr. Rahimy says. "In my practice environment, a large multidisciplinary network, whenever I have somebody with a vein occlusion, I'm closely communicating with their PCP about this event that happened, how we're treating it and how it's very important to comanage any systemic comorbidities. We often see some patients come in with RVOs who may not initially have other issues

going on elsewhere in their body, and this is where I think this type of study is valuable. Patients should know, even if they don't have anything now, it behooves them to take good care of themselves, lead a healthy lifestyle and continue with routine care assessments with their primary care doctor to check for the development of potential underlying cardiovascular or cerebrovascular risk factors down the line."

1. Wai KM, Ludwig CA, Koo E, et al. Risk of stroke, myocardial infarction, deep vein thrombosis, pulmonary embolism and death after retinal vein occlusion. Amer J Ophthalmol. August 23, 2023. [Epub ahead of print].

AAO Analyzes SLT as First-line Therapy

Periodically, the American Academy of Ophthalmology conducts Ophthalmic Technology Assessments to assess the clinical efficacy, effectiveness and safety of new and existing procedures, drugs, diagnostics and screening tests. Recently, selective laser trabeculoplasty underwent systematic review—its first since November 2011. The report, published in *Ophthalmology*, confirmed its clinical safety and identified areas for further research.[1]

A total of 30 articles—including the LiGHT Trial—were included. Evidence level ratings were assigned, with 19 studies assigned a level I rating and 11 studies assigned a level II rating.

The data from level I studies show that SLT has long-term effectiveness as a primary or supplemental treatment to medical therapy in open-angle glaucoma. First-line SLT and medications showed equivalent IOP control for open-angle glaucoma and ocular hypertension and may also be more cost effective and provide better long-term disease control than medications. Interestingly, SLT wasn't found to result in measurable quality-of-life improvement.

In level I studies, SLT and ALT were found to be equivalent in safety and long-term efficacy in several studies, with repeat SLT possibly more effective than repeat ALT in the long-term. Level I studies also showed that SLT's IOP lowering was equivalent to several other modalities including micropulse laser trabeculoplasty, pattern-scanning laser trabeculoplasty and titanium-sapphire laser trabeculoplasty. Level II data showed equivalence with excimer laser trabeculoplasty.

Additionally, studies indicated that perioperative corticosteroid and NSAID drops didn't hinder the treatment's IOP-lowering effects, though the reported impact of the drops varied across studies.

The review also identified several areas for further study, including a need for more randomized clinical trials with diverse patient populations and more randomized studies on treatment settings and repeatability.

1. Takusagawa HL, Hoguet A, Sit AJ, et al. Selective laser trabeculoplasty for the treatment of glaucoma: A report by the American Academy of Ophthalmology. Ophthalmology 2023;1-11.

Endophthalmitis in Glaucoma Surgery vs. Cataract Surgery

Infamous for being "the most feared complication" of ocular surgery, endophthalmitis is fortunately rare but occurs more often after glaucoma surgeries than other types of intraocular surgeries. In order to better understand the risk factors and the incidence of endophthalmitis, which can vary significantly across different types of glaucoma surgeries, researchers analyzed glaucoma surgery outcomes using a large Medicare claims database. They found that incidences were nearly double those of cataract surgery.[1]

In the retrospective, longitudinal study, 466,928 glaucoma surgeries were identified based on 2016-2019 Medicare Fee-For-Service and Medicare Advantage claims of patients 65 and older. Endophthalmitis cases within 42 days of surgery were identified based on ICD-10 codes. About

(Continued on p. 12)

INDUSTRY NEWS

Thea Addresses FDA Warning Letters
After the FDA issued warning letters to eight companies, including Similasan AG/ Similasan USA—Thea Pharma Inc.'s distribution partner for iVizia products—for marketing of unapproved homeopathic eye products for manufacturing or marketing unapproved ophthalmic drug products in violation of federal law, Thea Pharma issued a response letter. The company explained in the note that iVizia products are unaffected by the warning letter, that they are not homeopathic products and are manufactured by Laboratoires Théa in CMO facilities that are FDA-inspected and -compliant, and meet all applicable guidelines. They noted further that iVizia products are available in full supply at major U.S. retailers.

New Approval Addresses Drug Shortfall
Nexus Pharmaceuticals received FDA approval for fluorescein injection, USP 10%, available in 5 ml, single-dose vials in cartons of 10. Through the approval, the company said it hopes to address a supply shortfall of a critical medication on the Food and Drug Administration's drug shortage list.

Outlook Drug Doesn't Secure Approval
Outlook Therapeutics announced the FDA issued a Complete Response Letter in response to its application for ONS-5010, an investigational ophthalmic formulation of bevacizumab under development to treat wet AMD. While the FDA acknowledged the NORSE TWO pivotal trial met its safety and efficacy endpoints, it concluded it couldn't approve the BLA during this review cycle due to several Chemistry Manufacturing and Controls (CMC) issues, open observations from pre-approval manufacturing inspections and a lack of substantial evidence.

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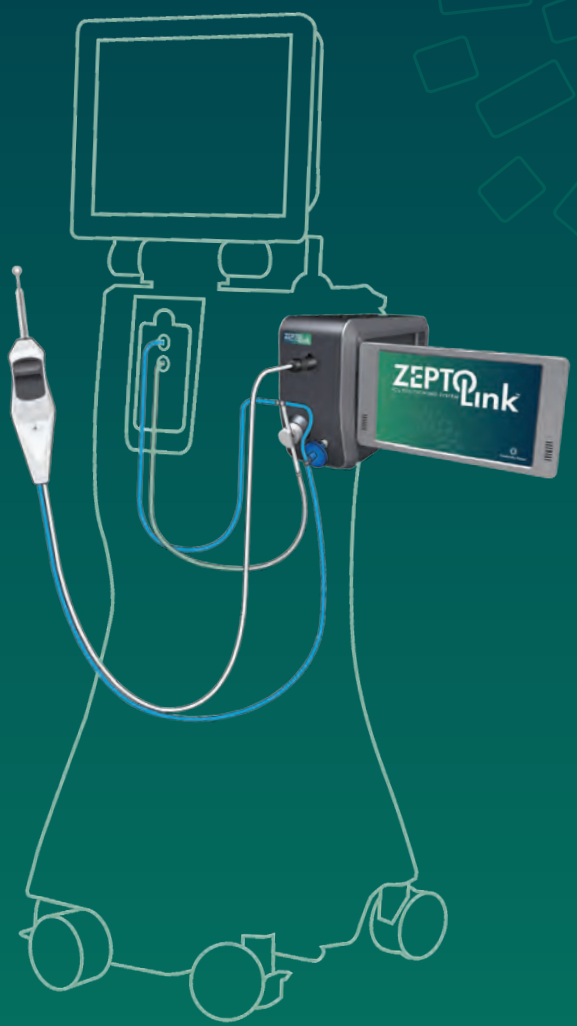

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FEATURES

Vol. XXX, No. 10 • October 2023

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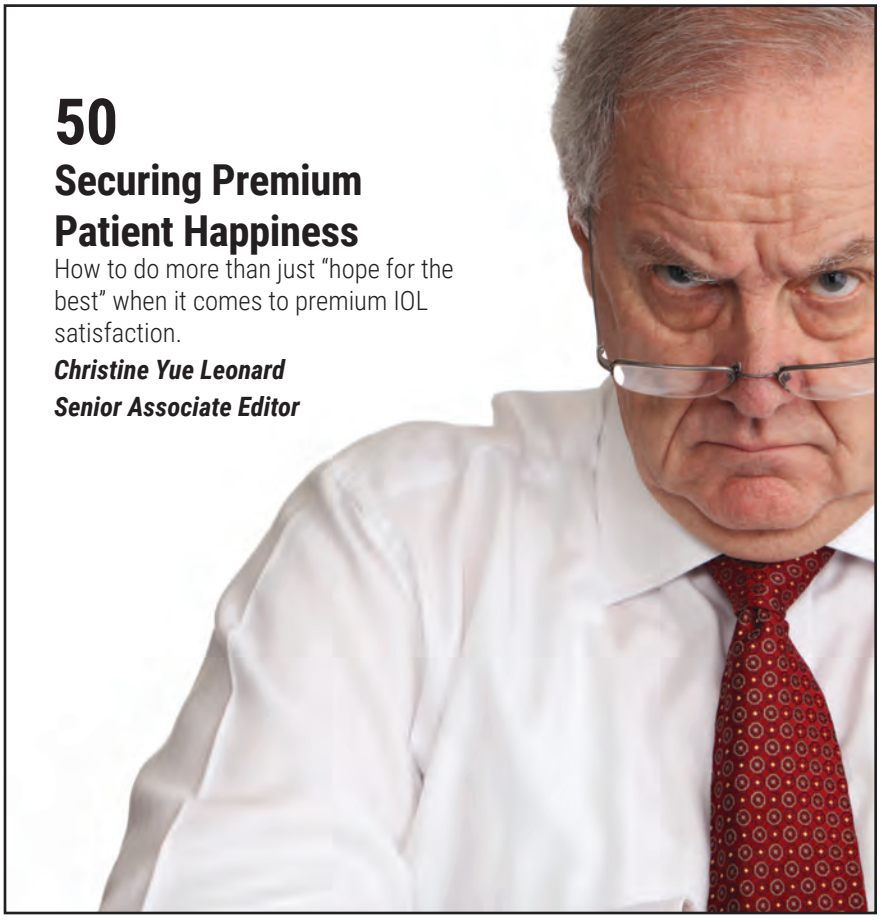
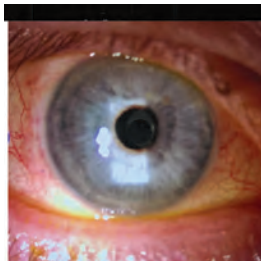
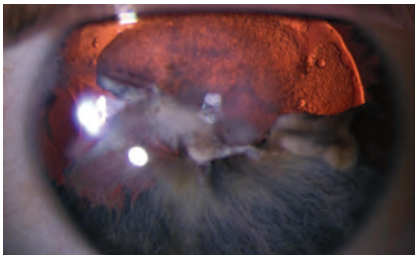
Read *Review's* weekly newsletter online at *reviewofophthalmology.com*.

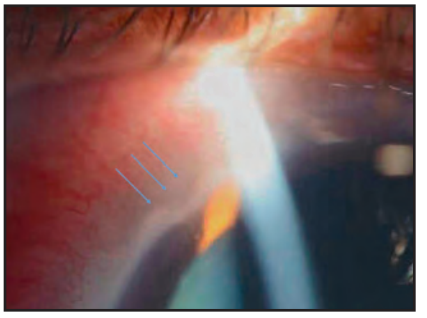


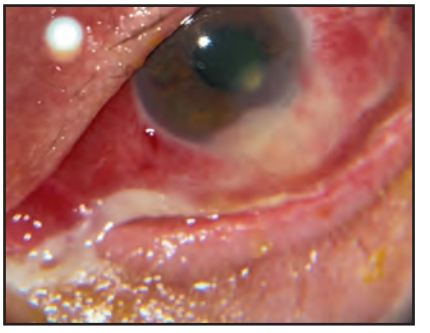




DEPARTMENTS

October 2023





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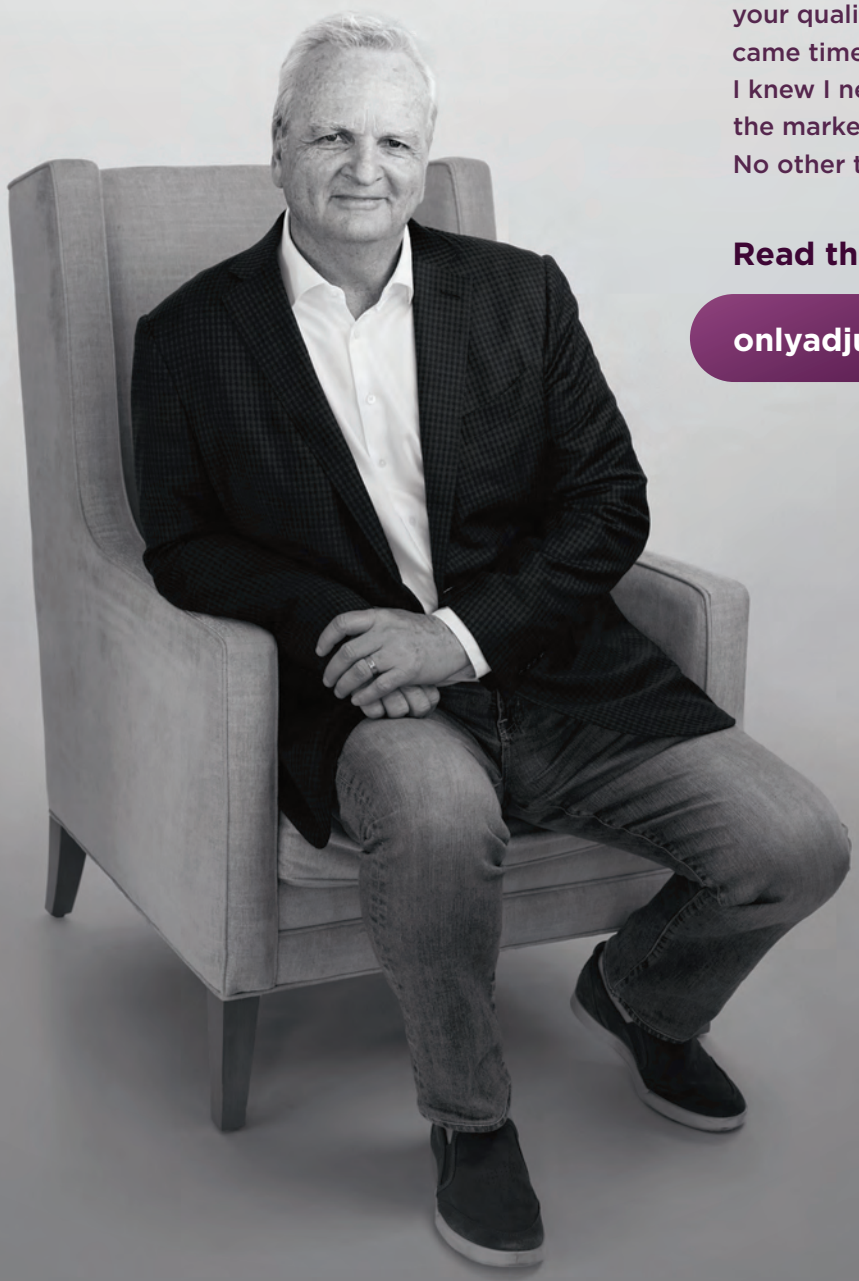
Light Adjustable Lens™

For *Andy Corley,* only adjustability will do.

After over 40 years in the eye care industry, I know exactly how important your quality of vision is. So when it came time for my own cataract surgery, I knew I needed to have the best IOL on the market: the Light Adjustable Lens™. No other technology even comes close.

Read the case study

onlyadjustability.com



Andy Corley is the Chair of the Board of RxSight, Inc. and owns equity interest in the company.

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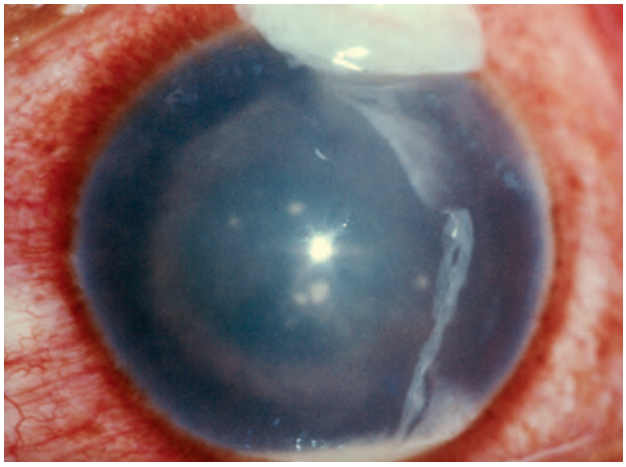
RxSIGHT

(Continued from p. 7)
two-thirds of the glaucoma surgeries were combined with cataract surgery. (The researchers used cataract surgeries alone [n=8,460,360] as a reference group.) Most of the glaucoma surgeries were MIGS (67.8 percent), followed by trabeculectomies (14 percent) and tube shunt procedures (10.9 percent). Other procedures made up 7.3 percent of surgeries.

A total of 572 cases of endophthalmitis occurred following all glaucoma surgeries (an incidence of 1.2 per thousand). The breakdown for incidences per thousand procedures were as follows: glaucoma surgeries alone 1.5, combined cataract/glaucoma 1.1 and cataract alone 0.8.

The researchers found that the median day of endophthalmitis diagnosis was later for glaucoma surgeries (16.5 days) than combined cataract/glaucoma (eight days) or cataract alone (six days).



In the study, the onset of endophthalmitis after glaucoma surgery was one to two weeks later than cataract surgery or MIGS.

They identified two significant risk factors for endophthalmitis with both standalone and combined surgery—tube shunts and Charlson comorbidity index. They also found that age and male gender were significant risk factors for only combined cataract/glaucoma surgeries.

"The median onset of endophthalmitis following traditional glaucoma surgeries was one to two weeks later than that following cataract or MIGS, suggesting that the wait time between sequential surgery on contralateral eyes should perhaps be slightly longer for traditional glaucoma surgeries unless immediate pressure lowering is needed," the researchers explained in their *Ophthalmology* paper.

They added that the identified risk factors will be "relevant in assessing surgical risk for the individual patient" and may serve as a national benchmark for endophthalmitis incidence after glaucoma surgery.

1. Sabharwal J, Dai X, Dun C, et al. Early endophthalmitis incidence and risk factors following glaucoma surgery in the Medicare population from 2016 to 2019. Ophthalmology 2023. [Epub ahead of print].

Light Adjustable Lens™

INDICATIONS FOR USE AND IMPORTANT SAFETY INFORMATION

INDICATIONS: The Light Adjustable Lens™ and Light Delivery Device™ system is indicated for the reduction of residual astigmatism to improve uncorrected visual acuity after removal of the cataractous natural lens by phacoemulsification and implantation of the intraocular lens in the capsular bag in adult patients with preexisting corneal astigmatism of ≥ 0.75 diopters and without preexisting macular disease. The system also reduces the likelihood of clinically significant residual spherical refractive errors.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS: The Light Adjustable Lens is contraindicated in patients who are taking systemic medication that may increase sensitivity to ultraviolet (UV) light as the Light Delivery Device (LDD®) treatment may lead to irreversible phototoxic damage to the eye; patients who are taking a systemic medication that is considered toxic to the retina (e.g., tamoxifen) as they may be at increased risk of retinal damage during LDD treatment; patients with a history of ocular herpes simplex virus due to the potential for reactivation from exposure to UV light; patients with nystagmus as they may not be able to maintain steady fixation during LDD treatment; and patients who are unwilling to comply with the postoperative regimen for adjustment and lock-in treatments and wearing of UV protective eyewear. **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; and 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. **PRECAUTIONS**: The long-term effect on vision due to exposure to UV light that causes erythropsia (after LDD treatment) has not been determined. The implanted Light Adjustable Lens MUST undergo a minimum of 2 LDD treatments (1 adjustment procedure plus 1 lock-in treatment) beginning at least 17-21 days post-implantation. All clinical study outcomes were obtained using LDD power adjustments targeted to emmetropia post LDD treatments. The safety and performance of targeting to myopic or hyperopic outcomes have not been evaluated. The safety and effectiveness of the Light Adjustable Lens and LDD have not been substantiated in patients with preexisting ocular conditions and intraoperative complications. Patients must be instructed to wear the RxSight-specified UV protective eyewear during all waking hours after Light Adjustable Lens implantation until 24 hours post final lock-in treatment. Unprotected exposure to UV light during this period can result in unpredictable changes to the Light Adjustable Lens, causing aberrated optics and blurred vision, which might necessitate explantation of the Light Adjustable Lens. **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%). **CAUTION**: Federal law restricts this device to sale by or on the order of a physician. **Please see the Professional Use Information Document for a complete list of contraindications, warnings, precautions, and adverse events.**

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Risk Factors for Exudative Progression in AMD

A group of international researchers from numerous countries, including Denmark, the Netherlands and the United Kingdom, systematically reviewed and reported the rate of exudative progression over time in patients with non-exudative macular neovascularization in age-related macular degeneration, as part of a review with prevalence and individual participant meta-analyses.[1]

Researchers searched 10 literature databases on March 26, 2023, for studies of consecutive patients with treatment-naïve non-exudative macular neovascularization in age-related macular degeneration.

The primary outcome of interest was time from diagnosis to exudative progression. Researchers conducted meta-analyses on the prevalence of exudative progression at one and two years. Wherever possible, they extracted individual participant data from studies and conducted an individual participant meta-analysis, as well as evaluated exudative progression using a time-to-event curve.

Researchers ultimately identified 16 eligible retina studies reporting on 384 eyes with non-exudative macular neovascularization.

Here are some of the results they reported:

- Exudative progression occurred in 20.9 percent (CI, 13.1 to 29.8) of eyes at one year and 30.7 percent (CI, 21.8 to 40.4 percent) of the study eyes at two years.
- Similar results were observed in the individual participant meta-analysis, showing exudative progression in 18.9 percent of eyes (CI, 13.5 to 26.3 percent) at one year and 31.3 percent (CI, 24.2 to 40 percent) of the eyes at two years.
- Risk factors for a fast exudative progression were presence of subretinal lipid globules, large macular neovascularization areas, rapid macular neovascularization growth, growth in pigment epithelium detachment height and width, appearance of a branching pattern and development of a hyporeflective halo around the MNV.

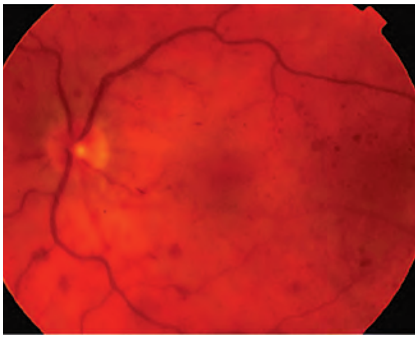
Researchers concluded that patients with non-exudative macular neovascularization in age-related macular degeneration were at high risk of exudative progression. They suggested that recognition of these lesions may enable better individualized follow-up regimens and closer monitoring to facilitate earlier identification of exudative progression.

1. Nissen AHK, Kiilgaard HC, van Dijk EHC, et al. Exudative progression of treatment-naïve non-exudative macular neovascularization in age-related macular degeneration: A systematic review with meta-analyses. Am J Ophthalmol 2023; Aug 31. [Epub ahead of print].

PVD As a Biomarker for Central Retinal Vein Occlusion

The vitreomacular interface is known to have important implications in the manifestations of retinal disease processes including retinal vein occlusion. Prior studies evaluating the influence of posterior vitreous detachment status in central retinal vein occlusion on retinal neovascularization in CRVO have suggested that complete PVD may be protective against neovascularization in eyes with ischemic CRVO. A recent study published in *Retina* has determined that cases of CRVO with complete PVD had significantly lower rate of cystoid macular edema (CME), lower central subfield thickness (CST) and lower anti-VEGF injection burden at one year.

The retrospective longitudinal cohort study assessed patients with acute, treatment-naïve CRVO diagnosed who had at least 12 months of follow-up.[1] Clinical characteristics, treatment patterns and outcomes were



analyzed between eyes stratified based on presence or absence of a complete PVD on OCT at presentation.

Of the 102 acute, treatment-naïve CRVOs identified, 52 (51 percent) had complete PVD at presentation and 50 (49 percent) did not. CST was significantly lower in those with complete PVD (12 months: 284.9 µm vs 426.8 µm; last follow-up: 278 µm vs 372.8 µm. One-year intravitreal injection burden was significantly less for those with a complete PVD than those without (5.1 injections vs 6.7 injections). At 12 months, those with complete PVD at presentation had significantly less CME than those with incomplete PVD at presentation (32 percent vs 65 percent).

"We suspect that the vitreous may serve as a reservoir and microenvironment for pro-inflammatory cytokines and molecules present in eyes with retinal vein occlusion," the researchers wrote in their paper. "The presence of a complete PVD in eyes with CRVO contributes to reduced levels of locally circulating pro-inflammatory molecules at the vitreomacular interface, as has been demonstrated in eyes with diabetic retinopathy."

They concluded that, "Assessment of the vitreomacular relationship on OCT at presentation in eyes with CRVO may serve as a prognostic imaging biomarker." ◀

1. Zheng Y, Woodward R, Feng HL, et al. Implications of complete PVD in eyes with central retinal vein occlusion. Retina. September 5, 2023. [Epub ahead of print].

REVIEW of OPHTHALMOLOGY

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WALTER C. BETHKE, EDITOR IN CHIEF

EDITOR'S PAGE

Handling Our Drug Problem

I've got a drug problem—actually, we all do, at least those of us in the United States: We're spending too much on prescription drugs when compared to other developed nations.

Though the increasing use of generic drugs helps contain medication costs, according to one study, the United States spends twice as much on prescription drugs per person vs. the average of comparable countries such as Germany, Canada, Japan and the United Kingdom. This amounts to $966 per capita vs. $466.[1] When these high prices hit government programs like Medicare, they put increased pressure to try to save money in other areas—or take away resources that might be better spent elsewhere. However, there are signs that our situation may be changing for the better.

In late September, Medicare put the word out that it was looking to hire nearly 100 new employees to staff its Medicare Drug Rebate and Negotiations Group. The new unit will be tasked with negotiating prices for 10 expensive medications, and is looking for individuals with experience in economics, data science and pharmaceuticals.[2] Sitting down at the bargaining table with drug manufacturers in order to negotiate fair prices for drugs would be a first for the United States, while other countries have been doing it for years.

The other, possibly even more intriguing, development on this front happened in mid-August: Blue Shield of California, which insures nearly 4.8 million people, announced that it was dropping CVS Health as its pharmaceutical benefit manager. Instead, the non-profit insurer is going to partner up with five other services, including Mark Cuban's Cost Plus Drugs company and Amazon. Blue Shield says it reached its breaking point when it found a $160 version of a cancer drug that normally would sell for $3,000, but CVS pushed back on them, refusing for five months to sell it at the lower price.[3] Now that Blue Shield of California is out from under CVS' thumb, the insurer estimates it can save around $500 million each year when the plan kicks off in 2025.

Circling back to ophthalmology, this renewed interest in controlling rampant drug prices will be an instance of "a rising tide lifts all boats" or, in this case, "falling prices lift the target from your back": In addition to keeping your patients from having to decide between food and their precriptions for the month, negotiating drug prices will also help lessen the constant drum beat of reimbursement cuts for your ophthalmic services. If/when the country is able to save possibly hundreds of millions of dollars thanks to lower drug prices, Medicare may call off the dogs sniffing around to take another 3-percent bite out of your bottom line.

— Walter Bethke
Editor in Chief

1. Peter G. Peterson Foundation. How much does the United States spend on prescription drugs compared to other countries? https://www.pgpf.org/blog/2022/11/how-much-does-the-united-states-spend-on-prescription-drugs-compared-to-other-countries. Accessed October 2, 2023.
2. Walker J. Uncle Sam wants you—To fight high drug prices. WSJ. https://www.wsj.com/health/pharma/uncle-sam-wants-youto-fight-high-drug-prices-42b3edee?mod=health_lead_pos5. Accessed September 25, 2023.
3. Santija B, Wingrove P. Blue Shield of California looks to cut reliance on CVS, taps Amazon. Reuters. https://www.reuters.com/business/healthcare-pharmaceuticals/blue-shield-california-drop-cvs-caremark-pharmacy-benefit-manager-wsj-2023-08-17/. Accessed October 2, 2023.

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

NOT JUST ANY SOLUTION

A RESOLUTION

Complete and long-lasting resolution of NK for most patients*[1-4]

- **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]

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

* 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 European patients with neurotrophic keratitis (NK) in 1 eye per group; 72% of patients completely healed; vehicle response rate 33.3%. Study NGF0214: 24 US patients with NK in 1 or both eyes per group; 65.2% completely healed; vehicle response rate 16.7%.[2,3]

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. Other adverse reactions occurring in 1% to 10% of OXERVATE patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing.

USE IN SPECIFIC POPULATIONS

Pregnancy

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.; 2019. **2.** Bonini S, et al. *Ophthalmology*. 2018;125:1332-1343. **3.** Pflugfelder SC, et al. *Ophthalmology*. 2020;127:14-26. **4.** Data on File. Clinical Study Report (NGF0212). Dompé U.S. Inc., 2016.

See more clinical data
OXERVATE.com/hcp

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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 Studies Experience

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

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).

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REVIEW of OPHTHALMOLOGY
Clinical advice you can trust

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The Refractive Impact Of Topical Meds

Glaucoma medications can cause some subtle and not-so-subtle changes in corneal optics. Here's what to watch out for.

KAVITHA R. SIVARAMAN, MD
CINCINNATI

Glaucoma drops, especially those containing preservatives, may exert a number of well-documented negative effects on the ocular surface. These topical agents can also affect visual quality by way of their effects on the diffraction, reflection, scatter and filtration of light. Here, I'll discuss several different classes of glaucoma medications, how they affect the refractive status of the eye and how these effects translate into actual symptoms patients may complain about.

Benzalkonium Chloride

As the most ubiquitous preservative in topical glaucoma medications,[1] benzalkonium chloride is something all glaucoma specialists and ophthalmologists deal with on a daily basis. BAK exerts some corneal and conjunctival epithelial toxicity in the form of cell loss, disruption of tight junctions and even apoptosis,[1] but the exact mechanism of that toxicity is still unclear.

There's evidence that BAK inhibits mitochondrial oxygen consumption in human corneal epithelial cells in a dose-dependent manner, with a steep decline in oxygen consumption with increasing concentrations of BAK.[2] This effect is enhanced in cells bearing mutations in mitochondrial complex-1, which is implicated in some forms of primary open-angle glaucoma, as well as other eye diseases.[2,3] So, there's even a potential that BAK toxicity could be amplified in some glaucoma patients compared with the general population.

Classic signs of BAK toxicity include superficial punctate keratopathy (*Figure 1*), conjunctival hyperemia, staining and follicles, blepharitis, increased osmolarity and reduced tear production and tear breakup time.[4]

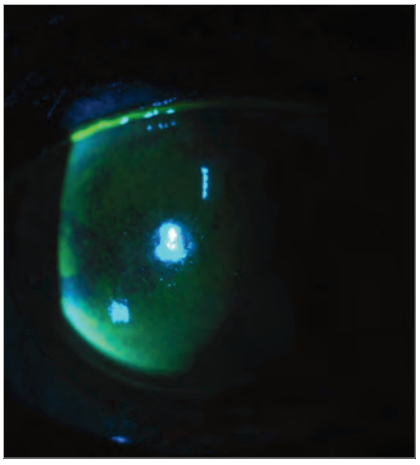

Figure 1. A patient with classic signs of benzalkonium chloride toxicity, with a confluent, almost limbus-to-limbus, pattern of punctate staining.

Placido-based topography does a good job of demonstrating the refractive effect of these punctate erosions. This typically manifests as disrupted mires, which is indicative of irregular astigmatism, an increase in backward light scatter and higher-order aber-

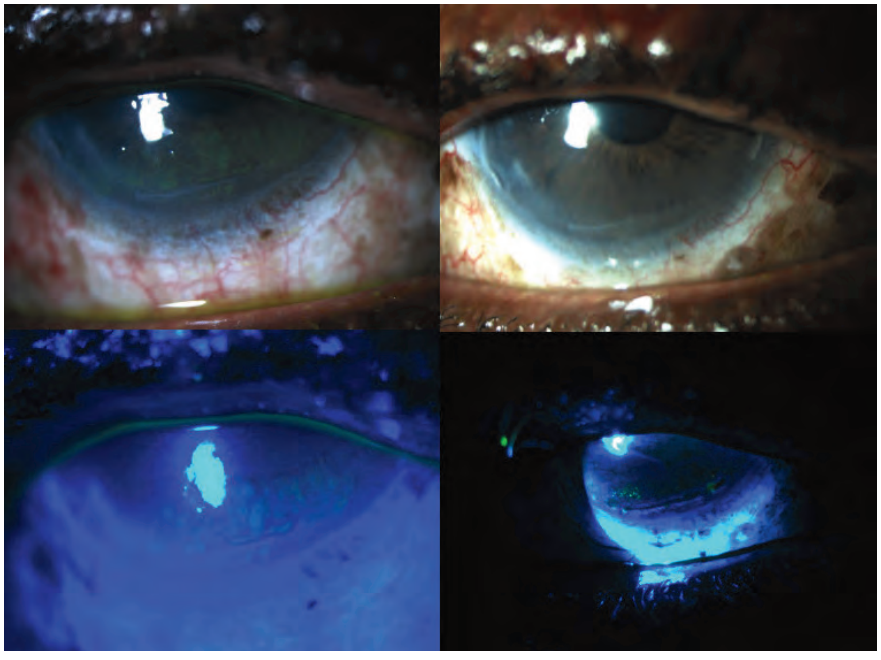

Figure 2. New-onset honeycomb edema (left) from ROCK inhibitor use that resolved (right) after withdrawing netarsudil in a severe glaucoma patient.

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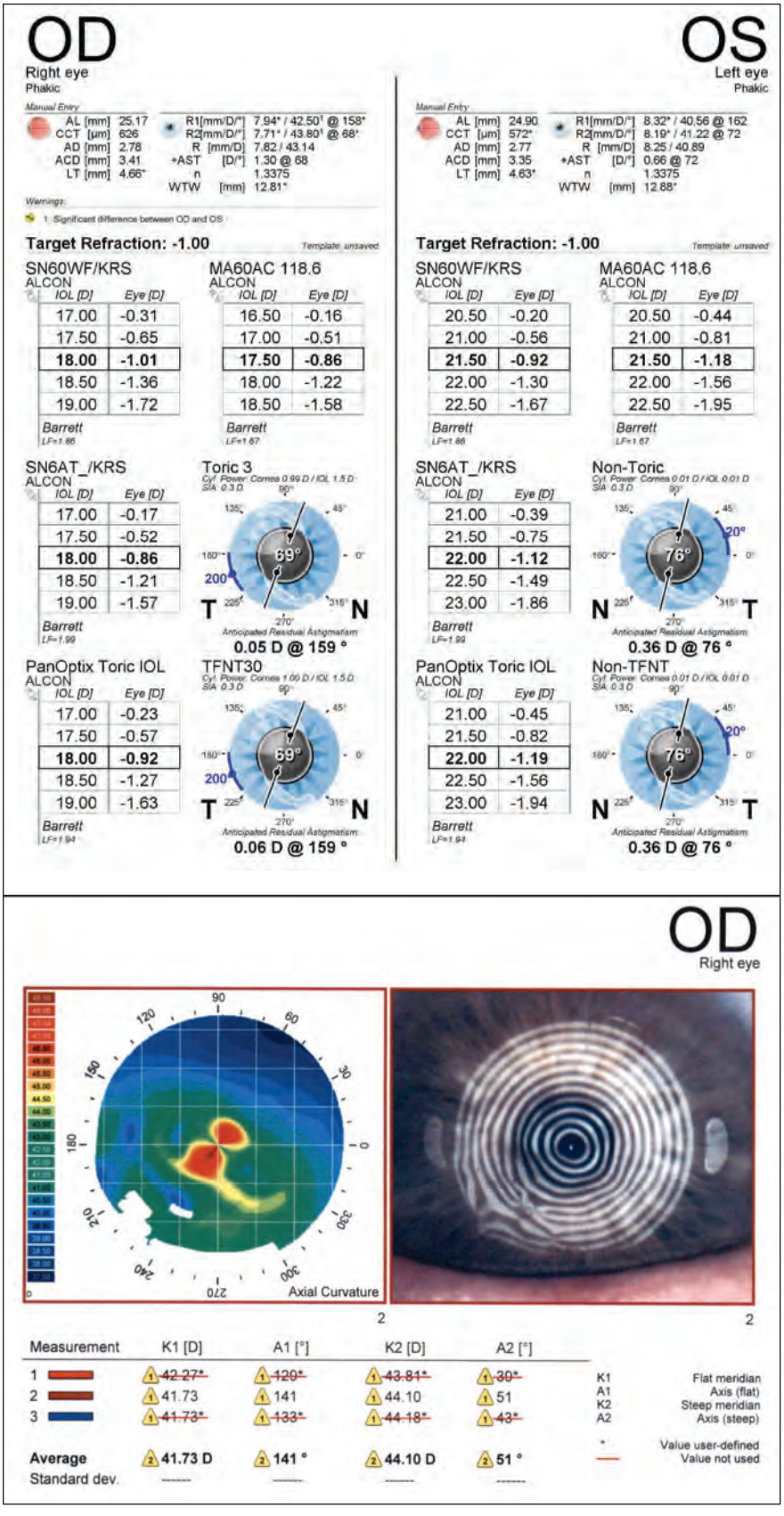

Figure 3. Epithelial edema can have a profound impact on biometry. Note the distorted mires despite a pattern of regular bow-tie astigmatism.

rations.[5] All of these factors could in turn lead to inaccurate biometry. These patients may experience blurred vision, glare and reduced contrast sensitivity—and postop unhappiness if they've had cataract surgery based on these measurements.

ROCK Inhibitors

Though they're used as therapeutic agents in corneal disease and for treating glaucoma, there's still much we don't understand about ROCK inhibitors and their effects on the cornea. Two notable side effects of the drug include honeycomb edema and refractive shifts.

Honeycomb edema is a classic finding with ROCK inhibitor use, usually occurring within a week or two of starting the drug. It tends to be seen in corneas with already compromised endothelium,[6] such as from Fuchs' dystrophy, prior keratoplasty, incisional glaucoma surgery or ACIOL implantation, but it may affect corneas with normal-appearing endothelium as well.

Figure 2 shows new-onset honeycomb edema (*left*) in a patient with severe glaucoma who has had multiple prior procedures. The edema began after starting Rhopressa (netarsudil 0.02%) in 2019 when it was new to the market. At that point, honeycomb edema had only been described with the use of ripasudil 0.4% (Glanatec), which wasn't and still isn't available in the United States. The honeycomb edema resolved (*right*) with discontinuation of the drug.

There have also been reports of significant myopic and hyperopic refractive shifts even in the absence of edema that reverse once the drug is withdrawn. In one case, a 72-year-old man with primary open-angle glaucoma, prior cataract surgery and prior radial keratotomy with no history of refractive shift in the past 20 years reported reduced visual acuity one month after starting fixed-dose combination netarsudil/latanoprost.[7] He had an approximately 1.5-D shift in both eyes, associated corneal con-

tour changes and no epithelial bullae or edema. His refractive error and corneal contour returned to baseline after he stopped netarsudil/latanoprost and was switched to timolol.

In another case, after adding Rhopressa to an existing regimen of timolol and latanoprost, a 4-year-old girl with secondary open-angle glaucoma developed 6.5 D of corneal flattening, which reversed after stopping netarsudil.[8] In the case report, the researchers noted the role of rho kinase inhibitors in corneal endothelial healing but added that if an excess of cell proliferation were to occur, that might induce stromal cells to abnormally secrete enzymes or proteins that could lead to corneal fibrosis and subsequent flattening.

Figure 3 shows an example of the effect of epithelial edema on biometry and cataract surgery. This patient who presented for cataract and corneal transplant evaluation had a history of Fuchs' dystrophy and primary open-angle glaucoma. His topography map showed a regular, bow-tie pattern of astigmatism and unremarkable biometry. He underwent a combined phaco-IOL-DMEK procedure with +18 D IOL, aimed at -1 D but ended up with a refraction of approximately +2.75 sph at one month.

On topography, the mires were in retrospect quite distorted, though the map showed regular astigmatism. Comparing the biometry of the right eye and left eye, which didn't have epithelial edema, showed differing keratometry values, with the right eye measuring much steeper. Fortunately, once the cornea fully healed, the patient drifted back closer to plano. However, this is a cautionary tale that those pockets of epithelial edema really do affect biometry significantly.

Miotics

Pilocarpine and brimonidine are the two most commonly used miotics (e.g., Vuity 1.25% and Lumify 0.025%, respectively). Pilocarpine is both a cycloplegic and a miotic, and is much more potent than brimonidine. This drug induces a refractive change through the pinhole effect and by inducing ciliary muscle contraction.[9] On the upside, this causes increased depth of focus and increased accommodation, but it also leads to poor night-time vision, restriction of peripheral vision and carries a risk of peripheral retinal traction and brow aches.

Ophthalmic Suspensions

Suspensions are a heterogeneous mixture of solid particles within a solvent. The two most prominent examples among glaucoma drugs are Azopt (brinzolamide 1%) and Simbrinza (brinzolamide 1%/brimonidine 0.2%).

> **A few things to consider are potentially switching to non-preserved agents, looking for morphologic changes in the cornea and asking yourself whether pupil size modulation or the formulation of the drops could be playing a role.**

Suspensions on the ocular surface can cause a temporary decrease in contrast sensitivity and increase in forward light scatter since the particles in suspension scatter light directed toward the ocular surface.[10] Both of these factors have the effect of reducing visual quality.

A study assessing Azopt's duration of effect found that reduced vision quality tends to linger for about five to 10 minutes after instillation.[10] While five minutes isn't long in the grand scheme of things, for an advanced glaucoma patient with already poor contrast sensitivity that's being made worse by instilling drops three times a day, that five to 10 minutes can become quite significant. Anecdotally, we've had patients complain of blur for much longer than this after instilling the drops.

In summary, any drops on the eye can have refractive consequences. If there comes a time where you're scratching your head about a refractive complaint in a glaucoma patient, a few things to consider are potentially switching to non-preserved agents, looking for morphologic changes in the cornea and asking yourself whether pupil size modulation or the formulation of the drops could be playing a role. ◀

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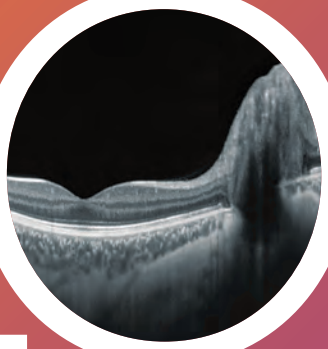

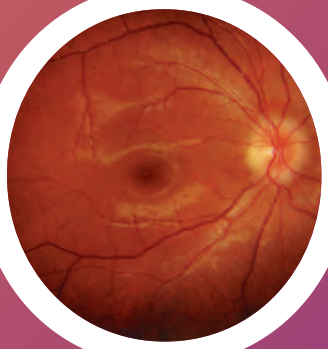

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The Eye, it's Always About the Eye

Musings on life, medicine and the practice of ophthalmology.

MARK H. BLECHER
CHIEF MEDICAL EDITOR

This time of year, I view the approach of fall with both hope and trepidation. Hope for a respite from the often grueling summer temperatures and trepidation with the arrival of the peak of hurricane season. As an East Coaster, it's a yearly ritual, but these days I'm fixated more than ever on the weather. Having spent the greater part of my life in the Northeast, hurricanes were usually something that happened to someone else—someone in Florida. Well, I'm now also that someone in Florida, spending almost half of my time there. I write this now on the most active day of the hurricane season, according to statistics. Not that it means that much, although the fall is typically when you really have to worry. And my worry really should be tempered by the fact that for the last two years there has been more hurricane damage in New Jersey than in my part of south Florida.

Hurricane Idalia earlier this summer reminded us that the damage can be catastrophic, especially for those in more vulnerable areas. There's been a lot written about the wisdom of continuing to build and move people into these particularly vulnerable locations. Barrier islands, low-lying coastlines, that sort of thing. However, in very few places have any regulations or rules been implemented to either impede further development or prevent rebuilding once the destruction has occurred. Americans generally don't like to be told they can't do something they would like to do. Fair enough, but what is the role of government and society in allowing and absorbing the costs for this?

WebMD

While we can argue about whether the storms are getting worse, or why they may be getting worse, it's pretty obvious where not to be should a storm hit. So why aren't we doing more to prevent putting people and property in harm's way? Why do we allow them to rebuild after? And who should pay for this?

You may have heard that in many of these areas, insurance companies are canceling policies. The free market at work. But for many individuals without insurance, they can neither buy a home nor rebuild one. You need insurance if you want to take out a mortgage, and the price is getting quickly out of reach even if it's available. In Florida, a state-owned agency provides insurance of last resort—which is nice I guess—but that just means that local taxpayers are subsidizing development and rebuilding in areas that we know will suffer an expensive disaster at some point, if not repeatedly. Who gets to decide how much risk and how much money we should risk? Clearly the insurance companies have had a say. But shouldn't society as a whole participate? Not only because the state insurer is really us, but none of the rebuilding could even begin to happen if government (local and state) didn't rebuild the damaged infrastructure, such as roads, utilities, etc. So clearly, at least indirectly, all of us are subsidizing continued risk without even being asked. And if we were serious about reducing loss of life and property, there should be a discussion of exactly what locations are off limits. But again, who gets to decide that? I respect free will and maybe wouldn't have a problem if individuals want to go it alone—but at their own risk, and entirely at their own cost. I do worry though that this approach could lead to chaos and, in the end, we'd still bail them out. It's sort of like saying that no one should be forced to buy health insurance if they don't want to if they agree to assume the risk. But, at the end of the day, we don't let people die in the street for lack of either insurance or money. Society steps in. Our humanity won't let us stand by while people suffer the consequences of bad decisions. So I submit that there's a point where we should sit down and agree to reasonable risk, a reasonable free choice that achieves that balance between what we want and what's prudent. It's difficult, like threading the eye of a needle. Or the eye of a hurricane. ◀

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

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Treating Peripheral Ulcerative Keratitis

PUK is often more than meets the eye. Here's guidance for managing these cases.

NINANI KOMBO, MD
NEW HAVEN, CONN.

Peripheral ulcerative keratitis is a sight-threatening inflammatory condition that causes progressive peripheral corneal thinning. The incidence is estimated to be 0.2 to 3 individuals per million population.[1] Prompt and aggressive treatment is needed to prevent not only corneal perforation but also morbidity and possible mortality in cases associated with a systemic collagen vascular disease.

Because of its association with underlying systemic disease, clinicians may need to put on their "rheum-ophthalmologist" hats to handle these tough cases. Here, I'll discuss the workup, diagnosis and treatment of this condition using two case examples from my practice.

In the Periphery

PUK may result from local or systemic causes as well as infectious and non-infectious causes. The condition arises from a complex interaction of host autoimmunity, environmental factors, and the unique features of the peripheral cornea.[2]

Briefly, in contrast to the central cornea, the peripheral cornea has a well-defined vascular and lymphatic supply that allows access to the immune system. Inflammation in the peripheral cornea occurs when proteolytic enzymes from recruited cells are released via this route.[3] Along with tight corneal collagen packing at the periphery, this allows for deposition of immune complexes such as IgM and C1 at the peripheral cornea[4,5] and further destructive processes leading to corneal melting.

Clinical Presentation of PUK

The condition classically presents with pain, redness, tearing, light sensitivity and decreased vision. Patients have an area of crescent-shaped damage in the limbal region of the cornea with thinning present. There is always an overlying epithelial defect, and inflammatory cells may be present in the anterior chamber. Approximately 36 percent of affected patients will have an associated scleritis.[6]

Differential Diagnosis

Diagnosing PUK requires meticulous clinical workup, including laboratory testing. The differential diagnosis for PUK includes:

- Mooren's Ulcer, a diagnosis of exclusion often associated with severe pain.
- Degenerative conditions presenting with mild thinning, such as Terrien's marginal degeneration, senile furrow degeneration and pellucid marginal degeneration. (None of these conditions has any pain or inflammatory processes associated with it.)
- Infection (comprising 19.7 percent of PUK cases)[7] from bacteria, viruses, fungi, *Acanthamoeba* spp. and others.
- Neoplastic etiologies such as carcinoma in situ.

More than half of PUK cases are associated with a systemic collagen vascular disease. It's crucial to identify these patients. They'll need more than local treatment and may have a life-threatening condition.

Among the collagen vascular diseases associated with PUK, rheumatoid arthritis is at the top of the list, accounting for an estimated 34 percent of all noninfectious PUK cases with bilateral involvement.[8] Others include polyarteritis nodosa, systemic lupus erythematosus, relapsing polychondritis and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides, which include granulomatosis with polyangiitis, Churg-Strauss syndrome and microscopic polyangiitis. Patients with these conditions may have involvement of other organs outside of the eye—notably the lungs and sinuses of those with ANCA-associated vasculitides, and the heart and kidneys of those with SLE.[9]

Workup

Workup for these patients includes rheumatoid factor (RF), inflammatory markers erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and Quantiferon for Mycobacterium tuberculosis infection. Tuberculosis sometimes presents with PUK, but more importantly, if you think the patient may need immunosuppression, ensure Quantiferon is negative (some drugs can reactivate

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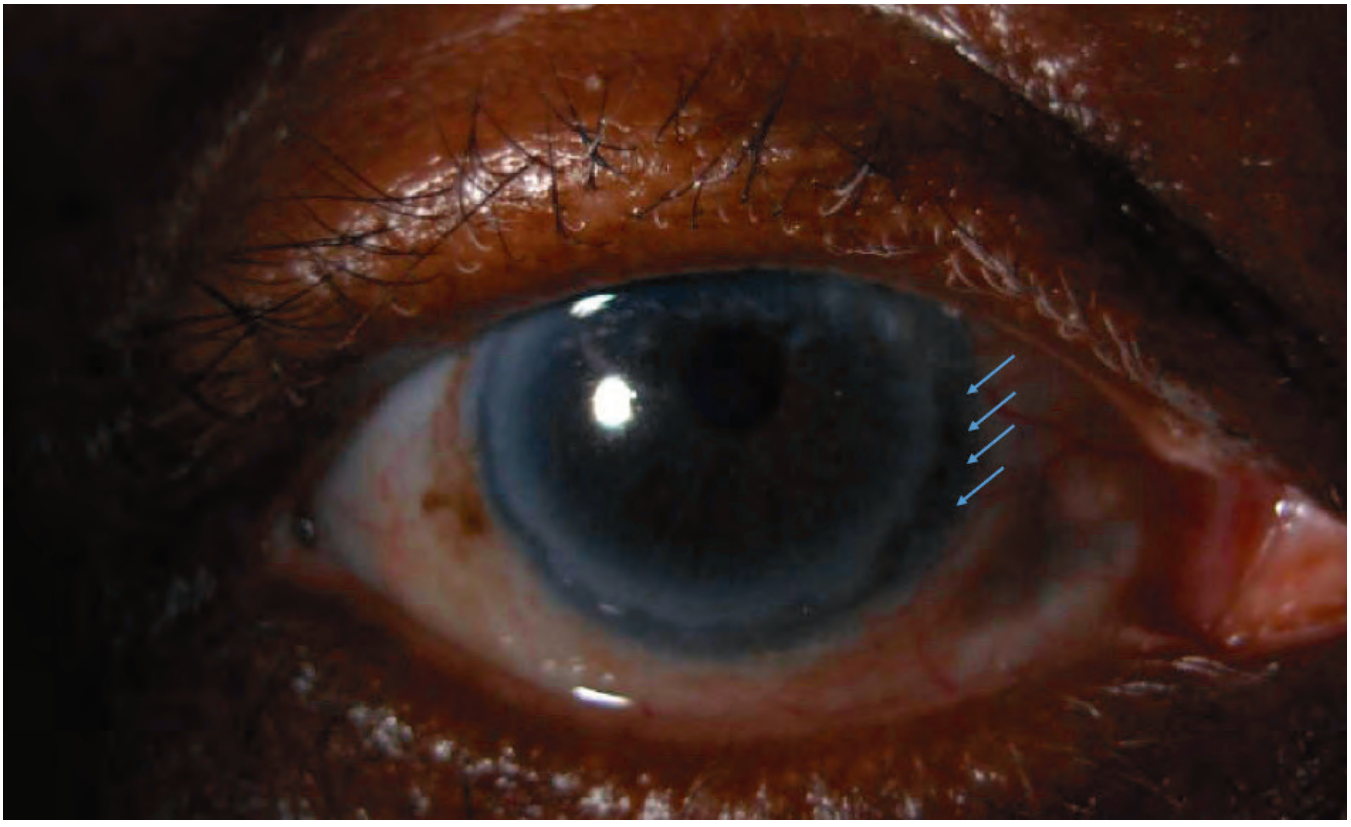


Figure 1. The right eye of the patient in Case 1 demonstrated nasal injection of the conjunctiva. Between 2:30 and 5:30 in the nasal cornea, there was significant corneal thinning.

latent TB).

Testing should also include antinuclear antibody (ANA) if there's suspicion for a connective tissue disease. A titer of 1:160 or above is usually considered a positive test result. An ANCA screening can be ordered for suspected autoimmune disease such as vasculitis to determine whether the patient has one or both types of autoantibodies targeting myeloperoxidase (p-ANCA) and proteinase 3 (c-ANCA).

A chest X-ray and CT of the chest may also be ordered because ANCA-associated vasculitides may have sinus and pulmonary involvement, so you'll want to rule these out before determining what type of treatment to put the patient on.

Treatment

In order to save the cornea, first lubricate it. With the epithelial defect, we're always worried about superinfection, so antibiotic drops such as moxifloxacin can be used as prophylaxis. Vitamin C is added to bolster the cornea, and doxycycline is used because of its anti-metalloproteinase activity, which also helps to prevent further melting. Oral prednisone is given, dosed at 1 mg per kg.

Note: Topical steroids aren't used in cases of corneal melting because we've found they may accelerate it. Think twice before using them and refrain from using them until the eye is stable. As for oral prednisone dosing, many clinicians will use much higher doses (60 to 80 mg) but it's good to be cautious about the diminishing returns of very high-dose oral steroids. There comes a point where the risk-benefit ratio flips. Once you surpass about 80 mg of prednisone per day, the added benefit of a higher dose may not be significant compared to the extreme risk to the patient.

A few other treatments are needed to counteract prednisone side effects. Bactrim Double Strength is initiated to prevent opportunistic infection of the lungs. Any time a patient is immunosuppressed using more than 20 mg of prednisone daily for an extended period, they're at risk for infection. Bactrim DS can be used, one tablet three times a week, as long as the patient isn't allergic to sulfa. Otherwise, use an alternative medication for sulfa-allergic patients. Vitamin D and calcium are given to bolster the patient's bones against prednisone. A proton pump inhibitor such as omeprazole is also commonly used to prevent ulceration of the stomach from the prednisone.

Lastly, in cases with severe corneal thinning, a shield at bedtime protects the patient from accidentally pushing on their eye and perforating the cornea.

Case 1

An 82-year-old woman presented with a 10-day history of blurry vision,

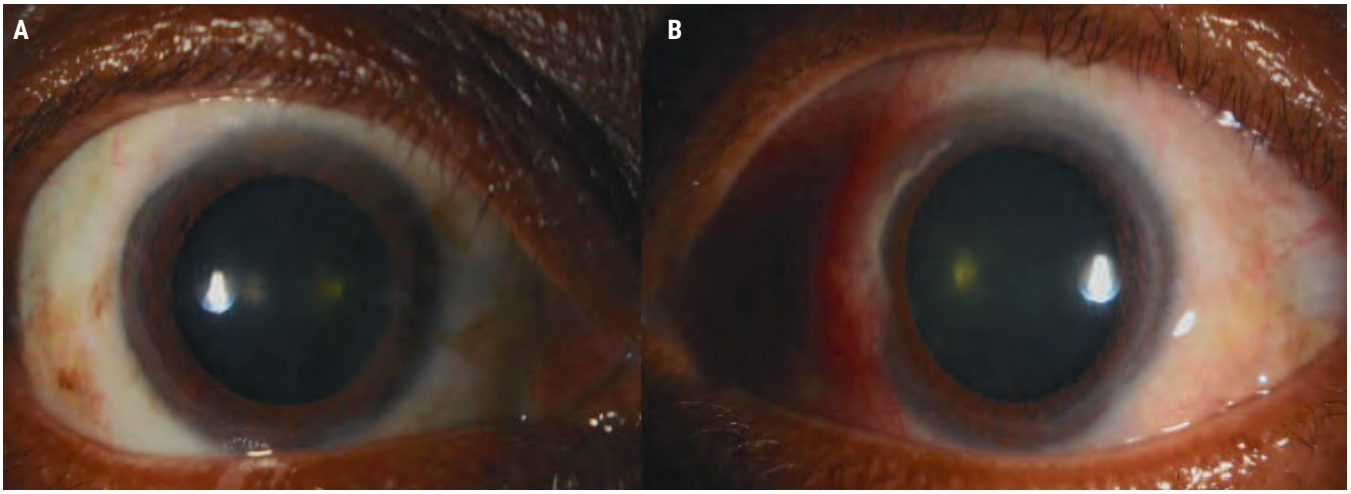


Figure 2A. The right eye (A) of the patient in Case 2 was unremarkable, but the left eye (B) had significant inflammation of the nasal sclera and conjunctiva.

pain, redness and photophobia in the right eye. Her vision was 20/200 in the affected eye, which was a decrease from her baseline of 20/30. Her left eye was at baseline (20/400). Intraocular pressures were normal at 12 mmHg OD and 13 mmHg OS, and pupils were round with brisk reaction and no relative afferent pupillary defect.

On exam of her right eye, the eyelids were smooth and well positioned. The conjunctiva was injected nasally. At the nasal cornea, between approximately 2:30 and 5:30, there was significant corneal thinning (*Figure 1*).

At this point, the clinician should be suspicious for an underlying systemic disease. Laboratory testing can help identify why the patient is having this inflammation.

• ***Workup.*** This patient had negative/normal RS, ESR, CRP and Quantiferon. She had a positive ANA 1:160. Her c-ANCA screen was positive, 1:160 with a repeat of 1:320, so we were fairly confident with the reliability of these results. Her chest X-ray was within normal limits and the CT of the chest and sinuses had no concerning abnormalities.

• ***Treatment***. Her treatment included:

— lubricating drops every two hours;

— moxifloxacin, one drop three times daily;

— vitamin C 500 mg to 1,000 mg daily;

— doxycycline 100 mg daily;

— prednisone 50 mg daily with a 10-mg taper every two weeks;

— Bactrim DS, one tablet three times per week;

— vitamin D/Ca++ daily;

— omeprazole 40 mg daily; and

— a shield at bedtime.

This particular patient had ANCA-positive testing, but because her manifestations were only ocular, the discussion with rheumatology found that using methotrexate was appropriate. Rituximab is the go-to in ANCA-associated disease, but in this case, the patient wasn't willing to undergo treatment with infusion. She was started on methotrexate 20 mg weekly, and after about 12 weeks prednisone was completely tapered. At her last follow-up, about one year from presentation, she had no recurrent inflammation.

Case 2

A 52-year-old woman presented with a three-day history of blurry vision, pain, redness and photophobia in her left eye. Her BCVA was 20/20 in the right eye and 20/50 in the left, decreased from a baseline of 20/20. Intraocular pressures were within normal limits—12 mmHg OD and 13 mmHg OS. Pupils were round with brisk reaction and no relative afferent pupillary defect.

On exam, the right eye was unremarkable, but in the left eye of concern, the nasal section of the sclera and conjunctiva was injected about 3 to 4+ injection (*Figure 2A*). Adjacent to that injection, the cornea demonstrated some inflammatory infiltrates as well as an area of significant corneal thinning between approximately 10:30 and 11:30 (*Figure 2B*).

• ***Workup and treatment.*** Her workup was significant for rheumatoid factor positivity. ANCA, ANA, ESR, CRP and Quantiferon were negative. Initial treatment for PUK was the same as in Case 1. She was started on adalimumab subcutaneous injections every two weeks. She successfully tapered off prednisone over 12 weeks, and after four years of follow-up, she had no recurrence of PUK and no rheumatoid arthritis manifestation.

Other Treatments

The most acute complication to prevent is perforation of the cornea. In addition to starting steroids, you can either glue or resect the conjunctiva to avoid a surgical intervention such as corneal tectonic graft or full

(Continued on page 31)

SYFOVRE®
(pegcetacoplan injection)
15 mg / 0.1 mL

GA unravels so much

Save retinal tissue by slowing progression[1–3]

INDICATION

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

IMPORTANT SAFETY INFORMATION

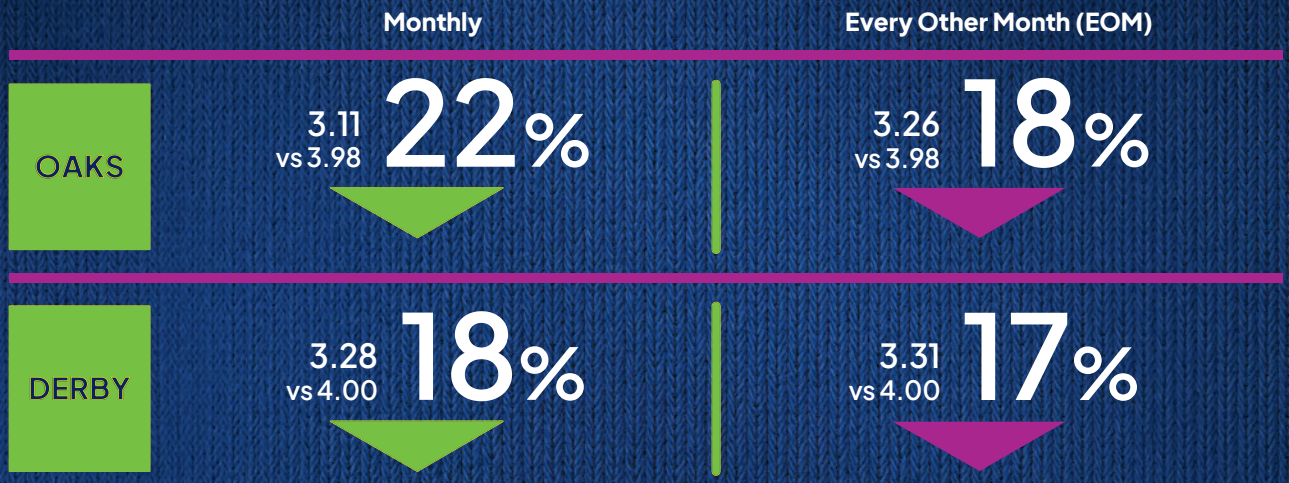
CONTRAINDICATIONS

- 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.
- **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.

SYFOVRE achieved continuous reductions in mean lesion growth rate* (mm^2) vs sham pooled from baseline to Month 24[1]



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

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

- **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.

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.

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

Apellis

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

Ocular or Periocular Infections

SYFOVRE is contraindicated in patients with ocular or periocular infections.

Active Intraocular Inflammation

SYFOVRE is contraindicated in patients with active intraocular inflammation.

WARNINGS AND PRECAUTIONS

Endophthalmitis and Retinal Detachments

Intravitreal injections, including those with SYFOVRE, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering SYFOVRE in order to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.

Neovascular AMD

In clinical trials, use of SYFOVRE was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (12% when administered monthly, 7% when administered every other month and 3% in the control group) by Month 24. Patients receiving SYFOVRE should be monitored for signs of neovascular AMD. In case anti-Vascular Endothelial Growth Factor (anti-VEGF) is required, it should be given separately from SYFOVRE administration.

Intraocular Inflammation

In clinical trials, use of SYFOVRE was associated with episodes of intraocular inflammation including: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, and anterior chamber flare. After inflammation resolves patients may resume treatment with SYFOVRE.

Increased Intraocular Pressure

Acute increase in IOP may occur within minutes of any intravitreal injection, including with SYFOVRE. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

ADVERSE REACTIONS

Clinical Trials Experience

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

A total of 839 patients with GA in two Phase 3 studies (OAKS and DERBY) were treated with intravitreal SYFOVRE, 15 mg (0.1 mL of 150 mg/mL solution). Four hundred nineteen (419) of these patients were treated in the affected eye monthly and 420 were treated in the affected eye every other month. Four hundred seventeen (417) patients were assigned to sham.

The most common adverse reactions (≥5%) reported in patients receiving SYFOVRE were ocular discomfort, neovascular age-related macular degeneration, vitreous floaters, and conjunctival hemorrhage.

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

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

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

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

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 neovascular AMD, endophthalmitis, and retinal detachments. 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-17Feb2023-1.0

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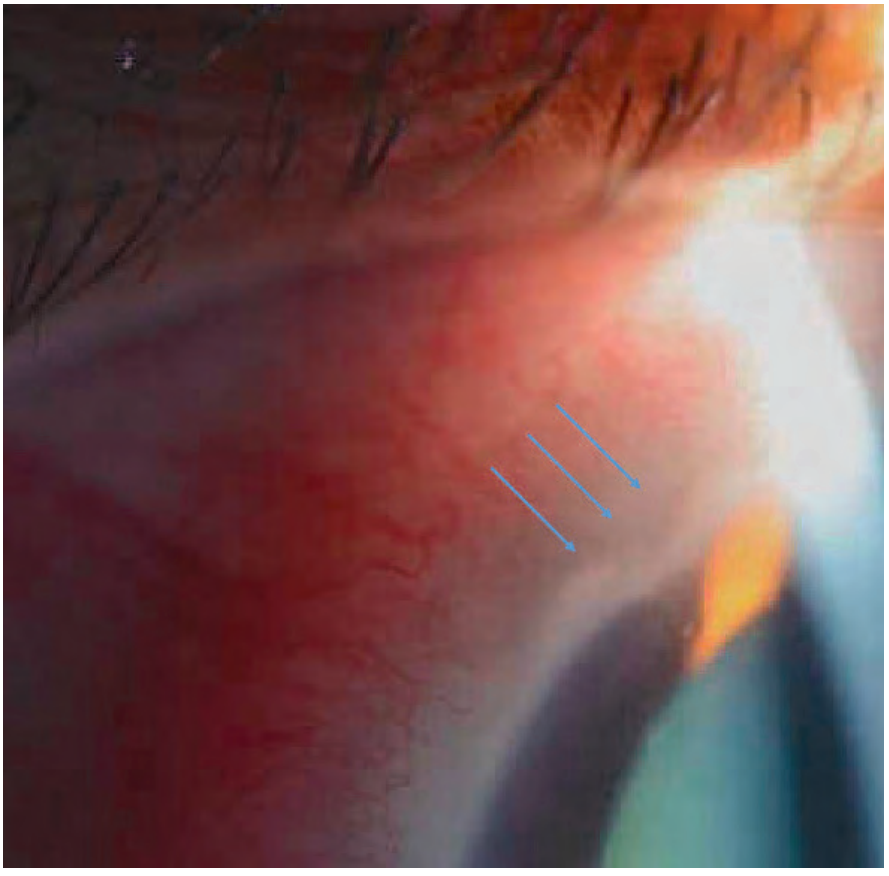

Figure 2B. Inflammatory infiltrates and an area of significant corneal thinning between 10:30 and 11:30 can be seen adjacent to the injection in the same patient.

(Continued from page 27)
corneal replacement. Here are my approaches:

• ***Cyanoacrylate glue (off label).*** It's thought that this glue prevents further melting and stabilizes the cornea by acting as a physical barrier to the inflammatory mediators entering into the cornea.[10] At the same time, it provides tectonic support by filling in the area of thinning.

The technique I use involves punching a hole through part of a plastic drape using a 3-mm dermatologic punch. I put this on the end of a cotton tip, place a drop of glue on it and then apply it in the area of thinning. This is a nice, controlled way of administering the glue that prevents it from getting all over the cornea. A bandage contact lens is placed over the glue to protect the eyelid from irritation, since the glued area is rough and uncomfortable. The glue typically falls off after three to four weeks.

• ***Conjunctival resection.*** This technique has been described to prevent further thinning from PUK. I performed this procedure for the patient in Case 2, who had significant inflammation of her nasal sclera and conjunctiva, because the inflammatory deposits in her cornea would have increased without intervention.

When performing conjunctival resection, I use a toothed 0.12-mm forceps and Wescott scissors. After injecting subconjunctival lidocaine with or without epinephrine, I cut along the limbus, making sure to hug it. Then, I cut about 3 to 4 mm posterior to the area of thinning or posterior to the cornea, just to make sure there's a nice space between the conjunctiva and cornea.

Uncovering Systemic Disease

If a patient has an uncontrolled systemic disease such as rheumatoid arthritis, or they come off their systemic treatment for one reason or another, they can develop flares that include ocular inflammation and PUK. Some patients aren't aware they have an underlying condition, and the ophthalmologist may be the one to make the diagnosis.

Anytime you see a patient with an inflammatory eye disease, you want to do an excellent history. That will guide you in many instances. In the case of rheumatoid arthritis, you can examine the patient's hands and look for the classic swan-neck joints or nodules. With ANCA-associated vasculitides, ask about nosebleeds or coughing up blood. If your review of systems and exam are negative, perform the bloodwork anyway, because these types of joint changes or nosebleeds are characteristic of late changes of those diseases.

Many cornea and uveitis providers are comfortable sending off the initial workup and enlisting the help of rheumatology once they find the results, but it all depends on your training and comfort level. This may be more difficult in non-academic settings or those far from an academic center because some of the labs may not be accessible.

Most ophthalmologists are less comfortable prescribing immunomodulating therapy because of the amount of monitoring that's required. Oftentimes, this is handed off to rheumatologists, though there are uveitis specialists who are very comfortable with systemic immunosuppression and will do all of this themselves. Nevertheless, being part of the treating team involves close collaboration with rheumatology.

The most important thing to keep in mind is that if a patient has a life-threatening autoimmune condition they must be immunosuppressed. If the patient doesn't receive adequate immunosuppression, there's significant mortality from inflammation affecting other parts of the body. In the literature, scleritis with rheumatoid arthritis has 30- to 45-percent

mortality at five years.

In conclusion, PUK is a vision-threatening condition that requires prompt treatment to stabilize the cornea. Don't wait until tomorrow to intervene. First, identify the underlying cause, because more than half of the time, there's an associated systemic condition that will require appropriate treatment. Based on the lab findings, select the best immunomodulating medication or treatment plan for the patient, though of course the patient has to be willing to undergo the type of treatment you choose, since many treatments such as infusions are very time consuming. ◀

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ABOUT THE AUTHOR

Dr. Kombo is an assistant professor and director of medical education of the ophthalmology and visual science department at Yale School of Medicine. She has no related financial disclosures.

REVIEW of OPHTHALMOLOGY

OPHTHALMIC Product Guide

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IOL CALCULATIONS FOR CHALLENGING PATIENTS

Cataract surgeons are often faced with atypical eyes that make hitting refractive targets trickier. Experts offer their guidance on the IOL formulas with the most reliable outcomes and the lenses to consider.

LIZ HUNTER
SENIOR EDITOR

IOL calculation formulas have undoubtedly improved over time, helping surgeons' accuracy and fostering patient satisfaction. However, as every surgeon knows, there still exists a subset of eyes that make calculations a little less predictable, leading to poorer outcomes. Among those categories surgeons often find challenging are long and short eyes, post-corneal refractive eyes (RK, LASIK, PRK), keratoconus and post-keratoplasty, to name a few. We asked several cataract surgeons how they approach these patient presentations and which IOL formulas show the most reliability for getting close to your target.

Understanding the Challenges

Certain factors such as anatomy, corneal power and refraction are just some of the data to consider when calculating IOL power, but the information is a bit more difficult to measure in challenging patient presentations.

Dagny Zhu, MD, a cornea, cataract and refractive surgeon practicing in Rowland Heights, California, says there are three variables that contribute to these challenging IOL calculations.

"We still have sources of error when it comes to predicting where the lens will sit," Dr. Zhu says. "The final effective lens position is really hard to predict in complex eyes, although it's better than ever before with our modern-day formulas. Short eyes are the most difficult to predict the effective lens position because of the anatomy of the eye, and it can change based on the anatomical features, including the ACD and the lens thickness.

"The other one is corneal power," she continues. "Not only is corneal power difficult to measure because there's often ocular surface disease that can make it hard to get consistent, accurate measurements, but especially in post-refractive eyes, if they've had LASIK, PRK, or RK, it's hard to measure the true total corneal power. All you can do is estimate it using topography to measure the anterior curvature, which ends up being more variable in these post-refractive eyes. This can then be used along with other factors to calculate a predicted posterior corneal curvature. The other option is to directly measure the posterior corneal curvature using a Scheimpflug device or swept-source OCT biometer, which is still not perfect. The ELP is also based on total corneal power, so all of that ties together and kind of confounds each other.

"And then the last variable I'd say is that these complex eyes are very difficult to refract in general," Dr. Zhu says. "There's a lot of fluctuation, especially with advanced keratoconus eyes, and so it becomes difficult when you're trying to fine tune your personal surgeon A-constant. All of these variables can hinder your ability to improve the consistency and accuracy of your refractive outcomes."

Recent formulas have been able to improve on earlier standards, which could lead to a myopic or hyperopic shift in atypical eyes. There are regression formulae (second generation) such as SRK II, vergence formulae (third generation) such as Holladay I and II, Hoffer Q, Haigis and Barrett. "Regression formulae such as SRK II make a lot of assumptions, and may fail to deliver in atypical eyes," says Nicole Fram, MD, who is the managing partner of Advanced Vision Care in Los Angeles. "For example, in short eyes, if you use the assumptive standard, first/second-

This article has no commercial sponsorship.

Dr. Fram consults for Zeiss. **Dr. Koch** is a consultant for Alcon, Johnson & Johnson Vision and Zeiss. **Dr. Zhu** consults and does research with Alcon, and consults for Johnson & Johnson Vision and Bausch + Lomb.

When Selecting a Prescription Dry Eye Treatment

DON'T MAKE HER WAIT.

Not an actual patient.

Indication

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

Important Safety Information

- Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients.
- In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.
- To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

xiidra® (lifitegrast ophthalmic solution)5%

CHOOSE XIIDRA

Because lasting symptom relief can start as early as 2 WEEKS[1*]

Access to Xiidra is better than ever[2]

*Xiidra reduced symptoms of eye dryness at 2 weeks (based on Eye Dryness Score compared to vehicle) in 2 out of 4 studies, with improvements observed at 6 and 12 weeks in all 4 studies.[1†]

Important Safety Information (cont)

- Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.
- Safety and efficacy in pediatric patients below the age of 17 years have not been established.

Please see Brief Summary of Important Product Information on adjacent page.

†Pivotal trial data
The safety and efficacy of Xiidra were assessed in four 12-week, randomized, multicenter, double-masked, vehicle-controlled studies (N=2133). Patients were dosed twice daily. **Use of artificial tears was not allowed during the studies.** The study end points included assessment of signs (based on Inferior fluorescein Corneal Staining Score [ICSS] on a scale of 0-4) and symptoms (based on patient-reported Eye Dryness Score [EDS] on a visual analogue scale of 0-100).[1]

Effects on symptoms of dry eye disease: A larger reduction in EDS favoring Xiidra was observed in all studies at day 42 and day 84. Xiidra reduced symptoms of eye dryness at 2 weeks (based on EDS) compared to vehicle in 2 out of 4 clinical trials.[1]

Effects on signs of dry eye disease: At day 84, a larger reduction in ICSS favoring Xiidra was observed in 3 of the 4 studies.[1]

References: 1. Xiidra [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp. **2.** Data on file. DRF Fingertip Formulary® Novartis Pharmaceuticals Corp; July 2022.

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

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

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

6 ADVERSE REACTIONS

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

- Hypersensitivity *[see Contraindications (4)]*

6.1 Clinical Trials Experience

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

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

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

6.2 Postmarketing Experience

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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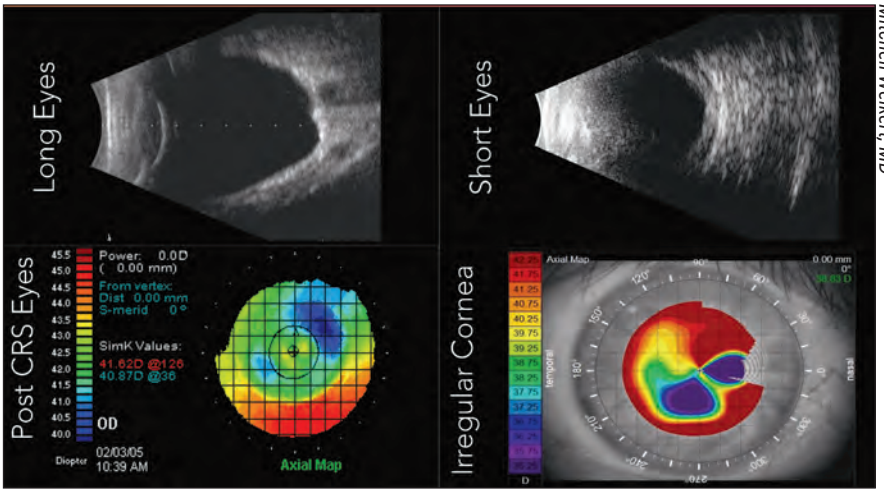


Mitchell Weikert, MD

Some of the most challenging categories of eyes include long and short eyes, post-corneal refractive and keratoconus. Studies have shown that certain IOL formulas are a better fit than others depending on the patient presentation.

generation formulas, you'll end up more myopic than expected because the effective lens position is more anterior than expected. Luckily, we have new AI generation formulas that aren't just simply regression or vergence formulae. Now, they can look at the variables that are most sensitive to effective lens position and use artificial intelligence to achieve better outcomes by inputting more and more data."

There are some proactive steps to take for all eyes to improve refractive accuracy, not just complex eyes, say experts. "You want to optimize the ocular surface," says Dr. Zhu. "I put all my patients on preservative-free artificial tears every hour, usually a lubricating ointment at night and have them start twice-daily lid scrubs and warm compresses. Sometimes I'll start them on a low-potency steroid as well and maybe even an immunomodulatory agent like cyclosporine or lifitegrast if they have more advanced ocular surface disease. I will have them follow this regimen for at least two weeks, and then repeat many of the preoperative measurements."

Douglas D. Koch, MD, professor and Allen, Mosbacher, and Law Chair in Ophthalmology at the Cullen Eye Institute, Baylor College of Medicine in Houston, asks his patients to follow a similar regimen. "They use preservative-free artificial tears four times a day, and lid scrubs and warm compresses at night in the two weeks before they come in for their measurements," he says. "I've found that the reproducibility of the measurements has really improved. I think the importance of that is magnified in these eyes with any kind of irregular cornea, such as the post-LASIK, post-RK, post-keratoplasty and keratoconus."

Dr. Zhu adds not to be shy on the amount of measurements either. "Try to take as many measurements as possible, at multiple time points and with as many devices as possible," she says. "The more data points you have, the more likely you are to hit the correct target. All of my preoperative patients are measured using two different biometers and one or two Scheimpflug or Placido disc topographers. All of that helps me to decide what the most accurate Ks are, as well as the most accurate astigmatism magnitude and axis, and as long as they all agree, you can be pretty certain that you'll hit the target."

It's also a good idea to explain the situation to patients to help them understand why they need to do this additional prep.

"These patients always warrant a longer preoperative discussion and counseling," Dr. Zhu says. "We often tell patients that their eyes aren't within the normal range and are more of a special case so we're going to take special care of their eyes by doing extra optimization of their ocular surface before surgery and taking multiple measurements. After surgery—even after all the careful and special calculations that we do—we ultimately explain that the way their eye heals is unique to them and there's no way anyone can predict that—only God would know.

"We counsel them on the small chance that if they're off, we'll have to do a touch up with laser vision correction or even an IOL exchange, or, if we're using the Light Adjustable Lens, I'll explain that process," she continues. "But this way they know that we've done all that we can and the remaining variable is on them. They're pretty understanding when we explain it that way. Also the extra effort on their part preoperatively to do all the treatments and the measurements shows that we're in this journey together. They understand that they have some responsibility in this as well."

Finding the Right Formula

Many of the most commonly used formulas have been tested by time and validated in large studies. And while the newest generation of formulas, several of which harness artificial intelligence, are far and away better than the early generations, surgeons still find themselves falling short of the target in certain eyes and say there's room for improvement.

Dr. Koch says short eyes and post-refractive eyes particularly don't get great results. He has two papers coming out, co-authored with Mitchell Weikert, MD, showing that results for short eyes are less than 75 percent within 0.5 D of target, and another paper on post-LASIK eyes. "If you look at the literature, almost all studies show that the percentage of eyes within 0.5 D of target is less than 75 percent," Dr. Koch says. "We have a paper coming out (with Dr. Weikert) showing that again, we're getting about a little over 70 percent within 0.5 D of target with one of the Barrett formulas. But again, these data are disappointing."

In the post-LASIK category, Dr. Koch says there probably are three reasons that IOL calculations are

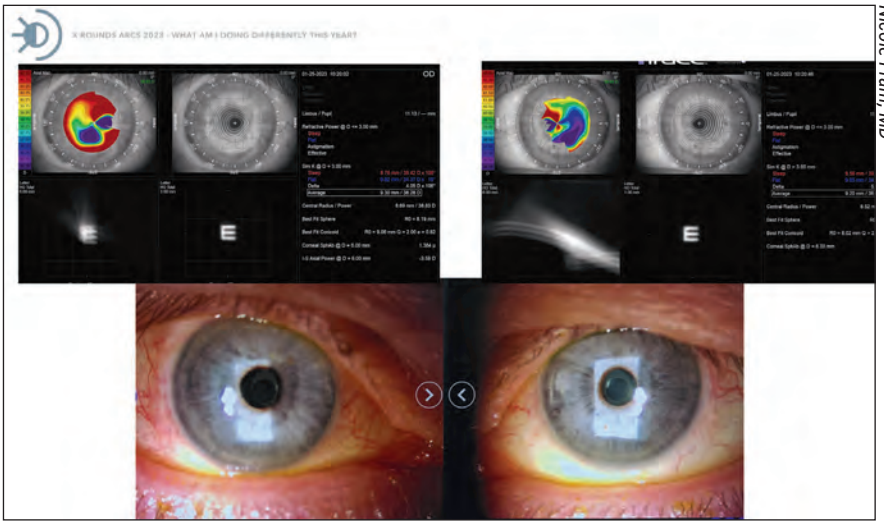
inaccurate with today's technology. "The first one being the prediction of the effective lens position, the second one being corneal power and the third one being any error introduced by refraction," he says. "All three of those are actually accentuated in the post-LASIK eye. The ELP is more complicated because most formulas for ELP use corneal power as one of the variables, and of course the corneal power has been modified. Corneal power as a source of error is present because the anterior cornea has more asymmetry, more higher order aberrations, more irregularity, making it harder to figure out what the 'true power' is. Also the anterior corneal power doesn't accurately predict what the posterior corneal power will be, so that induces error. Their refractions are more variable, they're softer endpoints. This is a situation where we do okay with standard formulas—if you're happy with 75 percent within a 0.5 D of target—but to get better with what we have now, we're looking at postoperative modification."

So, what are the formulas that work best in these complex eyes? Here's what our experts had to say:

• ***Long eyes.*** This is one category where experts say they do well. "That problem became really alleviated when Li Wang, MD, came up with the idea of optimizing the axial length," says Dr. Koch.

In 2011, Dr. Wang co-authored a study that evaluated the accuracy of four IOL formulas in eyes with axial length greater than 25 mm.[1] Eyes were randomized into two groups: one used to develop the method of optimizing AL by back-calculation; the other used for validation. In the validating group, the method of optimizing AL significantly reduced the mean numerical errors for IOLs greater than 5 D from +0.27 to +0.68 D to -0.10 to -0.02 D and for IOLs of 5 D or less from +1.13 to +1.87 D to -0.21 to +0.01 D, respectively (all $p<0.05$). The method significantly reduced the percentage of long eyes that were left with a hyperopic outcome.

"Other formulas have been catching up to that," continues Dr. Koch. "Long eyes should actually do quite well these days with current formulas. One of the reasons that you would expect them to do well is because the IOL power is low so the error created by the effective lens position should be diminished because a low-powered IOL moved in one direction or the other has much less impact on the outcome than an IOL that has higher power."



Nicole Fram, MD

New IOLs such as the Apthera/IC-8 may help surgeons get closer to their refractive target in eyes with irregular astigmatism, post-RK and keratoconus, say experts.

Dr. Fram says her favorite formuls for long eyes are the Wang-Koch adjustment, Barrett Universal II and Hill RBF. "By using the Wang-Koch adjustment formula for >26 mm eyes, we're hitting our refractive targets upwards of 90 percent," Dr. Fram says. "I also look at the Hill-RBF, the Barrett, the regression formula for Holladay, and Zeiss AI, but my most accurate moments are with the Wang-Koch adjustment. Kane is also an excellent choice. When you do hyperopic biometry calculations, the biometer will assume that the eye is longer than it is and you'll put in a lens that's less powerful, and then you end up with a hyperopic error and that's the heartbreak of any myope. It's helpful to look at different types of formulae and mechanism of action for increased consistency in these challenging eyes."

Dr. Zhu favors the Barrett II Universal, Kane, EVO and Hill-RBF for long eyes. "The Hill-RBF in particular is nice because it actually uses big data and AI to come up with the lens prediction," she says.

She's grateful for the evolution of these formulas. "I remember when I first started clinical practice and [one patient] had the longest eye I'd ever seen," Dr. Zhu recalls. "The patient was a -30 D refraction, and his axial length was almost 35 mm. In training, we were still taught to use the very old SRK/T formula for long eyes, so that's what I used. Thankfully, the IOL didn't even come that low in powers, so I couldn't even use the one that I calculated. I ended up using a higher power lens, which ended up getting me exactly where I wanted to be. I lucked out, but I ended up taking that case and back-calculating what the predictive power would have been for every formula, and in retrospect, I found that the Holladay 1 (with Wang-Koch adjustment), Kane and EVO would have been the most accurate, although the Barrett II and Hill-RBF would also have gotten me to within -0.5 D. Using the actual lens power calculated by SRK/T would have made the patient almost 3 D hyperopic. The modern-day formulas take into account the effective lens position and also the posterior corneal power, which are all very helpful for extreme eyes."

• ***Short eyes.*** The other side of the coin is the short eye, says Dr. Koch, which requires a high powered IOL. "The short eye has a wildly variable anatomy, ranging from a small corneal diameter

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*****Clinical results from a matched group of 317 manifest eyes and 323 analytic eyes. Using the Phorcides Analytic Engine for topography-guided surgery, 41.3% of the manifest group and 62.5% of the analytic group achieved 20/16 or better UDVA.

†Out of 124 patients from the clinical study, 122 responded that they would have LASIK again.

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1. Lobanoff M, Stonecipher K, Tooma T, et al. Clinical outcomes after topography-guided LASIK: comparing results based on a new topography analysis algorithm with those based on manifest refraction. *J Cataract Refract Surg*. 2020;46(6):814-819. doi:10.1097/j.jcrs.0000000000000176.

2. Stulting RD, Fant BS; T-CAT Study Group. Results of topography-guided laser in situ keratomileusis custom abalation treatment with a refractive excimer laser. *J Cataract Refract Surg*. 2016;42(1):11-18. Study description: Prospective, nonrandomized, multicenter study of 249 eyes with myopia (up to -9D) or myopic astigmatism of 6.0 D or less. Outcome measures included manifest refraction, UDVA, CDVA and visual symptoms up to 12 months.

For Important Product Information about Contoura® Vision, please refer to the adjacent page.

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WAVELIGHT® EXCIMER LASER SYSTEMS IMPORTANT PRODUCT INFORMATION

This information pertains to all WaveLight® Excimer Laser Systems, including the WaveLight® ALLEGRETTO WAVE®, the ALLEGRETTO WAVE® Eye-Q and the WaveLight® EX500. **Caution**: Federal (U.S.) law restricts the WaveLight® Excimer Laser Systems to sale by or on the order of a physician. Only practitioners who are experienced in the medical mangement and surgical treatment of the cornea, who have been trained in laser refractive surgery (including laser calibration and operation) should use a WaveLight® Excimer Laser System. **Indications**: FDA has approved the WaveLight® Excimer Laser systems for use in laser-assisted in situ keratomileusis (LASIK) treatments for: the reduction or elimination of myopia of up to - 12.00 D and up to 6.00 D of astigmatism at the spectacle plane; the reduction or elimination of hyperopia up to + 6.00 D with and without astigmatic refractive errors up to 5.00 D at the spectacle plane, with a maximum manifest refraction spherical equivalent of + 6.00 D; the reduction or elimination of naturally occurring mixed astigmatism of up to 6.00 D at the spectacle plane; and the wavefront-guided reduction or elimination of myopia of up to -7.00 D and up to 3.00 D of astigmatism at the spectacle plane. In addition, FDA has approved the WaveLight® ALLEGRETTO WAVE® Eye-Q Excimer Laser System, when used with the WaveLight® ALLEGRO Topolyzer® and topography-guided treatment planning software for topography-guided LASIK treatments for the reduction or elimination of up to -9.00 D of myopia, or for the reduction or elimination of myopia with astigmatism, with up to -8.00 D of myopia and up to 3.00 D of astigmatism. The WaveLight® Excimer Laser Systems are only indicated for use in patients who are 18 years of age or older (21 years of age or older for mixed astigmatism) with documentation of a stable manifest refraction defined as ≤ 0.50 D of preoperative spherical equivalent shift over one year prior to surgery, exclusive of changes due to unmasking latent hyperopia. **Contraindications**: The WaveLight® Excimer Laser Systems are contraindicated for use with patients who: are pregnant or nursing; have a diagnosed collagen vascular, autoimmune or immunodeficiency disease; have been diagnosed keratoconus or if there are any clinical pictures suggestive of keratoconus; are taking isotretinoin (Accutane*) and/or amiodarone hydrochloride (Cordarone*); have severe dry eye; have corneas too thin for LASIK; have recurrent corneal erosion; have advanced glaucoma; or have uncontrolled diabetes. **Warnings**: The WaveLight® Excimer Laser Systems are not recommended for use with patients who have: systemic diseases likely to affect wound healing, such as connective tissue disease, insulin dependent diabetes, severe atopic disease or an immunocompromised status; a history of Herpes simplex or Herpes zoster keratitis; significant dry eye that is unresponsive to treatment; severe allergies; a history of glaucoma; an unreliable preoperative wavefront examination that precludes wavefront-guided treatment; or a poor quality preoperative topography map that precludes topography-guided LASIK treatment. The wavefront-guided LASIK procedure requires accurate and reliable data from the wavefront examination. Every step of every wavefront measurement that may be used as the basis for a wavefront-guided LASIK procedure must be validated by the user. Inaccurate or unreliable data from the wavefront examination will lead to an inaccurate treatment. Topography-guided LASIK requires preoperative topography maps of sufficient quality to use for planning a topography-guided LASIK treatment. Poor quality topography maps may affect the accuracy of the topography-guided LASIK treatment and may result in poor vision after topography-guided LASIK. **Precautions**: The safety and effectiveness of the WaveLight® Excimer Laser Systems have not been established for patients with: progressive myopia, hyperopia, astigmatism and/or mixed astigmatism, ocular disease, previous corneal or intraocular surgery, or trauma in the ablation zone; corneal abnormalities including, but not limited to, scars, irregular astigmatism and corneal warpage; residual corneal thickness after ablation of less than 250 microns due to the increased risk for corneal ectasia; pupil size below 7.0 mm after mydriatics where applied for wavefront-guided ablation planning; history of glaucoma or ocular hypertension of > 23 mmHg; taking the medications sumatriptan succinate (Imitrex*); corneal, lens and/or vitreous opacities including, but not limited to cataract; iris problems including , but not limited to, coloboma and previous iris surgery compromising proper eye tracking; or taking medications likely to affect wound healing including (but not limited to) antimetabolites. In addition, safety and effectiveness of the WaveLight® Excimer Laser Systems have not been established for: treatments with an optical zone < 6.0 mm or > 6.5 mm in diameter, or an ablation zone > 9.0 mm in diameter; or wavefront-guided treatment targets different from emmetropia (plano) in which the wavefront calculated defocus (spherical term) has been adjusted; In the WaveLight® Excimer Laser System clinical studies, there were few subjects with cylinder amounts > 4 D and ≤ 6 D. Not all complications, adverse events, and levels of effectiveness may have been determined for this population. Pupil sizes should be evaluated under mesopic illumination conditions. Effects of treatment on vision under poor illumination cannot be predicted prior to surgery. **Adverse Events and Complications** Myopia: In the myopia clinical study, 0.2% (2/876) of the eyes had a lost, misplaced, or misaligned flap reported at the 1 month examination. The following complications were reported 6 months after LASIK: 0.9% (7/818) had ghosting or double images in the operative eye; 0.1% (1/818) of the eyes had a corneal epithelial defect. Hyperopia: In the hyperopia clinical study, 0.4% (1/276) of the eyes had a retinal detachment or retinal vascular accident reported at the 3 month examination. The following complications were reported 6 months after LASIK: 0.8% (2/262) of the eyes had a corneal epithelial defect and 0.8% (2/262) had any epithelium in the interface. Mixed Astigmatism: In the mixed astigmatism clinical study, two adverse events were reported. The first event involved a patient who postoperatively was subject to blunt trauma to the treatment eye 6 days after surgery. The patient was found to have an intact globe with no rupture, inflammation or any dislodgement of the flap. UCVA was decreased due to this event. The second event involved the treatment of an incorrect axis of astigmatism. The axis was treated at 60 degrees instead of 160 degrees. The following complications were reported 6 months after LASIK: 1.8% (2/111) of the eyes had ghosting or double images in the operative eye. Wavefront-Guided Myopia: The wavefront-guided myopia clinical study included 374 eyes treated; 188 with wavefront-guided LASIK (Study Cohort) and 186 with Wavefront Optimized® LASIK (Control Cohort). No adverse events occurred during the postoperative period of the wavefront-guided LASIK procedures. In the Control Cohort, one subject undergoing traditional LASIK had the axis of astigmatism programmed as 115 degrees instead of the actual 155 degree axis. This led to cylinder in the left eye. The following complications were reported 6 months after wavefront-guided LASIK in the Study Cohort: 1.2% (2/166) of the eyes had a corneal epithelial defect; 1.2% (2/166) had foreign body sensation; and 0.6% (1/166) had pain. No complications were reported in the Control Cohort. Topography-Guided Myopia: There were six adverse events reported in the topography-guided myopia study. Four of the eyes experienced transient or temporary decreases in vision prior to the final 12 month follow-up visit, all of which were resolved by the final follow-up visit. One subject suffered from decreased vision in the treated eye, following blunt force trauma 4 days after surgery. One subject experienced retinal detachment, which was concluded to be unrelated to the surgical procedure. **Clinical Data** Myopia: The myopia clinical study included 901 eyes treated, of which 813 of 866 eligible eyes were followed for 12 months. Accountability at 3 months was 93.8%, at 6 months was 91.9%, and at 12 months was 93.9%. Of the 782 eyes that were eligible for the uncorrected visual acuity (UCVA) analysis of effectiveness at the 6-month stability time point, 98.3% were corrected to 20/40 or better, and 87.7% were corrected to 20/20 or better. Subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: visual fluctuations (28.6% vs. 12.8% at baseline). Long term risks of LASIK for myopia with and without astigmatism have not been studied beyond 12 months. Hyperopia: The hyperopia clinical study included 290 eyes treated, of which 100 of 290 eligible eyes were followed for 12 months. Accountability at 3 months was 95.2%, at 6 months was 93.9%, and at 12 months was 69.9%. Of the 212 eyes that were eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 95.3% were corrected to 20/40 or better, and 69.4% were corrected to 20/20 or better. Subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms as "much worse" at 6 months post-treatment: halos (6.4%); visual fluctuations (6.1%); light sensitivity (4.9%); night driving glare (4.2%); and glare from bright lights (3.0%). Long term risks of LASIK for hyperopia with and without astigmatism have not been studied beyond 12 months. Mixed Astigmatism: The mixed astigmatism clinical study included 162 eyes treated, of which 111 were eligible to be followed for 6 months. Accountability at 1 month was 99.4%, at 3 months was 96.0%, and at 6 months was 100.0%. Of the 142 eyes that were eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 97.3% achieved acuity of 20/40 or better, and 69.4% achieved acuity of 20/20 or better. Subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: sensitivity to light (52.9% vs. 43.3% at baseline); visual fluctuations (43.0% vs. 32.1% at baseline); and halos (42.3% vs. 37.0% at baseline). Long term risks of LASIK for mixed astigmatism have not been studied beyond 6 months. Wavefront-Guided Myopia: The wavefront-guided myopia clinical study included 374 eyes treated; 188 with wavefront-guided LASIK (Study Cohort) and 186 with Wavefront Optimized® LASIK (Control Cohort). 166 of the Study Cohort and 166 of the Control Cohort were eligible to be followed at 6 months. In the Study Cohort, accountability at 1 month was 96.8%, at 3 months was 96.8%, and at 6 months was 93.3%. In the Control Cohort, accountability at 1 month was 94.6%, at 3 months was 94.6%, and at 6 months was 92.2%. Of the 166 eyes in the Study Cohort that were eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 99.4% were corrected to 20/40 or better, and 93.4% were corrected to 20/20 or better. Of the 166 eyes in the Control Cohort eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 99.4% were corrected to 20/40 or better, and 92.8% were corrected to 20/20. In the Study Cohort, subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: light sensitivity (47.8% vs. 37.2% at baseline) and visual fluctuations (20.0% vs. 13.8% at baseline). In the Control Cohort, the following visual symptoms were reported at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: halos (45.4% vs. 36.6% at baseline) and visual fluctuations (21.9% vs. 18.3% at baseline). Long term risks of wavefront-guided LASIK for myopia with and without astigmatism have not been studied beyond 6 months. Topography-Guided Myopia: The topography-guided myopia clinical study included 249 eyes treated, of which 230 eyes were followed for 12 months. Accountability at 3 months was 99.2%, at 6 months was 98.0%, and at 12 months was 92.4%. Of the 247 eyes that were eligible for the UCVA analysis at the 3-month stability time point, 99.2% were corrected to 20/40 or better, and 92.7% were corrected to 20/20 or better. Subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms as "marked" or "severe" at an incidence greater than 5% at 1 month after surgery: dryness (7% vs. 4% at baseline) and light sensitivity (7% vs. 5% at baseline). Visual symptoms continued to improve with time, and none of the visual symptoms were rated as being "marked" or "severe" with an incidence of at least 5% at 3 months or later after surgery. Long term risks of topography-guided LASIK for myopia with and without astigmatism have not been studied beyond 12 months. **Information for Patients:** Prior to undergoing LASIK surgery with a WaveLight® Excimer Laser System, prospective patients must receive a copy of the relevant Patient Information Booklet, and must be informed of the alternatives for correcting their vision, including (but not limited to) eyeglasses, contact lenses, photorefractive keratectomy, and other refractive surgeries. **Attention:** Please refer to a current WaveLight® Excimer Laser System Procedure Manual for a complete listing of the indications, complications, warnings, precautions, and side effects.

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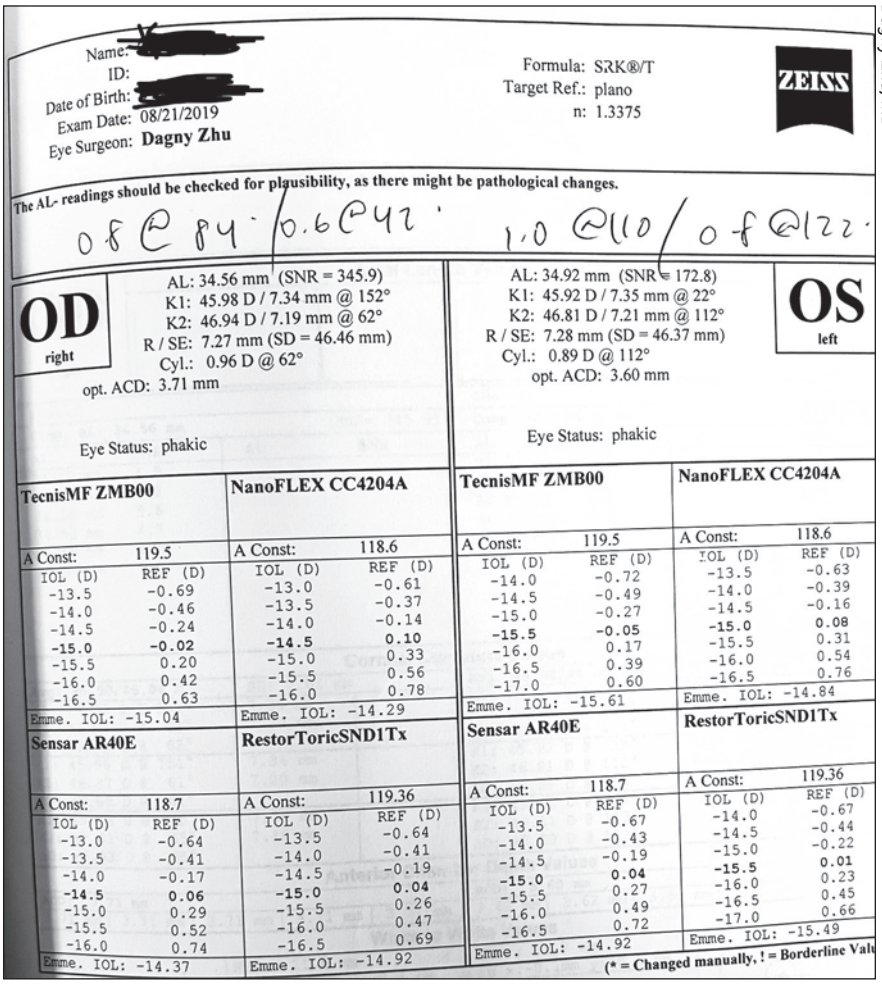
to a shallow anterior chamber to a relatively normal anterior segment for any given axial length, so there's a lot of variability," he says.

As referenced earlier, Dr. Koch and others from Baylor published a paper in the *Journal of Cataract and Refractive Surgery* looking at 15 formulas for short eyes (22 mm axial length or smaller).[2] The study included 278 eyes and used two axial length values: (1) machine-reported traditional AL (Td-AL) and (2) segmented AL calculated with the Cooke-modified AL nomogram (CMAL). It concluded that the Zeiss AI IOL calculator outperformed Barrett, Pearl-DGS and Kane. The Cooke-K6 formula outperformed some formulas depending on parameters.

"We found that this new formula, the Zeiss AI IOL calculator, actually came out best in terms of mean absolute error and in terms of the percentage of eyes within 0.5 D of target," he says. "Unfortunately, even though it was best, it was still less than 75 percent within 0.5 D of target. The other formula that actually turned out quite well was the Cooke-K6 formula. In some respects that was almost as good as the Zeiss AI. But those aren't great results."

Dr. Fram says she's excited about the potential of the AI formulas. "We're getting better and better, but the reality is, we were only hitting our targets on short eyes about 65 percent of the time with non AI formulae, and patients routinely end up myopic which they aren't accustomed to, causing discontent," she says. "It's really challenging, especially with refractive lens exchange. These are often hyperopes that do the best and we're putting in a multifocal. We need to be able to hit our refractive targets. Fortunately, we're improving outcomes with new generation formulae. Refractive outcomes are closer to 80 percent within +/- 0.50 D in small eyes using formulas such as the Hill-RBF, the Zeiss AI and the Cooke-K6 formula. We're in a much better place."

• ***Post-refractive eyes.*** "When you enter into calculating IOLs for post-refractive eyes, it becomes even more challenging because these are



Dagny Zhu, MD

This patient presented with an extremely long eye, with an axial length of almost 35 mm. At the time, Dagny Zhu, MD, used the SRK/T formula to calculate the lens power, but she didn't end up using it because the patient would have been left nearly 3 D hyperopic. Newer generation formulas take other variables into account that help reduce the chance of hyperopic or myopic shifts.

people that expect the same outcome from corneal refractive surgery with their cataract surgery," says Dr. Fram. "What I explain to the patient is that someone has manipulated their cornea and because of that, the formulas that we normally use aren't as accurate. And they still look at me like, 'Yeah, but you're going to hit your target, right?' The ASCRS and ESCRS calculators will create an average from many formulae to help in these post-refractive eyes and are critical to picking IOLs."

Running various formulas through a platform such as Veracity or the ASCRS calculator can be beneficial for these eyes, say experts. "For the post-refractive eyes, whether it be LASIK or PRK, we run the Barrett on the Veracity and we also run the ASCRS calculator which gives us several formulas and look at those," says Dr. Koch.

"I do look at the average of the ASCRS calculator, but the Barrett True K is really incredible," Dr Fram says. "When we look at the Barrett True K in our office, we're hitting our targets about 83 percent of the time within +/-0.5 D. Usually it's between 65 and 74 percent of the time. In the literature, there's a Barrett True K TK formula that shows even more promise; it looks at the posterior corneal curvature that can be measured either with Pentacam, Galilei or anything that measures posterior cornea, or you can use the IOLMaster 700 (Zeiss), which has built-in PK1 and PK 2. We're currently looking at

that and it looks like it gives us about a 4-percent advantage, although we're still examining the data. It's taking us from 83 percent on target to 87 percent. That little bit does matter when you think about how many patients you operate on in a year, and so, Barrett True K TK is still taking us to an even better level in terms of hitting our targets."

Dr. Zhu uses the Barrett True K for post-refractive eyes as well, in addition to the EVO.

Dr. Fram also uses intraoperative aberrometry for post-refractive cases. "At AAO we reported a paper looking at over 1,000 eyes of Barrett True K vs. intraoperative aberrometry formulae and intraoperative aberrometry did better than Barrett True K—approximately 76 percent vs. 69 percent within 0.5 D," she says. "I still use ORA for these cases as this is constantly being optimized with big data."

• ***Keratoconus.*** Many of the same formulas that have success in post-refractive eyes also work for keratoconus. "For keratoconus, I like to use the Barrett True K, which has a keratoconus mode—it's most accurate when you put in the actual measured posterior corneal curvature powers," says Dr. Zhu. "And Kane keratoconus also has a special keratoconus feature for its IOL formula. EVO also is good for keratoconus, especially when you put in the measured posterior corneal curvature powers."

Dr. Fram says it's not unusual to end up with a hyperopic outcome because of underestimating the cornea. "A lot of people in the past would just use SRK/T and aim -1, which is pretty arbitrary, but Kane and Barrett have keratoconus formulas that are performing really well," she says. "They're still only approximately 60 to 65 percent on target, but at least it's an improvement in this challenging population."

"For keratoconus formulas, we released a paper in the *Journal of Refractive Surgery*," says Dr. Koch. "What we found for keratoconus is that the new keratoconus formulas, Barrett-KC and Kane-KC do quite well in keratoconus eyes when the corneal power is less than 50 D—getting within approximately 70 percent within a 0.5-D target.[3] But once the corneal power is 50 and up, then the accuracy falls way off and we're talking about less than 20 percent within a 0.5 D. You can argue that you should use the Light Adjustable Lens for these eyes, and that's certainly a possibility.

"The problem with the keratoconus eye and also for the RK eyes is the question of stability," he continues. "Are they going to change over time? That's one of the unknowns. It doesn't mean you shouldn't try to be as accurate as you can the first time around but you can't promise the patient this will last indefinitely."

IOL Selection and Patient Counseling

Surgeons should give consideration to which lens is going into these challenging eyes. Much like the formulas, some IOLs are a better fit than others.

"In these eyes I would typically end up using a monofocal lens," says Dr. Zhu. "I'm not going to use a multifocal lens in eyes with any sort of irregular astigmatism or higher order aberration, which can commonly be seen with keratoconus or post-refractive eyes. But if some eyes have very mild forme fruste keratoconus and regular astigmatism, I'll still consider using a toric lens, maybe even an EDOF toric lens. It's similar for post-refractive eyes, if the ablation is well-centered, and if it didn't induce a high level of higher order aberrations, I'm comfortable using EDOF and even multifocal lenses in post-myopic and post-hyperopic LASIK eyes. I've looked at my own outcomes and I've had pretty good results with those types of patients as long as I screen properly. The eyes still have to be relatively regular."

In post-myopic LASIK eyes, Dr. Fram says she prefers to use a lens with some negative spherical aberration to match the positive spherical aberration of the cornea or to mitigate it. "The Tecnis Eyhance (Johnson & Johnson Vision) or the LAL are my favorite lenses for post-myopic LASIK," she says. "For post-hyperopic LASIK, I use a lens that has zero spherical aberration profile or very minimal in the center, so I'll use an MX60 enVista or the LI61AO (Bausch + Lomb), or I'll do LAL, and that's been a great approach. The Zeiss CT Lucia 621 is also a really excellent lens for any type of eye.

"I rarely choose a diffractive technology in post-LASIK eye with abnormal topography such as decentered ablation or irregular Placido imaging because if they have dysphotopsia afterward, I'm not going to know what's coming from the cornea and what's coming from the lens, and it becomes a bit complicated. These eyes may benefit from a small aperture technology," she continues.

"For long and short eyes, you're limited based on what IOL power is available," says Dr. Zhu. "A lot of the multifocal lenses don't go very low or very high. They're usually around 10 to 30 D and the astigmatism is limited as well, correcting up to approximately 3 D, or 2.5 D for against-the-rule astigmatism. So in those cases, you're kind of stuck with using a monofocal."

Patients should also be counseled on outcomes, especially for long and short eyes. "I think the only caveat with short eyes is that when we're planning an EDOF or a multifocal lens, you want to make sure that patients understand that there's a risk of being off target and they may need an IOL exchange, or, if you're really off target, a laser vision enhancement," says Dr. Fram. "As far as IOLs, I always use what's in the patient's best interest and I use every different type of IOL.

"The same goes for long eyes, but if they have a history of retinal detachments, or retinal detachments in their family, I'll try to avoid silicone if I can because if they have a retinal detachment and it's not amenable to repair with laser and gas, they may need silicone oil in the future," she continues. "But if silicone is the best lens for them for a variety of reasons, I still use it."

Newer IOLs, including the LAL and Apthera/IC-8, are contributing to accuracy in these eyes, say these experts. "We do have newer IOLs that provide even greater accuracy in these complex

(Continued on page 90)

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PRACTICE MAKES PERFECT: STAFF MANAGEMENT

Experts in ophthalmic practice management weigh in on how training and retaining staff are major parts of managing a successful office.

ANDREW BEERS
ASSOCIATE EDITOR

Managing a practice can be difficult, and it's harder if you have a lot of staff turnover or run into trouble hiring good people. Having a well-established team of technicians, managing partners, administrators and desk staff members can help improve a practice's overall efficiency and profitability. Here, experts in ophthalmic practice management share their tips on how to properly hire, train and retain staff.

Getty

Training employees to retain them is always good practice. According to a 2021 AAO survey, 20 percent of employed technicians were trained as Certified Ophthalmic Assistants, 6 percent were trained as Certified Ophthalmic Technicians, 36 percent were trained in various certifications, 20 percent were trained but not certified and 18 percent have no training or certification at all.

Bringing People In

"Having the mission, vision and values clearly defined allows new people in your organization to feel connected to something, which then promotes satisfaction and, hopefully, retention," says Laura Baldwin, senior consultant at BSM Consulting, an ophthalmic practice management firm based in Reno, Nevada. "The mission, the vision and the values of the organization—those need to be clearly defined so employers can articulate, 'Why would someone want to come work for me?' People coming into employment want to know that there's meaning behind the work, that they're going to work with good people, that they're going to be valued and they're going to be able to deliver value," she says.

There are many systems for hiring staff, but recruitment has gotten more difficult over the years. "A couple of years after the pandemic, the difficulties have been paramount, and we're just now beginning to see

This article has no commercial sponsorship.

Mr. Pinto is President and founder of J. Pinto & Associates, an ophtalmic practice management firm. **Ms. Baldwin** is Senior Consultant at BSM Consulting, a practice managment firm specializing in ophthalmology, optometry and other medical specialities. **Ms. Jahnle** has no financial intererests to disclose.

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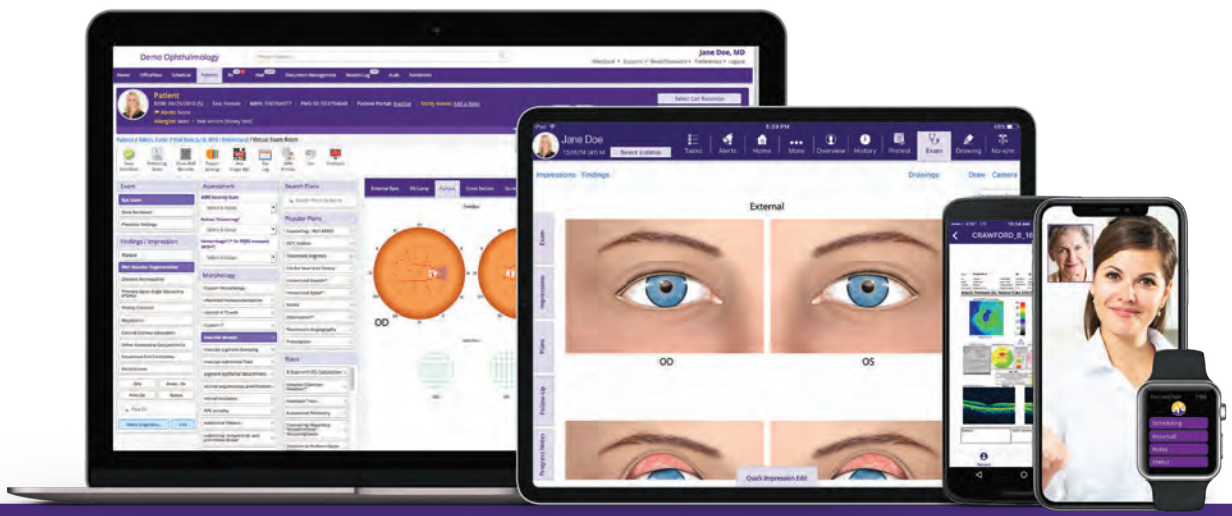

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In 2021, the AAO surveyed 9,000 ophthalmologists about their practices. Of the results, one-third of participants experienced physician burnout. This was due to individual challenges and unexpected burdens from the COVID pandemic. According to the survey, physican burnout impacted solo practices (23 percent) less than group practices (27 percent) and practices in larger patient concentrations (health systems, hospitals, multispecialty facility; 51 percent).

in our clients some softening of that difficulty," says John Pinto, president and founder of J. Pinto & Associates, an ophthalmic practice management firm based in San Diego. "The typical smart administrator is spending more time than they had in the past trying to develop a candidate pool, both through online routes like Indeed, and also through encouraging the existing staff to refer their friends and community contacts to the practice."

For lists of ophthalmic job openings, societies such as the American Academy of Ophthalmology and the American Society of Ophthalmic Administrators post job boards online. According to their websites, job postings are only available to organization members, but all website visitors can freely create a profile, apply to the posted jobs and monitor recent applications.

Experts say that practices need to be accepting of individuals with little to no health-care experience for certain office positions. "I always tell clients, 'If you're at Starbucks and you get really great service from a barista and it's somebody you want to work your front desk, then you can train them on the skills,'" says Ms. Baldwin. "Hire them for personality and attitude, train them for the skills."

> **We want to hire nice, kind people who want to do the work and show up, but don't necessarily have experience or a certain degree.**
>
> ***— Erica Jahnle***

Erica Jahnle, the chief operating office and practice administrator for Jahnle Eye Associates, a suburban Philadelphia practice with a staff of 40, says that prospective employees are often interested in a higher salary and some way to help achieve a work/family balance. "Salary requests have gone up a lot," she says. "They've increased about 20 percent over the past two to three years—it's remarkable. This applies even to our starting salary, for people with no experience in an ophthalmic, optometric or even a medical office. We want to hire nice, kind people who want to do the work and show up, but don't necessarily have experience or a certain degree.

"One thing that's the hardest for both current staff as well as those coming in is balancing childcare with work," Ms. Jahnle continues. "That's one of the reasons people sometimes leave or go part-time. We generally try to accommodate that need, because if we like someone, we want them to be here. However, it's hard to balance, because we simply need staff when patients are coming in for their appointments. Sometimes that means hiring additional staff if someone has to cut down their hours. Unfortunately, we've lost some fantastic staff because we can't help employees a lot with this, but it's something they're looking for. I wish the U.S. would change the system so providing childcare wasn't such an extraordinary cost."

Retaining Good Staff

After employing new staff members, the next step is to train them. Mr. Pinto says, "The average practice 20 years ago didn't have, for example, an operating manual describing, 'How do we answer the phones?' Or 'How do we escort a patient down the hall and put them in Room 3?' There's an awful lot of work that's been done to manualize practices, write down the standardized operating procedures and review those procedures. Those written manuals are not only useful as training guides, but also as a process of maintenance documentation, a kind of accountability document to ensure everyone works the way they're first trained."

It's best to understand the impact staff training has on a practice and how it can be used to retain staff in the future. "Nowadays, staff training puts more burden on a practice because you're bringing in people who are new to the specialty or in some cases new to eye care," says Ms. Baldwin. "Therefore, it's not just

about the initial training. It's about ongoing training and development for employees who've been there for a year or two, and who've become proficient at their jobs. What are you doing to continue to grow and develop that employee so that they see value in staying with your organization and see the opportunity for perhaps a career path in your organization? You train to retain."

Ms. Jahnle says that her staff's ability to move into a new role can help keep people engaged and refreshed. "In performance reviews, we ask if there are additional things a staff member is interested in learning," she says. "We've had some who've moved to different departments: For example, two individuals started out as receptionists but then became billers after many years. A receptionist became an optician, and we've also had receptionists graduate to becoming ophthalmic technicians. Sometimes, people come in thinking they want to do just one thing here, but after a while they think, 'Maybe I could do the other thing instead.'"

In order to successfully train staff members, practices need their physicians, managers and administrators to become experts in leadership. "Employers really have to understand the motivation of each team member and how to coach, mentor, teach and train them to get the best out of them," says Ms. Baldwin. "They're not only having to deal with the operational leadership of a practice, but most importantly the human leadership of the practice, the unique generational differences within organizations, and what motivates somebody who may have been in the workplace for 30 years versus what motivates somebody who's just coming into the workplace."

Ms. Jahnle says one of the keys to retaining staff is communication. "I think the thing that I value, or most staff members seem to value, is being willing to listen to them," she says. "They should feel that they can come to me if they have a problem with another staff member or a patient, or even a personal problem. For some managers, sometimes it's easier to avoid things, but I feel it's better to take things head on. For instance, this morning we had a meeting from 8 to 10. Before the meeting, we asked everyone if there's a concern or something they want to address at the meeting. We spent a lot of time letting staff discuss tips for other staff and their concerns. It helps everyone feel that they've bought in on what we're doing.

"I also keep them in the loop on how the business is doing," Ms. Jahnle continues. "What are our goals, and what's the product we're selling?"

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Ongoing Challenges

Of course, there are instances in life that may affect staff retention. In 2020, many staff members were furloughed due to the pandemic and individuals weren't seeking positions in ophthalmology. According to the Bureau of Labor Statistics, 58,600 technicians were employed in the United States in 2019. In 2020, due to the pandemic, there were 57,310 ophthalmic technicians in the United States. Due to this drop, BLS projected that approximately 65,700 technicians would need to be employed by 2030. According to recent BLS data, 66,060 technicians were employed in 2022, filling the projected total of ophthalmic technicians in the United States.

"I would say one of the most important things that the average practice leader learned from the pandemic was to not sweat the small stuff," says Mr. Pinto. "We used to think that losing an important staff member or losing your leads or having a doctor who's productive give their notice was a major crisis. In light of, and in comparison to, what COVID inflicted, those things are just kind of a walk in the park. Leaders gained a new appreciation for how they could manage in the face of any number of other crises that occur.

"I tend to not catastrophize, and I suspect that even if we had another COVID pandemic like the original version and the incidents and severity was equivalent to the last round we had in 2020, that not only will the national public health response be different, but also the individual clinic response will be different," continues Mr. Pinto. "There'll be less of a 'run for your lives' feeling, and more of an appropriate proportionate response."

If a practice needs help recruiting, retaining or managing their staff, then investing in a practice management firm specializing in ophthalmology can be beneficial, since they've seen many of the problems that you're just experiencing for the first time. "Think about this in clinical terms," says Mr. Pinto. "For every patient that a doctor sees, they've seen thousands of other patients with exactly the same presenting condition. When you now look over on the other side of the aisle, and that same doctor, or even the administrator, is looking at their business problems, they probably only looked into one or two practices for recommendations over the course of their entire career."

In the end, everyone manages their practices differently, but times are always changing. "Physicians should be open to the talent that's out in the workplace," says Ms. Baldwin. "It may look different, sound different and not have the same experiences as it used to, but people have great attitudes, great motivations, and great desire to come into your workplace, and when given the right opportunity, can end up being one of the best employees you've ever hired if you're open to it. We've got to look at the world differently." ◀

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SECURING PREMIUM PATIENT HAPPINESS

How to do more than just "hope for the best" when it comes to premium IOL satisfaction.

CHRISTINE YUE LEONARD
SENIOR ASSOCIATE EDITOR

Patient unhappiness inevitably comes with the premium lens territory at one point or another, but there are a number of steps surgeons can take both preoperatively and postoperatively to reduce the likelihood of these trying scenarios. "You have to have a mechanism for dealing with the unhappy patient once they're on the other side of surgery," says Kevin Miller, MD, a professor of clinical ophthalmology and the Kolokotrones Chair in Ophthalmology at the David Geffen School of Medicine at UCLA. "Before surgery, it's a matter of explaining what we can do."

Here, veteran cataract surgeons share their top tips and techniques for dealing with unhappy premium lens patients and offer pearls for minimizing unwanted outcomes.

Keep Calm & Carry On

"It's a different thing when you're dealing with unhappy premium patients and they're your own patient versus one who's been referred to you versus one who's come to you on their own for a second opinion," says Steven G. Safran, MD, who's in private practice in Lawrenceville, New Jersey. "The dynamics of these interactions are very different. Usually, patients are less angry when they're referred to me by another doctor. The patient is still following that doctor's plan, still on their team. Most of these patients' complaints are pretty reasonable: negative dysphotopsias, ocular surface issues.

"When a patient seeks me out on their own, very often they've broken away from their doctor and have lost faith," he continues. "They come in, and they're typically angrier. They want you to validate their misery, and it's very important not to do that. Instead, get to the bottom of the patient's concern. Why are they unhappy? Do they have realistic expectations? Is it a lens-related problem? A residual refractive error? An anatomical problem? Are they upset about the money they spent? Figure out where the patient wants to go and how to get them there."

When your own patient complains, it can be difficult not to take it personally. "Becoming defensive and deflecting the blame is a common first reaction," says Dr. Miller, "but it's important to step back and focus on next steps. These patients are frustrated with the situation and may be a little bit afraid of what their life is going to be like in the future. Listen to the patient, let them know you understand, and repeat their concerns back to them, as any psychologist would do. Let the patient know that there's a plan in place and that you'll stick with them. The worst thing you can do is abandon the patient."

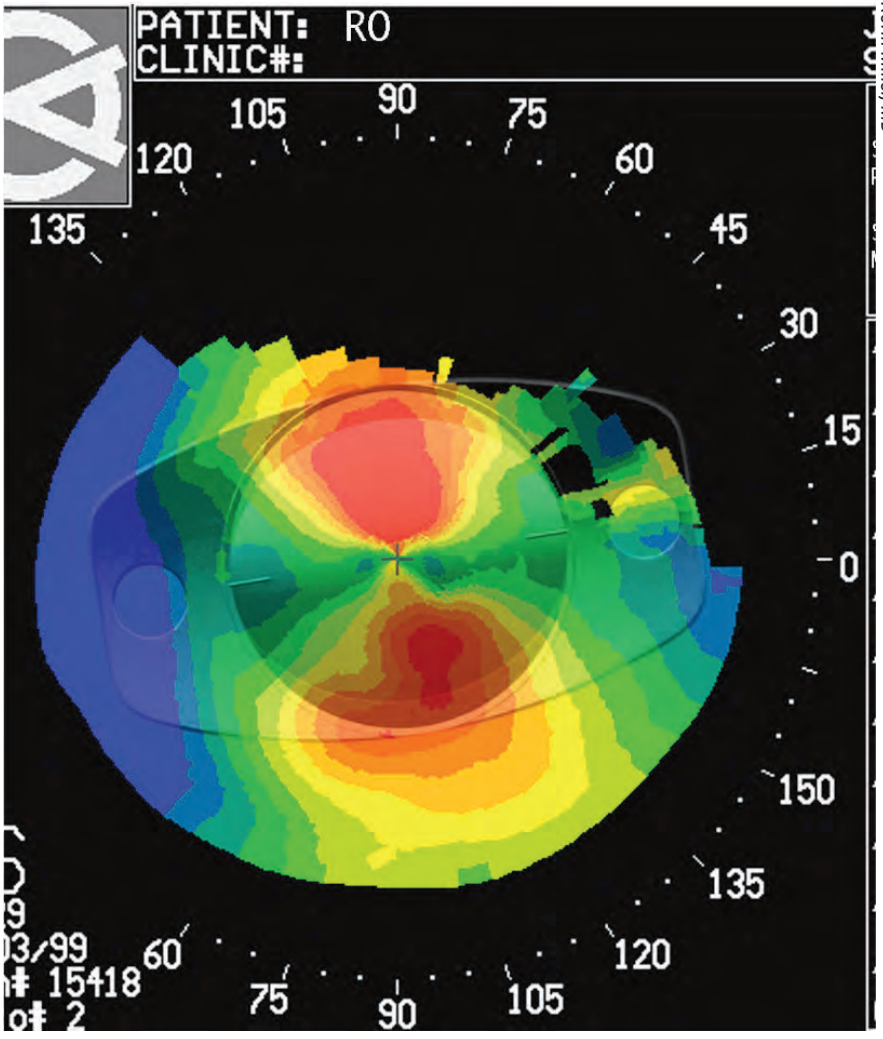
Dr. Miller says that at this point, it may not be possible to achieve the outcome the patient is looking for, but you can promise to do your best. "Nobody can promise perfection, and people realize that's the way life is," he says. "Patients just don't want to be kicked to the curb."

No Magic Bullets

Unrealistic expectations about what's achievable with surgery or intraocu-

This article has no commercial sponsorship.

Dr. Miller is a consultant for Alcon, Johnson & Johnson Vision, BVI, Oculus, Longbridge Medical and LensAR. **Dr. Khandelwal** is a consultant for Alcon, Bausch + Lomb, Carl Zeiss Meditec, Dompé, Kala Pharmaceuticals and Ocular Therapeutix. **Dr. Loden** is a clinical investigator for Johnson & Johnson Vision. **Dr. Safran** has no related financial disclosures.



Kevin Miller, MD

Toric IOLs may end up off axis for a number of reasons, including incorrect positioning at the time of surgery, incorrect calculation of the postop steep axis or rotation after implantation.

lar lens technology are a common reason for patient unhappiness. "There's a lot of hype about premium lenses, but everything in the cataract world is a trade-off or compromise," Dr. Miller says. "You give up something to get something. For instance, the patient may be giving up the ability to look at lights at night and not see halos in order to have a multifocal lens. We have to counsel patients that halos are just one of the realities of multifocals. That said, most patients who get multifocals are quite happy with them and would choose a multifocal again if given the opportunity."

Dr. Safran points out that most premium lenses have worse quality of vision than monofocals. "Premium lenses are often sold as upgrades, but patients need to understand they're not better or upgraded lenses," he says. "There's no lens that does everything perfectly. I explain to patients that the lens they may be unhappy with would make a different patient very happy. It's a matter of making the right match."

"I make sure to tell all the multifocal patients ahead of time that I'm not going to get them out of glasses," Dr. Miller says, adding that he often has to remind unhappy patients of this fact. "Multifocals won't eliminate the need for glasses, but they can reduce dependence on glasses."

Surgeons say it's important to set up patients' expectations for the early postoperative period as well. "Patients are quite patient if they know that they're not going to be stuck with whatever it is they're experiencing at the moment and that you have a plan," Dr. Miller points out.

For early postoperative unhappiness, complaints usually stem from foreign body sensation from the incision and occasionally some corneal edema. "Reading vision seems to be particularly affected in multifocal patients when there's any central corneal edema," Dr. Miller says. "I tell all the multifocal patients that the day after surgery they'll notice that their distance vision will come in first. That will sharpen first and then a few days later their reading vision will start to come in.

"I also tell them not to panic if their reading vision isn't that good with just one eye done," he adds. "Multifocals split light, so the contrast isn't going to be as good as their other eye, which hasn't been operated on yet. I tell them that once their other eye is done, the two eyes will work together and then they'll see the increase in contrast that occurs with binocularity and really appreciate the reading vision."

"When I see the patient on day one, it's too early to assess what the refractive surprise is, if there is one," says Sumitra Khandelwal, MD, an associate professor of ophthalmology at Baylor College of Medicine, Cullen Eye Institute, and medical director of the Lions Eye Bank of Texas in Houston. "Waiting to refract will also give the patient time to experience their new vision. When you bring them back, if they're happy, that's great that the outcome is working for them. If they're still unhappy, we'll look closer."

"In the postop period, let patients know that corneal swelling is normal, and that vision will improve as that settles down," Dr. Miller says. "If they're concerned that they're going

(Continued on page 55.)

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INDICATION

IZERVAY™ (avacincaptad pegol intravitreal solution) is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD)

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- IZERVAY is contraindicated in patients with ocular or periocular infections and in patients with active intraocular inflammation.

WARNINGS AND PRECAUTIONS

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  - Intravitreal injections, including those with IZERVAY, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering IZERVAY in order to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.

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  - Transient increases in intraocular pressure (IOP) may occur after any intravitreal injection, including with IZERVAY. Perfusion of the optic nerve head should be monitored following the injection and managed appropriately.

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- Most common adverse reactions (incidence ≥5%) reported in patients receiving IZERVAY were conjunctival hemorrhage, increased IOP, blurred vision, and neovascular age-related macular degeneration.

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

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1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

IZERVAY must be administered by a qualified physician.

2.2 Recommended Dosage

The recommended dose for IZERVAY is 2 mg (0.1 mL of 20 mg/mL solution) administered by intravitreal injection to each affected eye once monthly (approximately every 28 ± 7 days) for up to 12 months.

2.4 Injection Procedure

Only 0.1 mL (2 mg) should be administered to deliver a single dose. Any excess volume should be disposed.

Prior to the intravitreal injection, patients should be monitored for elevated intraocular pressure (IOP) using tonometry. If necessary, ocular hypotensive medication can be given to lower the IOP.

The intravitreal injection procedure must be carried out under controlled aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum topical microbicide should be given prior to the injection.

Inject slowly until the rubber stopper reaches the end of the syringe to deliver the volume of 0.1 mL. Confirm delivery of the full dose by checking that the rubber stopper has reached the end of the syringe barrel.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure (IOP). Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay.

Each vial and syringe should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial and syringe should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter needle, and injection needle should be changed before IZERVAY is administered to the other eye. Repeat the same procedure steps as above.

Any unused medicinal product or waste material should be disposed of in accordance with local regulations.

3 DOSAGE FORMS AND STRENGTHS

Intravitreal solution: 20 mg/mL clear to slightly opalescent, colorless to slightly yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

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4.2 Active Intraocular Inflammation

IZERVAY is contraindicated in patients with active intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections may be associated with endophthalmitis and retinal detachments. Proper aseptic injection techniques must always be used when administering IZERVAY in order to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management.

5.2 Neovascular AMD

In clinical trials, use of IZERVAY was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (7% when administered monthly and 4% in the sham group) by Month 12. Patients receiving IZERVAY should be monitored for signs of neovascular AMD.

5.3 Increase in Intraocular Pressure

Transient increases in intraocular pressure (IOP) have been observed after an intravitreal injection, including with IZERVAY. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

6 ADVERSE REACTIONS

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

- Ocular and periocular infections
- Active intraocular inflammation
- Endophthalmitis and retinal detachments
- Neovascular AMD
- Increase in intraocular pressure

6.1 Clinical Trials Experience

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

The safety of avacincaptad pegol was evaluated in 733 patients with AMD in two sham-controlled studies (GATHER1 and GATHER2). Of these patients, 292 were treated with intravitreal IZERVAY 2 mg (0.1 mL of 20 mg/mL solution). Three hundred thirty-two (332) patients were assigned to sham.

Adverse reactions reported in ≥2% of patients who received treatment with IZERVAY pooled across GATHER1 and GATHER2, are listed below in Table 1.

Table 1: Common Ocular Adverse Reactions (≥2%) and greater than Sham in Study Eye

Adverse Drug Reactions	IZERVAY N=292	Sham N=332
Conjunctival hemorrhage	13%	9%
Increased IOP	9%	1%
Choroidal neovascularization	7%	4%
Blurred Vision*	8%	5%
Eye pain	4%	3%
Vitreous floaters	2%	<1%
Blepharitis	2%	<1%

* Blurred vision includes visual impairment, vision blurred, visual acuity reduced, visual acuity reduced transiently.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of IZERVAY administration in pregnant women. The use of IZERVAY may be considered following an assessment of the risks and benefits.

Administration of avacincaptad pegol to pregnant rats and rabbits throughout the period of organogenesis resulted in no evidence of adverse effects to the fetus or pregnant female at intravenous (IV) doses 5.1 times and 3.2 times the human exposure (based on AUC) at the maximum recommended human dose (MRHD) of 2 mg once monthly, respectively.

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

Animal Data

An embryo fetal developmental toxicity study was conducted with pregnant rats. Pregnant rats received daily intravenous (IV) injections of avacincaptad pegol from day 6 to day 17 of gestation at 0.1, 0.4, 1.2 mg/kg/day. No maternal or embryofetal adverse effects were observed at any dose evaluated. An increase in the incidence of a non-adverse skeletal variation, described as short thoracolumbar (ossification site without distal cartilage) supernumerary ribs, was observed at all doses evaluated. The clinical relevance of this finding is unknown. Plasma exposures at the high dose were 5.1 times the MRHD, based on Area Under the Curve (AUC).

An embryo fetal developmental toxicity study was conducted with pregnant rabbits. Pregnant rabbits received daily IV injections of avacincaptad pegol from day 7 to day 19 of gestation at 0.12, 0.4, 1.2 mg/kg/day. No maternal or embryofetal adverse effects were observed at any dose evaluated. Plasma exposure in pregnant rabbits at the highest dose of 1.2 mg/kg/day was 3.2 times the human exposure at the MRHD, based on AUC.

8.2 Lactation

There is no information regarding the presence of avacincaptad pegol in human milk, the effects of the drug on the breastfed infant or on milk production.

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

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the total number of patients who received IZERVAY in the two clinical trials, 90% (263/292) were ≥65 years and 61% (178/292) were ≥75 years of age. No significant differences in efficacy or safety of avacincaptad pegol were seen with increasing age in these studies. No dose adjustment is required in patients 65 years and above.

17 PATIENT COUNSELING INFORMATION

Advise patients that following IZERVAY administration, patients are at risk of developing neovascular AMD, endophthalmitis, elevated intraocular pressure and retinal detachments. If the eye becomes red, sensitive to light, painful, or if a patient develops a change in vision, instruct the patient to seek immediate care from an ophthalmologist.

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

Manufactured by:
IVERIC bio, Inc., An Astellas Company. Parsippany, NJ 07054

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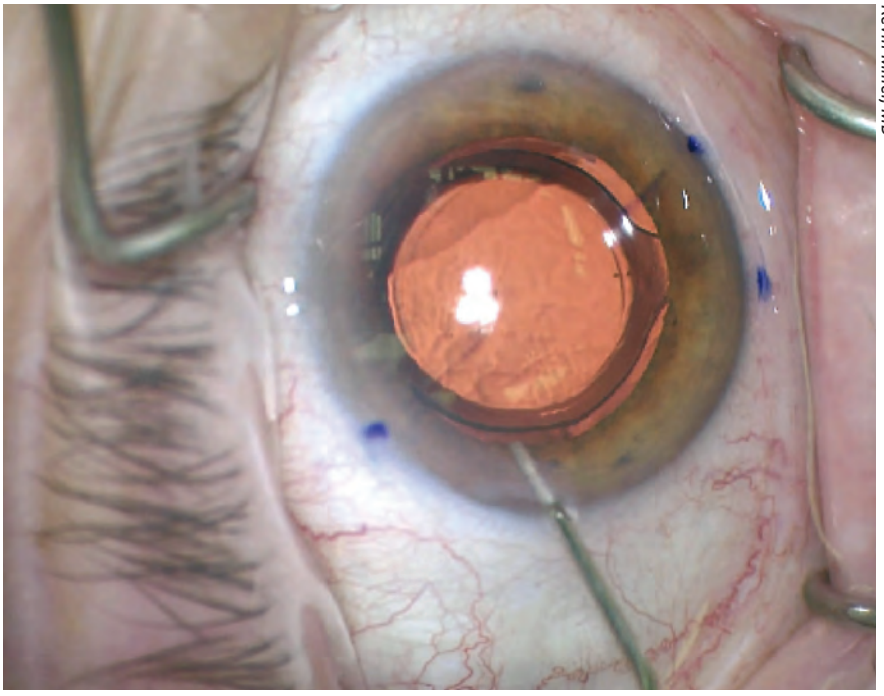

Kevin Miller, MD

Here, a surgeon aligns the toric lens with the steep axis of postop astigmatism.

(Continued from page 51.)

to have a refractive error, make sure to tell them that you have a plan for that, whether that's glasses or LASIK/PRK enhancements."

Setting Up for Success

Minimizing the chances for patient unhappiness begins on the front end. Catching potential issues early on will guide the discussion with the patient, helping to set realistic expectations.

"We rely heavily on Placido-disc or Scheimpflug imaging like Pentacam or Galilei to make sure the topography is nice and smooth," says James Loden, MD, who's in private practice at Loden Vision Center in Nashville. "One of the biggest things is making sure the patient doesn't have chronic dryness or irregular astigmatism. Then, we also look at an OCT of the macula in every potential premium patient. We don't like getting bushwhacked by unrecognized epiretinal membranes, lamellar macular holes, partial macular holes or anything that could cause potential distortion of vision. If the patient is paying $5,000 for a premium IOL, they don't expect you to miss a diagnosis and tell them after the fact that there's an issue. They want to know ahead of time, and it's much more effective to just not schedule the patient for a premium service than to have to refund them and go through that process afterwards."

Dr. Khandelwal says that meticulous preoperative biometry and keratometry will help avoid refractive surprises after cataract surgery. "We never want to use just one formula for refractive cataract patients," she explains. "We look at several formulas. The most important thing is to make sure you have good data going in, that your keratometry, axial length and other measurements are all reliable to avoid refractive error.

"Secondly, really assess and address astigmatism, especially against-the-rule astigmatism," she continues. "It's very easy to dismiss small amounts of astigmatism and implant a non-toric premium lens, but if you're going to end up leaving residual, against-the-rule astigmatism, you may want to go ahead and take the extra step to put in a toric presbyopia-correcting lens. It certainly isn't costing the patient any more money or your practice any more money, but it can really affect the outcome. Try to minimize the astigmatism to less than 0.5 D."

Anatomic Issues

Diffractive lens optics have very complex wavefronts that are easily affected by ocular pathology and astigmatism. "Multifocal lenses have diffractive steps that create in-phase and out-of-phase light patterns," Dr. Safran explains. "Anything that scatters light, such as dry eye or corneal guttata, will disrupt the quality of vision with these lenses."

Ocular pathology that goes unidentified preoperatively or crops up postoperatively is often a cause for patient unhappiness. Here are some issues to watch out for:

• ***Dry eye.*** "Dry eye is very common and needs to be addressed before surgery," Dr. Khandelwal says. "Put the patient on a regimen that works for them to improve their ocular surface and be sure to counsel the patient that they may need to remain on this regimen for life in order to get the best quality of vision from their lenses. It's very important to set the expectation that something else is going to affect their vision.

"Postoperatively, if they develop ocular surface disease, it's important to determine whether it's aqueous deficiency, evaporative dry eye or a combination of the two to tailor treatment," she explains.

Punctal plugs, artificial tears, Tyrvaya nasal spray, Restasis, Xiidra, steroids and immunomodulators are a few options. "Thermal expression can be done in the office to help patient outcomes," she says. "Ideally, you should diagnose and treat them before surgery."

• ***Anterior basement membrane dystrophy.*** Like dry eye, one of the challenges with ABMD is that it worsens after cataract surgery. "Patients who didn't know they had

ABMD are going to be very unhappy if it worsens after surgery," Dr. Khandelwal says. "For the best outcome, you may want to treat the ABMD with a superficial keratectomy or medical management ahead of time."

• ***Lid problems.*** Some patients complain of tearing after cataract surgery. Dr. Khandelwal says to look carefully at the lids to ensure patients don't have mild ptosis, inferior lagophthalmos or conjunctivochalasis. "Some of those can worsen a bit after doing any procedure that opens up the eyelid," she notes.

• ***Irregular astigmatism.*** "Irregular astigmatism is a pain," Dr. Miller says. "Most patients don't want to wear rigid contact lenses to hide the irregularity. Sometimes we can put them on miotic drops to pinhole the pupil, so they don't see as much of their irregular cornea, but many patients don't want to put drops in every single day to reduce their pupil size because the surgeon didn't identify their irregularity ahead of time."

• ***Prior RK or LASIK.*** "I'd discourage multifocal lenses in any patient with prior radial keratotomy," Dr. Loden says. "These eyes have a tendency to be very unpredictable and the vision fluctuates a lot. They also tend to have a lot of higher order aberrations that interact with the multifocal lens. I'd be cautious in post-LASIK eyes as well. If the patient has a lot of spherical aberration or any residual astigmatism or de-centered ablations, definitely don't put a multifocal lens in. These patients will be difficult to satisfy."

• ***Retinal pathology.*** Lamellar holes, retinitis pigmentosa, obvious diabetic retinopathy, anything beyond mild macular degeneration and epiretinal membranes involving the fovea will result in poor vision quality with premium lenses. "I repeat the OCT of the macula because sometimes there's subtle macular edema or subtle worsening of an epiretinal membrane that you want to make sure to catch," Dr. Khandelwal says.

What's Holding Premium Lenses Back?

Kevin Miller, MD, a professor of clinical ophthalmology and the Kolokotrones Chair in Ophthalmology at the David Geffen School of Medicine at UCLA, says, "The industry complains that we aren't growing the premium market, that it's been stuck at a pretty low level for a long time. There are a couple reasons for that.

"One is that physicians who haven't trained in the refractive arena or haven't done oculoplastics just aren't comfortable having the money talk and charging patients for services," he says. "That's always been covered by insurance, so it's difficult for a lot of physicians and many just avoid the whole thing by not offering premium services to patients.

"The second thing holding doctors back is that after their first few premium lens cases they also get their first unhappy multifocal or EDOF patient," he continues. "These patients consume so much of the surgeon's time, and the surgeon may say, 'Forget it. It's not worth it. I'm just going to stop' because they haven't thought through all of the scenarios for when these patients come along.

"These patients are in your regular practice too, but when you throw cash into the mix, patient expectations become much higher," he explains. "You take the patient and turn them into a consumer. It's a completely different mentality. Patients have problems that you fix. Consumers are looking for a good financial deal. They want whatever it is to be perfect, or they want their money back or they want to trade it in. It's a new attitude that you have to grapple with as a physician who isn't used to dealing with patients as customers."

• ***Capsular wrinkles.*** "Capsular wrinkles or opacities are very common causes of patient unhappiness," Dr. Miller says. "When the refractive error is good and almost no glasses prescription is needed, and the patient still isn't happy, most of the time there's some wrinkling in the capsule behind the lens implant. I tell those patients that the wrinkles may pull out over time or may get worse over time, and either way we have to wait until the capsule locks on and is holding the lens implant securely before we can address it. Bring the patient back six months later to reassess and then you may ultimately perform a laser capsulotomy."

• ***Neuralgia.*** Many patients have subtle neuralgias from the incision. "Anytime you make a cut in the cornea, you're cutting through nerve endings, and those nerve endings don't always regenerate normally," Dr. Miller says. "So, patients can get a kind of funny feeling at the incision. Sometimes it's just a matter of hand-holding the patient through the recovery phase, which may take several months."

• ***Neurological problems.*** In particular cases, if there's any question of atrophy of the nerve or glaucoma, Dr. Loden looks at the nerve as well to make sure there's nothing neurological affecting the outcome.

• ***Loose zonules.*** "This is an example of what's called a 'potentially problematic condition,' where you could probably get away with it but down the road, it may not go so well," says Dr. Miller. "A patient with loose zonules and pseudoexfoliation, for example, may have a perfectly centered lens for a few years but over time the lens may start to decenter and so will the quality of vision. In this case, it'd be wiser to go with a monofocal lens, so that if the lens does decenter down the road, the vision won't degrade nearly as much as with a multifocal, which is heavily dependent on centration."

• ***Interocular pathology.*** Eye misalignment, for example, may point to a poor premium candidate from the outset. "A cataract patient with good potential vision, no ocular pathology but eye misalignment might have great distance vision in both eyes or multifocality but when they use their eyes together they'll have double vision, requiring prism glasses," Dr. Miller says. "Since they'll need glasses anyway, why not just give them progressives with prisms?"

When It's the Lens

It's important to distinguish ana-

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tomic issues from lens-related issues when figuring out why a premium patient is unhappy. "If a patient has a multifocal and they're unhappy with glare, halos and their quality of vision, and they say to me, 'I don't mind wearing glasses,' then obviously, the multifocal wasn't the best lens choice for the patient," Dr. Safran explains. "Then you have to look at the risks associated with a lens exchange.

"Each lens has its own little bag of issues that you'd expect to hear," he continues. "If a patient comes to me with a PanOptix, and they're complaining of glare and halos, those are reasonable things for someone with a trifocal to experience. If a patient has a Symfony EDOF, and they're complaining about starbursts, that's also reasonable. If, on the other hand, they're complaining about quality of vision with the Symfony, then that's unlikely to be a lens-related issue, so it may be something else."

Dr. Loden says his practice uses the Visiometrics ocular scatter index to assess the lens's modulation transfer function. "Much of the time you'll find that these eyes are highly aberrated and the quality of vision that the patient is reporting is indeed very poor," he says. "If you don't have a pathologic reason for why that's occurring, it's probably the optic of the multifocal lens. What we found is that for many of these patients, simply explanting the multifocal and exchanging it with a monofocal will dramatically improve the ocular scatter index and modulation transfer function."

Refractive and Lens-based Procedures

"The number one reason for premium patient unhappiness is refractive error," Dr. Loden says. "If the patient comes in saying they're unhappy with the quality of their vision, it's often undiagnosed refractive error—even as little as a quarter diopter.

"The average multifocal or trifocal patient will lose one line of vision for every quarter diopter of residual astigmatism," he explains. "So, you may have a patient who's +0.25 or -0.75, the spherical equivalent of that is really low, ±0.5 D, but the patient complains vociferously that they're unhappy with their vision. The issue is that many doctors ignore these very small amounts of astigmatism, but some patients just aren't happy with that, and the only thing that can treat that small amount is PRK or LASIK touch-up."

Dr. Loden adds that though his practice discourages self-referral consults, in those instances he performs rigorous testing that includes iDesign. "We do a manifest refraction based on our iDesign measurements, in addition to a comprehensive exam," he says.

Dr. Safran says that about two-thirds to three-quarters of the unhappy premium patients referred to him didn't have a good refractive outcome. "Nobody is going to be happy with a multifocal or EDOF lens where the refractive outcome is off," he says. "Autorefractors aren't always accurate with EDOFs. If the technician follows the autorefractor and puts that data into the phoropter, the patient's refraction may be off, creating a lot of problems. Very often I see a patient who's unhappy with their multifocal lens, and they're actually a +1 D refractive error rather than plano like the doctor thought. There's your answer to the unhappiness right there."

Dr. Khandelwal agrees that postoperative refraction must be done carefully in patients who had EDOF lenses implanted. "It's easy to say, 'Hey, they're 20/20. They should be happy.' But it's important to take the extra step to have your technician refract," she says. "Sometimes a little bit of astigmatism or plus power wasn't captured. Put a soft contact lens on the patient and correct some of that refractive error. If they're really happy with the outcome—I usually give it a bit of time and then repeat the refraction to make sure it's stable—then you can do a corneal refractive procedure on them later. That's one way to handle refractive errors."

"If it turns out that the patient has a refractive error, an easy option is to give the patient some glasses," Dr. Miller says. "Contacts are another option, but almost no one in the cataract age range wants to wear contacts because oftentimes their eyes are a little dry and it's just a hassle.

"Refractive options include PRK and LASIK," he continues. "They each have their pluses and minuses. PRK is kind of a painful procedure to go through, and it takes the older patients two to three months to settle down. It's not terribly predictable for small corrections. LASIK has a faster recovery, but in my experience there's a little more tendency for it to produce dry eye. That said, if you have to do an enhancement, it's much easier to do a LASIK enhancement than PRK. PRK requires scraping the cornea, which is uncomfortable in the recovery phase. SMILE isn't an option for enhancing cataract surgery because the corrections we're doing are smaller on average than what SMILE treats.

"Sometimes relaxing incisions are the best option," Dr. Miller notes. "They can be performed in patients with some mixed astigmatism, or maybe the spherical equivalent refractive error is zero or close to zero and the patient has some cylinder, and the status of capsular bag isn't important.

"For residual astigmatism after toric IOLs, if the capsular bag is intact and the patient isn't too far out from cataract surgery, toric IOL repositioning is a good option if the spherical equivalent refractive error is within 0.5 D of target," he continues. "If it's greater than 0.5 D, a toric IOL exchange may be the best approach."

Dr. Safran says he's quick to do a lens exchange since he does about four or five per week. "I'm very

BRIGHTER LOOKING EYES WITH ONE DROP

The Conversation Eye Care Providers Should Be Having with Patients

Melissa Toyos, MD
Practices at Toyos Clinic located in Tennessee, Mississippi, and New York

Aesthetics are an important patient concern that can affect how they feel about themselves and around other people. Patients commonly use products and services that promise aesthetic enhancement, including lash extensions, eyelash growth treatments, colored contact lenses, eye makeup, eye creams, and serums. Increasingly, patients also seek out redness-relieving eye drops to improve the appearance of their eyes.

Ocular Redness: A Key Patient Concern

Demand is substantial: 4 in 10 sales in the over-the-counter (OTC) eye drop category are for redness relievers.[1] Because ocular redness is often caused by "minor" eye irritations, patients may not recognize it as a valid concern that they can discuss with their eye care provider (ECP) and are, therefore, not always professionally counseled on which redness reliever is best for them. Without their ECP's input, patients can sometimes lean on potentially unreliable sources, such as the store shelf, their peers, commercials, or the internet. Herein lies an opportunity to educate patients and guide them through the enormous ocular redness market while also addressing the root cause of their symptoms.

LUMIFY®: A Clinically Proven Approach to Treating Ocular Redness

LUMIFY® (brimonidine tartrate ophthalmic solution) 0.025% drops are indicated for relieving redness of the eye due to minor eye irritations.[2] Most redness relievers are α1- or α1/α2-adrenergic receptor agonists; α1-adrenergic receptor agonism constricts corneal arterioles, hindering oxygen delivery to the cornea, which causes rebound redness. Brimonidine tartrate, by contrast, is selective for the α2-adrenergic receptor, primarily constricting ocular surface venules, which do not affect ocular surface oxygen delivery and therefore is not associated with high levels of rebound redness.[3]

In 6 clinical studies with over 600 patients, low-dose brimonidine tartrate demonstrated a 1 minute onset of action, which persisted for up to 8 hours.[4] It had a favorable safety profile and, consistent with its mechanism of action, a low incidence of rebound redness (1.2%).[4,5,6] Adverse event rates did not significantly differ from control, and the most common adverse events in brimonidine-treated eyes were reduced visual acuity (4.0%) and conjunctival redness (2.6%).[5]

Opportunity for ECPs to Step In

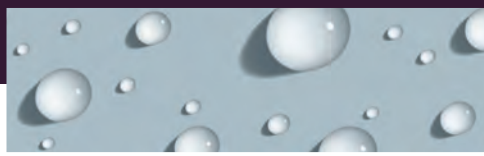
Market research indicates that patients report using of redness relievers an average of 3 days per week.[7] Ocular redness is a key concern for many patients, but the OTC eye care market contains an often overwhelming array of products. Understanding and communicating the benefits and challenges of available products is key to helping patients narrow down which products—out of everything on the shelf—might work best for them.

> **LUMIFY® provides safe and effective redness relief for my patients dealing with minor eye irritations**

LUMIFY® is a redness reliever drop differentiated in its mechanism of action, rapid effects, and minimal rebound redness. LUMIFY® provides patients with excellent redness relief. In recommending a product as efficacious and reliable as LUMIFY®, ECPs can establish themselves as trusted professionals who can address patients' needs—both clinical and aesthetic. This can lead not only to improved patient outcomes and satisfaction but could also enhance trust in their relationship with their ECP.

Incorporating ocular aesthetics into the patient conversation

- Ask patients if they are happy with how their eyes look and feel
- Ask patients if they use OTC eye care products and if they are satisfied with them
- Consider that the aesthetic aspect of eye care may be just as important to a patient as the clinical aspect
- Be ready and willing to provide OTC recommendations



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7. Data on file. Bausch & Lomb. Rochester, NY

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comfortable doing lens exchange," he says. "One thing you don't want to do is dig a deeper hole and make it harder to deal with the patient's problems by say, doing LASIK over the lens they have. If they're not happy with the lens, I'd rather take it out before I double down. Sometimes the lens is tilted or dislocated, and then a surgeon does LASIK over it, compensating the cornea for a problem with the lens."

"If you think the patient isn't tolerating the lens because of dysphotopsias, glare, halo or streaking at nighttime, avoid doing a posterior capsulotomy until you're absolutely sure that the lens is going to stay in the eye forever," Dr. Khandelwal advises. "It can certainly be done, but it's going to make your life much more complicated if the patient has an open posterior capsule."

Pricing Additional Services

If the patient requires an IOL exchange, be sure to work out in your practice how you'll address the return to the operating room, says Dr. Khandelwal. "A corneal refractive procedure such as LASIK or PRK is a bit easier when it comes to the finances, but for patients who need to go back to the operating room, you have to consider their deductibles and how you're going to replace the lens. You want to have a plan in place before your first challenging case. If you're putting any sort of IOL in, you should know how to take one out. IOL exchanges can be very helpful for some of these refractive surprises."

If the toric is off alignment, Dr. Loden takes the patient back to the OR for free. "We own our own surgery center facilities, so we take the patient back and re-rotate it," he says. "That's part of our process, though it's very rare because our laser platform [Lensar] integrates with our topography system. It uses real-time iris recognition to mark the axis of astigmatism on the posterior capsule, so we can immediately see on postop day one if the lens is aligned on the capsular tags that are pre-marked by the laser. We can also see if the lens rotated over the last week, though lens rotation is rare nowadays."

Dr. Loden says that about 15 years ago, when his practice first entered the premium IOL business, they charged separately for the multifocal or accommodating lens and the LASIK or PRK enhancement procedure. "However, we found customers were really unhappy with that model," he says. "A few actually accused us of deliberately missing the IOL power so that we could charge them for a LASIK touch-up. Now we use a package deal where everything's included, from YAG laser to LASIK, PRK and dry-eye treatments.

"We've been doing that for many years now and it's been the best process for us, not trying to break it down," he continues. "If the patient has any questions about why our price is a little higher, we explain that it's an all-inclusive price. We're not going to come back and ask for anything more. What's included will get the patient across the finish line and happy with the outcome." He adds, "We've been quite successful with the Light Adjustable Lens for some of these complex eyes that didn't do well with multifocals but wanted to be dialed in to 20/20 vision."

Dr. Miller's practice offers a service called postoperative refractive enhancements. "It's like an insurance plan," he explains. "The patient has the option to pay $500 for this, and if they need PRK or LASIK afterwards, it's already covered. Our costs for LASIK or PRK are much higher than $500, but they get it for $500. If they don't need it, then they've lost the money, like with typical insurance."

Pearls for Success

Cataract surgeons offer these tips:

• ***Wait for preoperative unhappiness.*** "If you operate on a patient with a bad cataract, they'll be more likely to be happy with what you do for them," Dr. Safran says. "Many doctors are operating on people earlier, before they have significant cataract changes. Many are doing more refractive lensectomy. It's much easier to make a patient unhappy if they weren't unhappy to start with. I try to put off cataract surgery until I think the patient is hungry enough where the food will taste good. Waiting until they're unhappy is a good way to make them happy.

• ***Implant based on the probability of success.*** "I work in a mostly referral practice at the university where I see all the problems that occur in the community," Dr. Miller says. "I think it's really important not to push multifocals and EDOF lenses onto people who aren't good candidates for them. I've seen patients who have had radial keratotomy or PRK or LASIK getting multifocals. Sometimes they get lucky, and it works out, but I see ones where it doesn't work out. Then you have to ask, why did the surgeon do that?

"You want to implant based on the probability of success," he continues. "When you have a patient with prior refractive surgery, the odds of getting the lens power perfect aren't the greatest, so you're setting yourself up for disappointment.

"One of my pet peeves is that I see financial incentives biasing doctors' judgment," he adds. "Sometimes they get away with it and sometimes they don't. About half of my patients—and as a mostly referral practice I'm a little bit skewed toward patients with a lot of pathology—aren't eligible for multifocals or EDOFs, and another 80 percent of them don't need toric lenses. So, maybe a third of my patients overall are going to get a premium lens and the other two-thirds aren't. And that's okay."

• ***Handle the lens carefully.*** "It's important to never touch the optic," Dr. Miller says. "Leave the lens in the loading bay of the injector until it's ready for implantation."

• ***Don't mix and match multifo-***

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ophthalmic solution) 0.02%/0.005%

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cals. "Multifocals work best when there's binocular summation at distance and near," Dr. Miller says. "If the two lenses have different near focal points, this won't occur optimally. Patients will always prefer one eye over the other and blame the IOL in the poorer-seeing eye for any under-performance."

• ***Listen carefully and attentively to the patient.*** The doctor's body language sends an important message to the patient that can easily cancel out any spoken words. "You can't be looking at a computer or looking at studies," says Dr. Safran. "You have to actually look and listen to the patient. What are they complaining about? You want to get a feel for them, for what's bothering them, what the nature of their complaint is. Try to determine if it's a reasonable complaint or an economic issue. Or maybe they didn't really need surgery. Put everything together and then come up with a strategy to make them happy."

• ***Use trial frames to demonstrate potential visual outcomes.*** "It's really hard for patients to understand what their vision could look like after enhancements in a phoropter setting, so I put their glasses prescription in a trial frame, put them in and let them walk around the office. I say, 'This is going to simulate what you'll be able to see after we do an enhancement procedure.' I tell them to look at magazines, walk down the hall, walk out the door, walk around outside to simulate real life. If this looks good, then I tell them we can probably solve their complaint with LASIK or PRK. If it doesn't solve their problem or other issues, then it gets a little more complicated.

• ***Don't overlook the contribution of the vitreous.*** "The vitreous itself is often cloudy and degenerative, and that disrupts the wavefront of a multifocal or diffractive lens much more," Dr. Safran says. "Very often, a vitrectomy will help these patients, and you don't necessarily have to do a lens exchange."

He adds that listening carefully to how the patient describes their vision can clue you in to vitreous problems. "Are they describing something that's constant or does it vary?" he asks. "They may say things like, 'It's cloudy but not always cloudy' or 'If I look to the left or right, it's not as cloudy' or 'It's like a cloud that passes in front of me.' "

> **Let the patient know that there's a plan in place and that you'll stick with them. The worst thing you can do is abandon the patient.**
>
> ***— Kevin Miller, MD***

"Sometimes the patient complains about their vision but doesn't see a lot of floaters," Dr. Khandelwal says. "Not every case will require vitrectomy. I often counsel patients about these worsening vitreous floaters and let them know that if the floaters are still causing problems in six months to a year, I'll refer them to a retina specialist."

• ***Sometimes a refund is the best option.*** "When you reach an impasse where you aren't going to find a resolution, sometimes the cheapest thing is refunding the patient," Dr. Loden says. "Sitting and having 20 postop visits with one patient in a calendar year isn't an efficient use of your time. Sometimes it's just better to move on, refund the patient, put a monofocal lens in and say, 'We tried.'"

• ***Let the patient know that they don't need to feel rushed into decisions.*** "Sometimes when you meet a patient for the first time, they're already scheduled for surgery," Dr. Khandelwal says. "If you're finding that the preop is taking a lot more discussion than you anticipate, it may be time to say, 'Let's hold off on surgery so you can do some reading and think it over more.' One of the challenges I see with unhappy multifocal patients is that they didn't feel like they had time preoperatively to understand the lens options, so afterwards they're very surprised by some of the side effects they're experiencing from the lens."

When it comes to lens exchange referrals, Dr. Safran says feeling rushed is another source of patient unhappiness. "Many patients are under the impression that the lens has to come out within a month or three months or six months, and they feel rushed," he says. "They feel this urgency. I tell them that there's no rush—we can take the lens out after a year or two years or even five years. I let them know that I'll get the lens out and that they can take time to think about it. They can even try glasses first. That often helps a lot, just letting them know that.

"Other times unhappy patients come to me, and their second eye is already scheduled, and they weren't happy with the first eye," he continues. "I say, 'Let's get the first eye where you can live with it before you get the second eye done.' A lot of doctors want to get that second eye done right away, when the eyes will work better together, but I think this makes many patients nervous."

Ultimately, whether it's refractive error or pathology that's causing patient unhappiness, surgeons say the patient needs to feel like they're part of the team. "Patients need to know that you're looking for an approach that will help improve their vision," Dr. Khandelwal says. "They want their complaints heard, and they want to know that you're not going to abandon them or give up on them." ◀

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TARSO-CONJUNCTIVAL FLAPS FOR SEVERE KERATITIS

This technique can rid the eye of the infection and help preserve vision in severe cases.

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A sclero-keratoplasty is a surgical procedure that can be used to preserve the eye in the setting of bacterial keratitis with scleral extension. In cases of severe scleromalacia in the setting of infectious keratitis, large donor grafts may be used to excise persistent keratitis and preserve ocular function. In cases of severe bacterial keratitis, a tarso-conjunctival flap may help aid in scleral coverage, by providing conjunctiva and a blood supply to assist with surface repair and healing.

Here, we describe two cases in which a tarso-conjunctival flap is used in conjunction with a sclero-keratoplasty to treat scleromalacia in the setting of bacterial keratitis and in the setting of endophthalmitis.

Infections and Sclero-keratoplasty

Bacterial keratitis, an acute or chronic infection of the cornea, has a reported incidence of 28 per 100,000 in the United States and an increased incidence of 130 per 100,000 among contact lens wearers.[5] Though the leading cause of bacterial keratitis is prolonged use of contact lenses, possible underlying factors consist of ocular surface diseases, corneal trauma, use of immunosuppressive medications and postocular surgery.[2] Topical antibiotics are the mainstay of treatment with consideration of systemic antibiotics in severe infections. In cases of corneal thinning or perforation, the physician can attempt corneal gluing.[3] For deeper perforations, a small or large diameter patch graft may be used based on the size, depth and location of the ulcer. In instances involving scleromalacia, sclero-keratoplasty has shown to be a successful surgical intervention for patients.

While the use of sclero-keratoplasty has proven to be an effective method in repairing corneal defects, it's been associated with rejection and, most notably, post-keratoplasty infectious keratitis. PKIK typically involves infection stemming from gram positive bacteria and fungi such as *Candida* spp. Risk factors include topical corticosteroids, suture-related problems, ocular surface diseases and previous corneal infection.[11] Although infection may further complicate recovery, patients with PKIK and rejection are often good candidates for corrective procedures such as Descemet's stripping automated endothelial keratoplasty and penetrating keratoplasty.

Sclero-keratoplasty may develop complications based on a number of factors, the most prevalent being graft size. In comparison to small grafts, larger sized corneoscleral grafts were observed to have higher incidences of intraoperative complications and postoperative problems such as issues with sutures, graft failure, graft rejection and the development of secondary glaucoma.[13]

Medical interventions to improve outcomes of sclero-keratoplasty appear to be promising. Recently, there have been findings to suggest that during postoperative management, immunosuppressants such as mycophenolate mofetil (MMF) and cyclosporine may improve results of sclero-keratoplasty, with results showing significantly im-

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Dr. Alapati is a uveitis fellow at Northwestern University. **Dr. Miller O'Dell** practices at the Oklahoma City Veterans Hospital. **Mr. Morcos** is medical student at the University of Missouri-Kansas City. **Dr. Goins** is a professor of ophthalmology at the University of Kansas. **Dr. Sokol** is the interim chair of ophthalmology at the University of Kansas.

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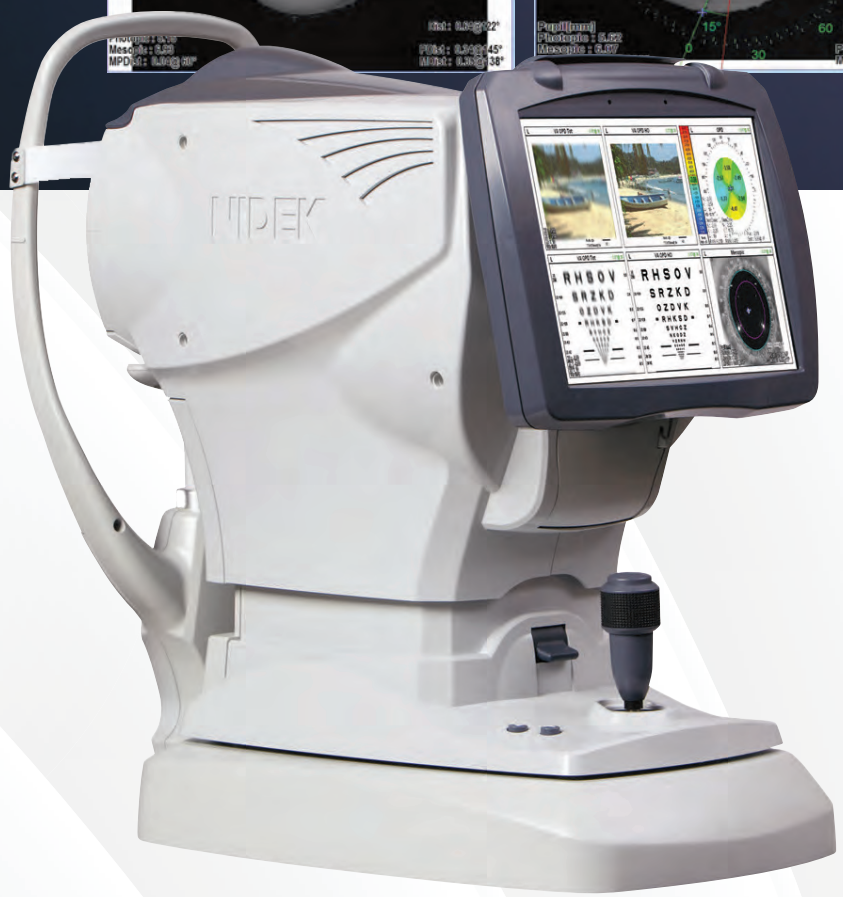

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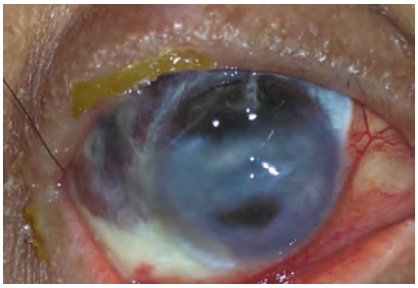
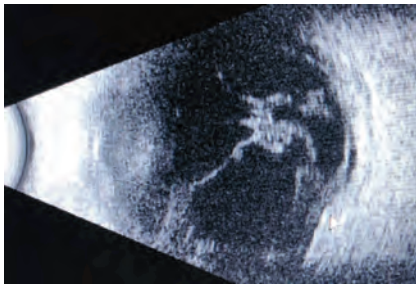
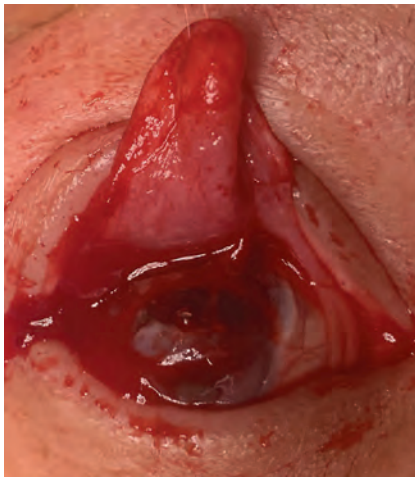


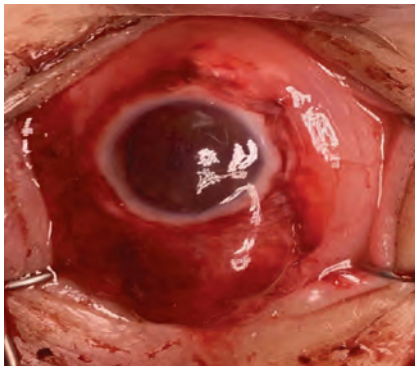
Case 1. Image taken at the preoperative examination. There is superior full thickness corneal melt which is plugged with iris and another smaller full thickness corneal melt just below the visual axis, also plugged with iris. Extensive scleromalacia is noted from 6 o'clock to 2 o'clock.



Case 1. B-Scan ultrasonography taken on preoperative examination. Vitreous debris still observed from initial presentation.



Case 1. Intraoperative photograph of the tarsal conjunctival advancement flap constructed during the procedure. This flap covered the area of scleromalacia from 6 o'clock to 2 o'clock.



Case 1. Intraoperative photograph of the completed sclero-keratoplasty with placement of a tarso-conjunctival flap.

proved rejection-free graft survival rates at one year postoperatively.[4]

With initial use in 1937, Hughes tarso-conjunctival flaps were first developed to correct full-thickness defects in the lower eyelid.[8] Most of the success is attributed to the blood supply offered by the upper lid. The use of the flap subsequently evolved into repairing full-thickness defects in the upper lid as well. Today, the flap's use has been expanded to surgical interventions for inflammatory ocular surface disease. The main goal of flaps in these procedures is to recover the integrity of the corneal surface as well as to prevent gradual corneal ulceration and secondary infection. Patients additionally also experience pain relief, reduced drop burden and enhanced aesthetic appearance, which in many cases has replaced the option of invasive surgery or enucleation.[15] This case report describes the integration of a sclero-keratoplasty with a tarso-conjunctival flap in order to treat bacterial keratitis with extensive scleromalacia for an optimized structural outcome.

Case 1

A 55-year-old female with a medical history of ovarian cancer status post chemotherapy presented with a corneal ulcer of the right eye.

Her presenting illness began at an outside hospital where she was treated with Tobradex, Pred Forte and ketorolac for eye pain and clear discharge. Her symptoms progressed into pain, redness and purulent discharge for which she presented to the emergency room. Her past ocular history is pertinent for extended contact lens use and high myopia.

On clinical examination, a large epithelial defect measuring 10 mm x 6 mm with an area of central coagulative necrosis and extension into the superior sclera was noted. The A/C was deep and formed with a dense hypopyon. B-scan ultrasonography was performed and demonstrated vitritis, which was concerning for endophthalmitis.

For medical management, the patient was hospitalized and initiated on topical vancomycin 25 mg/ml per hour and tobramycin 14 mg/mL per hour. Due to her immunosuppressive state, a broad differential for underlying infectious agents was considered, and the patient was treated with systemic Levaquin for intraocular penetration. She demonstrated improvement with a resolving hypopyon and was stable for discharge.

Due to social circumstances, the patient then followed up in the clinic two weeks post discharge, though she had been compliant on the tapered antibiotic regimen. On exam, the eye appeared grossly quiet with no signs of acute infection. The anterior chamber, however, was flat with a corneal perforation. Due to the extensive scleromalacia from the 6 to 2 o'clock position, a sclero-keratoplasty with an adjunct tarso-conjunctival flap and possible amniotic membrane transplant was recommended.

Case 1: Surgical Management

Intraoperatively, a vascular flap from the tarsal conjunctiva was harvested first by everting the upper eyelid and using a #64 blade incision through the horizontal extent of the upper eyelid tarsal plate. This was then dissected posteriorly so as to create a pedicle flap which could be rotated into the correct orientation. Attention was then turned towards securing a full thickness scleral graft from the 6 to 2 o'clock position. A sclero-keratoplasty donor button was sewn into place. Interrupted sutures were used to secure the conjunctival hinge graft, using the pedicle flaps to ensure that the stromal side of the flap approximated the scleral patch graft. The pre-existing conjunctiva was also secured to the new scleral rim. The resulting stromal exposure of the su-

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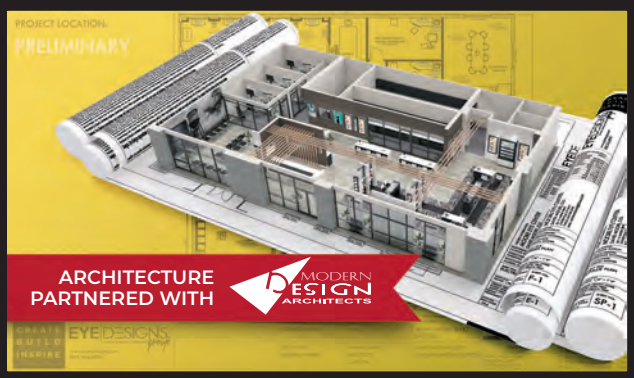

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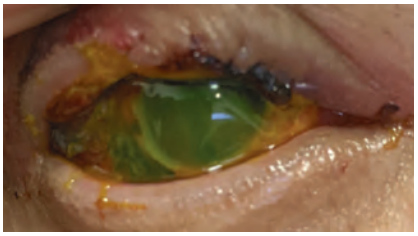
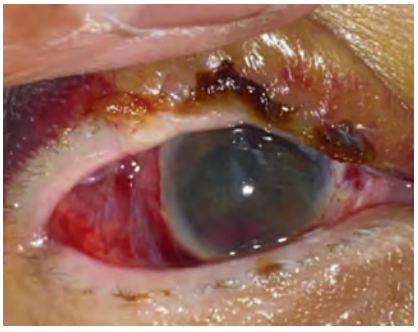


Case 1. External photograph of the right eye on primary gaze one day postoperatively. Anterior chamber is deep and the amniotic membrane is intact covering the surface.

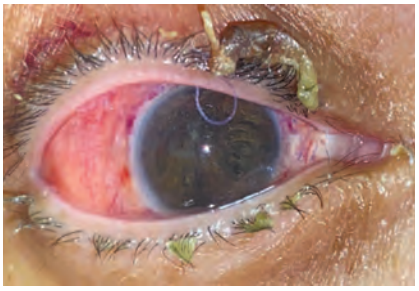


Case 1. External photograph of the right eye in primary position taken at one week postoperatively. The amniotic membrane has melted. Anterior chamber is deep with resolving anterior chamber hyphema.

perior bulbar conjunctiva was covered with an amniotic membrane, placed carefully to ensure that the basement membrane was in contact with the surface of the eyelid. An amniotic membrane was also placed over the sclero-keratoplasty, with the basement membrane this time facing towards the globe of the eye. A large contact lens was placed to serve as a barrier to prevent symblepharon formation.

Postoperative Follow-up

On day one of postoperative follow-up, the visual acuity was 20/200 with a normal intraocular pressure. The anterior chamber was deep and well-formed, and all wounds were Seidel negative. The patient was seen a week later when visual acuity was reduced to hand motion (HM), notably due to a hyphema and a pupillary membrane. At the one-month follow-up, vision improved to count fingers at the distance of 1 foot. The hyphema and anterior chamber reaction appeared



Case 1. External photograph of the right eye taken at one month postoperatively. The corneal surface is intact and the stroma is clear. Pupillary membrane was noted in visual axis. There's no sign of infection persistence.

to be resolved, however, the pupillary membrane was obstructing visual potential. Overall, the graft was intact and the cornea appeared clear.

Case 2

54-year-old female with history of Stevens Johnson syndrome (SJS) and complicated ocular history including placement of Xen gel stent with use of mitomycin C developed scleral melt following endophthalmitis. She developed pain, photophobia and injection of the left eye and on exam was found to have layered hypopyon with vitritis consistent with endophthalmitis. This was thought to be related to the Xen gel stent which had been placed nine months prior as she had a previous episode of endophthalmitis in the same eye.

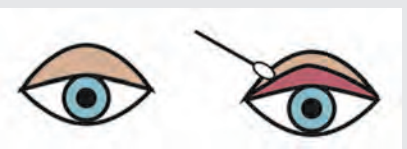
She was started on medical treatment including Vigamox and tobramycin every two hours, moxifloxacin 400 mg daily (although the patient refused to take this due to concern for SJS), Tobradex ointment as needed, and Durezol every two hours. She was taken that afternoon for removal of the Xen stent with vitreous tap and injection of 0.1 cc of vancomycin and 0.1 cc of ceftazidime. She also received subconjunctival injections of dexamethasone and cefazolin. The vitreous cultures didn't grow any organisms.

She was followed closely and over the following month the steroids and antibiotics were tapered appropriately. Unfortunately, at a follow-up visit one month after removal of the Xen gel stent, scleral melt was noted. A Kontour lens was placed and the Durezol and Vigamox were increased to four times daily. She was also started on valacyclovir 1,000 mg twice daily.

She continued to be followed closely, and was taken for amniotic membrane grafting to the area of scleral melt. However, within three weeks the amniotic membrane failed to produce

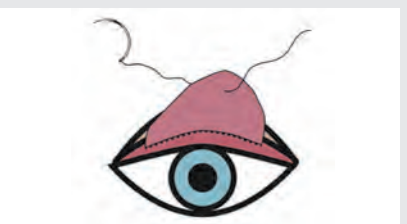
Surgical Diagrams

1) *Flip the lid*—upper eyelid was everted over a cotton-tipped applicator



2) *Begin incision*—#64 Beaver blade incision was made horizontally through the upper eyelid tarsal plate

3) *Dissect out conjunctival flap tissue*—flap was then elevated by dissecting the tarsus away from the levator aponeurosis across the horizontal extent of the upper eyelid



4) *Placement*—tarso-conjunctival advancement flap was rotated inferiorly via a pedicle conjunctival flap so that the stromal side could be placed directly onto the scleral surface, leaving conjunctival surface epithelium exposed

5) *Attachment*—tarsus was sutured to the globe after the cornea graft was fixated

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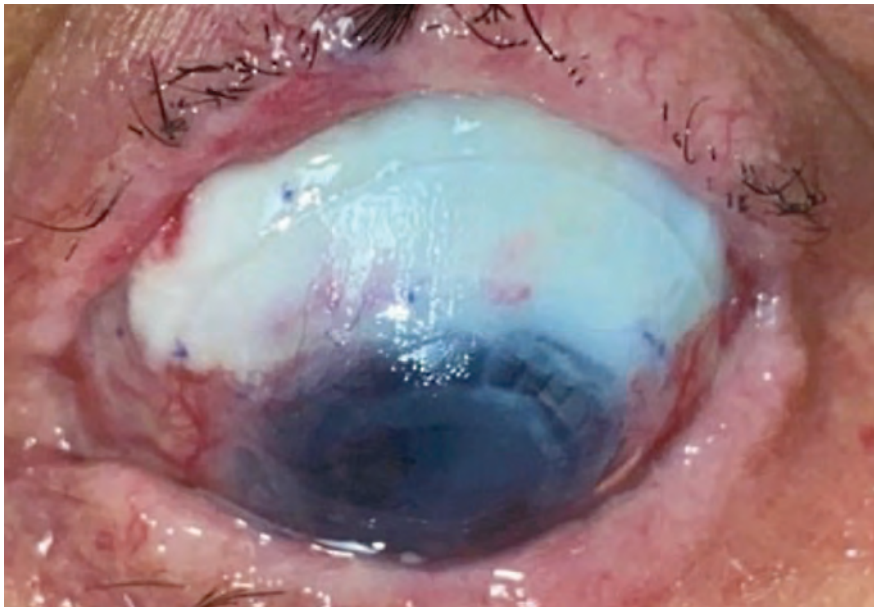

Case 2. Preoperative superior scleromalacia with avascular sclera and Kontour lens in place.

sufficient healing and an avascular area of scleromalacia was progressing. The decision was made to perform a tarso-conjunctival flap to promote healing.

Case 2: Surgical Management

The upper eyelid was everted over a cotton tip applicator *(See Surgical Diagrams on p. 70)*. A #15 Beaver blade was used to incise horizontally through the upper eyelid tarsal plate. A tarso-conjunctival advancement flap was created by dissecting between the tarsus and the levator aponeurosis across the horizontal extent of the upper eyelid. This was then rotated inferiorly onto the necrotic sclera and sutured into place. Amniotic membrane was sutured into place to cover the flap and was extended posteriorly into the fornix. This was further secured with Tisseel fibrin glue. A single tarsorrhaphy suture was placed to immobilize the lids and promote healing.

Postoperative Follow-up

On a postoperative-day-one telemedicine visit, the patient was doing well. However, a week later, the vision had decreased from hand motion to light perception and the flap had dehisced. Re-suturing was performed in the operating room the next day, and the flap remained secure.

Discussion

The use of a tarso-conjunctival flap has been quite impactful in ocular surface surgeries, allowing patients to experience improved healing. Although use is primarily indicated in non-infectious ocular surface diseases, application in bacterial keratitis with extensive scleromalacia can be beneficial. Use of a flap may reduce the size of the graft needed, thereby lowering failure rates of scelero-keratoplasty grafts.[13] In addition to reducing size, tarso-conjunctival flaps serve as a source of vascularized tissue for the cornea. Increased blood flow and lymphatics account for a remarkable increase in growth factors and cellular components that prime the corneal surface for repair. The result is an increased resistance to anti-collagenolytic substances that prevent subsequent stromal ulceration. With regard to inflammation, tarso-conjunctival flaps have further shown to prevent pro-inflammatory mediators from reaching the affected area, leading to decreased instances of stromal lysis.[1,10,12] Use of a tarso-conjunctival flap is of the utmost importance in instances where other conventional methods may not be possible. Although amniotic membranes have been shown to be largely advantageous in sclero-keratoplasty cases by substantially facilitating epithelial closure, they may not always be readily available.[9] In these circumstances, the use of a conjunctival flap can be used as a low-risk measure to facilitate healing and provide coverage to all scleral areas. ◀

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Up to 50% of patients with GD may develop TED, a separate and distinct disease which can progress if left untreated. Look out for the early signs and symptoms[3-6]:

- **Proptosis**
- **Diplopia**
- **Dry eyes**
- **Sensitivity to light**
- **Grittiness**
- **Pain or pressure behind the eyes**

If you identify new or changing signs or symptoms, consult with an eye doctor who specializes in TED right away.[1,7]

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HORIZON

EFFECTIVE APPROACHES TO IRIS REPAIR

Smaller defects can be repaired with sutures, while an artificial iris is better for larger ones, say surgeons.

MICHELLE STEPHENSON
CONTRIBUTING EDITOR

Patients with damaged or congenitally malformed irises can suffer from myriad conditions: severe photophobia; reduced vision; halo; and glare. However, newer surgical techniques and the advent of lifelike artificial irises can give these patients new leases on life. Here, experienced surgeons discuss the ways they approach these sometimes challenging cases.

Surveying the Damage

According to Michael E. Snyder, MD, who is in practice at Cincinnati Eye Institute, the first consideration when choosing between these treatment options is to assess the amount and type of iris damage. "Small defects are more easily repaired than larger defects," he says. "We also look at the quality of the remaining iris tissue. If there's a traumatic injury and only a small amount of iris tissue is lost out of the wound and the remaining iris tissue is normal, that's a pretty straightforward repair. If a lot of tissue is lost and/or the remaining iris is of poor quality, then it's much harder to repair, and an artificial iris may be needed," he says. Assessing both the iris stromal tissue and the degree of iris pigment epithelial loss is similarly important. If residual iris tissue has marked transillumination defects, the eye might look okay after a repair, but the patient may still be profoundly photophobic.

Recently, Dr. Snyder has also started considering patient age in the treatment decision. "That's another piece of the puzzle. I'm seeing some patients now who had their irises repaired using a cerclage suture a decade or two ago. A number of these patients are reappearing because the suture material has cheese-wired through the natural iris tissue. Then, the question about suture repair or prosthesis use includes whether the patient has a long horizon or, perhaps, a shorter horizon," he adds.

An additional factor is the status of the natural lens. "In a patient who has a normal, clear crystalline lens, we often try to defer doing anything surgically in the anterior segment. We can't put an iris prosthesis into a patient who has a natural lens still in place, and if we do a repair in the presence of a clear, normal crystalline lens, we might induce a cataract. In these cases, we might be much more conservative and try to manage the situation with optical means, like tinted specs or opaque periphery contact lenses as best possible. If patients have a cataract or a lens implant in place and a larger defect or poor quality of the residual remaining iris tissue, then a prosthesis becomes a wiser choice," he explains.

Dr. Snyder also stresses the importance of realistic patient expectations. "When we're doing iris repair or prostheses, the pupillary opening is a fixed size, usually about the size of the average pupil in normal indoor room lighting. It doesn't expand; it doesn't contract. So, in very dim lighting, it might be a little smaller than the fellow eye. In very bright lighting, it might be a little bigger than the fellow eye. The devices are custom-made so that they look much like the picture that we sent to [the company] of the fellow eye, and the matches are pretty good, but not perfect. I always tell my patients that the matches are like a cocktail-party match, meaning that with cocktail-party lighting and cocktail-party distance, it looks pretty good—especially after a cocktail," he says.

This article has no commercial sponsorship.

Drs. Fram and **Miller** have no financial interests to disclose. **Dr. Snyder** is a consultant for HumanOptics.

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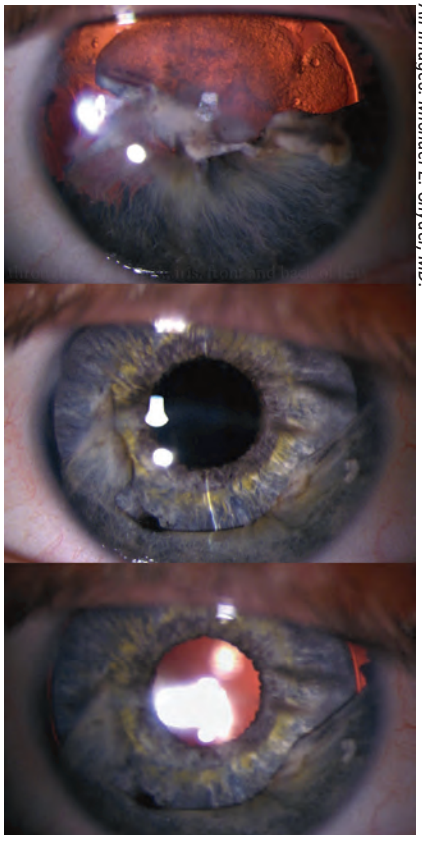
Iris Repair

According to Nicole Fram, MD, who is in practice at Advanced Vision Care in Los Angeles, if the defect is less than three clock hours, surgeons can attempt suturing the defect. "I use 10-0 Prolene, or polypropylene, and you can use many different needles," she says. "Ethicon makes a CIF-4 tapered needle that's very commonly used. It's nice because it's very sharp going through the iris, because it's tapered; however, the surgeon should exit the cornea through a paracentesis, as it can cause a leak in the cornea if it's primarily exited at the limbus. Or, you can use spatulated needles, such as the Ethicon CTC-6L or Alcon PC-7 needle. For iridodialysis repair, where the iris disinserts from the iris root, surgeons can use a straight needle like Ethicon's STC-6 needle that we bend a little bit or the CTC-6L (curved)."

Kevin M. Miller, MD, in practice at UCLA Health, agrees that the best suture for iris repair is 10-0 Prolene. "It's a little bit wiry and hard to work with, but it doesn't dissolve; it does a good job. And then there's just the matter of how to tie the knots," he says. "There are different techniques, which fall into three categories. The first category is the McCannel suture, which was first described by Malcolm McCannel, MD. The suture is passed through the defect, and then a paracentesis is performed. We make a cut in the peripheral cornea near where the iris defect is located, then pull the sutures up to the corneal incision, tie the knot there at the incision, and trim the ends of the suture. The knot drops back inside the eye after you cut the sutures.

Next is the Siepser sliding knot technique. With this technique, there is no need to pull the iris up to the incision. You can actually tie a slip knot outside the eye, loop it around a couple of times and pull the knot back inside the eye. There are a few variations on this approach, but they're basically the same.

The third technique was popularized by Ike Ahmed, MD, with intraocular tying instruments, like microsurgical



All Images: Michael E. Snyder, MD.

Figure 1. This patient had a corneal nail penetration through the visual axis, iris and lens into the vitreous cavity. Half of the iris tissue was lost (top image). Synechiolysis, capsule-preserving cataract surgery, removal of fibrous ingrowth, capsular tension ring placement and iris prosthesis placement eliminated the photophobia and restored a more normal body image, recovering 20/50 uncorrected vison and 20/30 with pinhole vision, despite the corneal scar (middle image). On transillumination, note the marked reduction compared to preoperatively. The capsular tension ring can be seen in the perimeter of the bag, just outside the edge of the iris prosthesis (bottom image).

tyers. The knot is tied inside the eye. It's like building a boat inside a bottle. All three techniques work, although some are easier to do than others. The technique we choose is based on the circumstance."

Dr. Fram says she uses the "Sharpie Pen" test for peripheral small iris defects to make sure iris repair will fix the symptoms. "Sometimes, there are small iris defects, like a laser peripheral iridotomy that was made too large, or it's properly sized but hitting the tear meniscus of the upper lid," she explains. "In that case, you can take a small marking pen and color over the cornea in the area of the iris defect and ask the patient if the symptoms improve. These iris defects can have symptoms consistent with ghosting or multiple images, so darkening the area or using an opaque contact lens to show the patient what it would look like if the defect was closed surgically is a helpful test before repairing the defect."

Transillumination defects are another common indication for small iris repair. This is commonly caused by iris prolapse during cataract surgery in the setting of intraoperative floppy iris syndrome. Postoperatively, surgeons will see transillumination defects where the posterior pigment of the iris sloughs off. "When the temporal iris is missing or damaged in that exposed region, patients can be very symptomatic and sensitive to light," Dr. Fram says. "In that case, we'll first put on an opaque contact lens to prove that suturing the defect with an imbricating suture would help. With an imbricating suture, you weave in and out of where the iris defect is, and you bunch up the tissue so that the transillumination defect is less. Sometimes, sectoral areas are missing, where the phaco has eaten up part of it, or they've amputated part of the iris because of severe prolapse during the case. These sectorial defects can also be repaired as long as they're less than two to three clock hours and the tissue is healthy."

Patients can also experience traumatic mydriasis, where the pupil sphincter muscle is damaged and isn't working anymore. For this condition, Dr. Fram uses a pupillary cerclage. "We weave in and out in the area where the sphincter muscle was functioning, and we use a purse-string approach to cerclage or close for 360 degrees," she explains. "Then, we tie the suture in a Siepser or Ahmed fashion. This procedure is probably technically the most difficult surgery I do. It requires you to be very fluent with your right and left hands, and it requires you to be very patient

2023 YEAR IN REVIEW

As practicing ophthalmologists, our readers have numerous demands on their time: patient exams; surgery; postop visits; and practice management duties, just to name a few. With so much going on, it's tough for busy physicians to keep up with every article we publish, or even to remember in which issue an interesting article appeared.

That's where our *2023 Year in Review* issue comes in. This digital-only 13th edition will include articles that run the gamut of ophthalmology topics, ranging from practical, how-to cataract surgery articles and tips for dry-eye management to expert takes on glaucoma, retina, pediatric ophthalmology and oculoplastics. After perusing our *Year in Review*, ophthalmologists can feel confident that they didn't miss out on anything important from 2023.

DETAILS:

- Digital-only 13th edition
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REVIEW of OPHTHALMOLOGY

After a highly successful launch with our 2022 edition (at right), we'll now accept ad placements when 2023's edition publishes this December.

while you're doing the procedure."

Artificial Iris Implantation

When the defect is too large to close with sutures, surgeons use an artificial iris. "We can close iris defects, like iridectomy-type defects, maybe up to 1.5 clock hours in size," Dr. Miller says. "The iris is pretty stretchy, and it will pull together if you do it right. But once you get above about 1.5 clock hours of defect, you can't pull it together; the sutures will cheese-wire through the iris tissue. In these cases or in cases where there are multiple defects in multiple locations, it's often just easier to implant an artificial iris device rather than having to deal with closing so many different defects. I implant many more artificial iris devices than I do suture repairs, but that's because other surgeons send their worst cases to me."

Only one artificial iris is currently FDA approved. In the United States, the HumanOptics ArtificialIris is distributed by VEO Ophthalmics in Cleveland. It was FDA-approved in 2018. "The artificial iris is an elastomer silicone implant that's color-matched to the other unaffected eye," explains Dr. Fram. "So, you take a picture of the eye that doesn't have the iris trauma. The patient then views and approves the picture, and then it gets sent to VEO/HumanOptics in Germany. They go through this incredible process of putting pigment in the elastomer that's color-matched to the native iris in the other eye."

According to Dr. Miller, there are two ways to place an artificial iris in the eye. "Surgeons can either place it with some kind of forceps, or it can be injected through a large injector, like a lens implant injector," he says. "Then, surgeons need to decide how to fixate the device inside the eye. There are two categories of fixation techniques: passive and active. With passive fixation, you're basically just placing it in there in some location where it's not going to move. The two passive locations where you can put the iris are inside the capsular bag and within the ciliary sulcus if there's good zonule support.

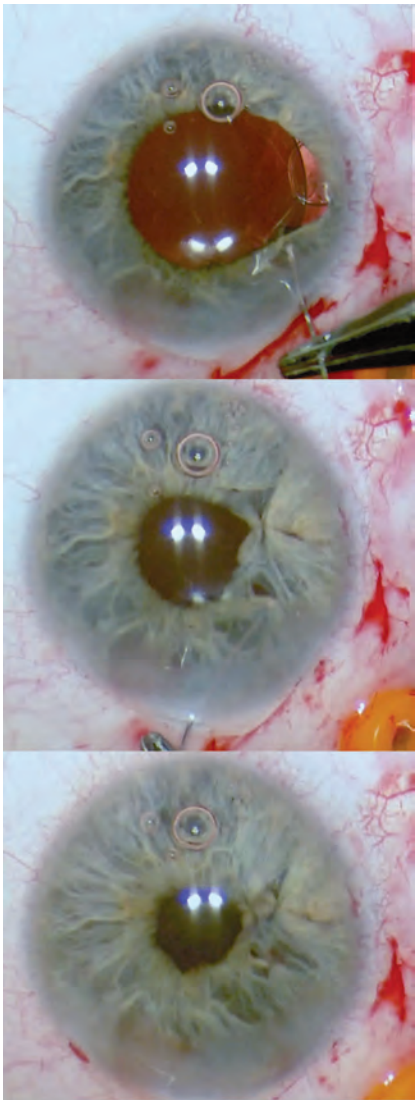

Figure 2. Iris sector defect repair with imbricating sutures at the start of the repair (top), after the first suture placement (middle), and after completion (bottom).

In all cases, the natural lens must be sacrificed. Patients who have a clear lens are ineligible for an artificial iris."

With the active fixation techniques, the artificial iris is secured with sutures. "The most common is suturing the iris to the sclera," Dr. Miller says. "You can suture the artificial iris to residual native iris tissue if you have enough and it's not too atrophic. We don't do much of that, but it's doable. You can suture the iris to a lens implant that you then suture to the sclera. We used to do a lot of that in the early days, when somebody needed an iris and a lens. But more commonly nowadays, if they need an iris and a lens, we either suture the iris and lens together, and then we suture the iris to the sclera, or we suture both independently to the sclera. You get four-point fixation rather than two-point fixation when you suture an iris implant to the sclera. Then, some surgeons suture the artificial iris to a lens implant, and then they Yamane the lens implant to the sclera. We don't know if this approach will stand the test of time."

Artificial irises can also be used in albino patients, which can be life changing. "Most of the time, albinos have no pigment at all," Dr. Miller explains. "Therefore, the light that enters the eye just scatters, causing fairly profound glare-like sensitivity issues. And in those patients, there's no pigment to stretch to cover any defect. In these patients, an iris prosthesis is a uniquely wonderful option."

Dr. Fram adds that there are some caveats to this technology. "Every patient should be consented regarding three major comorbid conditions: glaucoma; corneal edema; and retinal pathology (tear, detachment, cystoid macular edema)," she says. "Because these patients usually have trauma or a history of multiple surgeries, they have some secondary glaucoma to begin with and may need a filtering procedure in the future. Patients should also be consented that we'll need to check their retinas after surgery to make sure there are no retinal tears or detachments or cystoid macular edema. Then, patients need to be consented that the cornea could require an endothelial keratoplasty in the future. I always do endothelial cell counts and pachymetry, retinal nerve fiber layer, and macular OCT, wide-angle fundus imaging prior to surgery to counsel them about their risk profile prior to surgery."

She adds that the consenting process should be performed by the surgeon and not delegated, as patients need to understand that this may not be the last surgery that they have. "They need to know that it's a journey and that you'll be with them the whole way through," she adds. ◀

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Dear Resident Program Director and Coordinator,

We would like to invite you to review the upcoming 2nd-Year Ophthalmology Resident Wet Lab Programs for the 2023–2024 Residency Year in Fort Worth. These programs offer a unique educational opportunity for second-year residents. To better familiarize beginning ophthalmologists with cataract surgery, these programs will consist of both didactic lectures and a state-of-the-art, hands-on wet lab experience. Technology and technique will be explained and demonstrated and surgeons will leave better prepared to optimize outcomes and manage complications when they arise. The programs also serve as an opportunity for your residents to network with residents from other programs.

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

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

Registration Open: www.ReviewEdu.com/CSE2ndYr2023-24

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

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TREATING THE UNTREATABLE: HOW OPTOGENETICS WORKS

Restoring complete vision loss is one of ophthalmology's most ambitious goals. Learn how one concept could be changing the future of treatment.

ANDREW BEERS
ASSOCIATE EDITOR

Optogenetics is a modern technology that is just beginning to see real-world applications in health care. In ophthalmology, optogenetics can play a role in treating various diseases, from common cases to rare forms of vision loss. This article will examine the unique treatment and how it's being applied to ophthalmology today.

What is Optogenetics?

In 2005, Karl Deisseroth, MD, PhD, a professor at Stanford University, published his paper on optogenetics. Along with MIT professor Ed Boyden, PhD, they pioneered a novel concept to target and control cells in the biological systems of animals. Optogenetics is the combination of genetic and optical methods to achieve gain or loss of function of well-defined events in specific cells of living tissue.[1] Basically, optogenetics uses light-sensitive technology in the form of opsin proteins to deliver light into tissues, target the control tools to cells of interest and obtain compatible readouts and analyses,[1] allowing for diagnostic implications.

In ophthalmology, optogenetics aims to restore vision by replacing lost or dysfunctional photoreceptors by inserting opsins, or light-sensitive proteins, into the downstream retinal neurons that have no intrinsic light sensitivity.[2] Opsin genes are divided into two groups: microbial opsins and animal opsins. Microbial opsins derived from algae and other microorganisms are more widely used as optogenetic tools in neuroscience in order to impart light-induced membrane permeability to neurons.[2]

"There are more simple systems that you find mainly in microbial organisms," says Joseph N. Martel, MD, an assistant professor of ophthalmology at the University of Pittsburgh School of Medicine. "These are very rudimentary simple systems. Usually, light-gated ion channels that change the polarization of the cells. Then, there are more sophisticated systems in the mammalian system. For example, light sensitive G protein-coupled receptors that when activated by light, they initiate an intercellular cascade of signals that then change the intercellular dynamics and activate or deactivate the cell depending on the type of channel, or the type of opsin."

Channelrhodopsins (ChR), which are isolated from the green algae *Chlamydomonas*, were the first opsins to be identified as optogenetic tools.[2] Other opsin classes that have been used in ophthalmology treatments include halorhodopsin (HR), melanopsin (OPN4) and human rhodopsin (RHO).

For optogenetic vision restoration, adeno-associated virus vectors are used to deliver opsin proteins into the retinal cells. AAV is a non-enveloped virus that can be engineered to deliver DNA to target cells.[3] Optogenetic treatments in the current FDA pipeline use intravitreal injections to administer AAV vectors, but studies have shown that subretinal injections are also a viable option.[2]

Depending on the optogenetic therapy, the opsins used will function differently in the retina. "Most

This article has no commercial sponsorship.

Dr. Martel was principal investigator for GenSight Biologics' PIONEER trial. **Dr. Sun** has no financial interests to disclose.

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

Program Highlights Include

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

Dear Resident Program Director and Coordinator,

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

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

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

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

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

REGISTRATION IS OPEN NOW at www.ReviewEdu.com/PAASS2024

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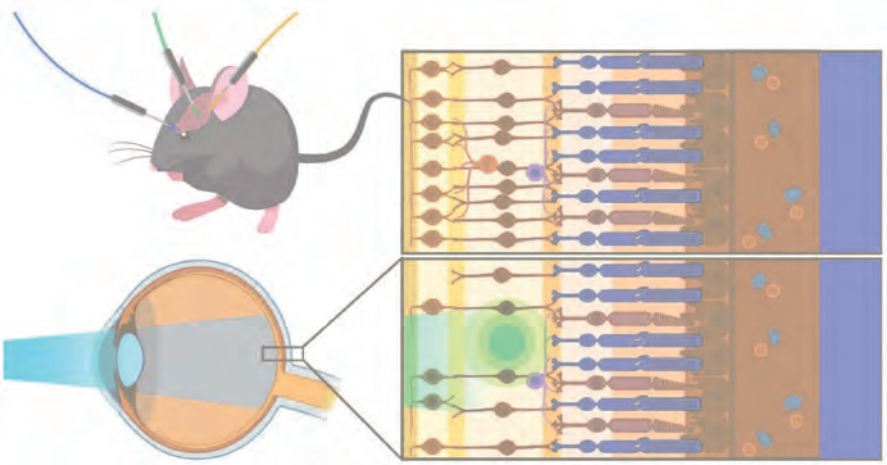

This mouse model represents how different opsin proteins are activated by specific wavelengths of light illumination. In this case, the blue light is targeting and activating the optogenetic molecules represented by the green indicator, but not the molecules represented by yellow indicator. Therefore, the blue light is at the appropriate wavelength for the green indicator and not the yellow indicator. Adapted from "Prosseda PP, Tran M, Kowal T, et al. Advances in ophthalmic optogenetics: Approaches and applications. Biomolecules 2022;8;12:2:269" under the terms of https://creativecommons.org/licenses/by/4.0/#.

of them target the retinal ganglion cells, but the multi-characteristic opsin, the MCO-010, targets the bipolar cells," says Dr. Martel. Furthermore, different opsin proteins will have different thresholds of light sensitivity. "There are other trials, like the GenSight PIONEER trial, that uses CrimsonR, which is a very simple opsin. That particular protein is only sensitive to a very narrow band of wavelength of light, which I think is around 580 to 600 nm," he continues. In this case, pharmaceutical companies, like GenSight, have developed medical devices to assist with vision restoration by adjusting light wavelengths.

Optogenetic therapy is currently being developed in ophthalmology for diseases leading to severe vision loss. The diseases at the core of optogenetic pharmaceuticals are retinitis pigmentosa, choroideremia and Stargardt's disease. Retinitis pigmentosa is a group of disorders that produce a gradual loss of vision, and it affects one in 5,000 people worldwide.[4] Choroideremia leads to the degeneration of the retinal pigment epithelium, photoreceptors and choriocapillaris, and it affects between one in 50,000 to one in 100,000 people worldwide.[5] Lastly, Stargardt's disease is the most common cause of juvenile macular dystrophy and it leads to the accumulation of lipofuscin in the retina.[6] It affects 10 to 12.5 per 100,000 people in the United States.[6]

"I think the last couple years have demonstrated an important milestone in establishing the proof of principle of optogenetics—of therapeutic optogenetics—for vision restoration, but there's still more that needs to be done," says Dr. Martel. "There are different diseases that play a role here and there's some phenotypic variation in which cellular components of the retina degenerate and which are relatively preserved. So, there may be certain opsins that are more advantageous. We need to fine tune which opsins are best under which circumstances."

Current Pipeline

The current FDA pipeline for optogenetic therapy features five novel treatments. These treatments are still undergoing trials for approval.

• ***MCO-010 (Nanoscope Therapeutics).*** According to Nanoscope, MCO-010 is being clinically developed to treat retinitis pigmentosa and Stargardt's disease. The optogenetic therapy has been granted Orphan Drug and Fast Track designation by the FDA for both diseases. This treatment is injected into the retina combining a multi-characteristic opsin protein with an AAV vector system to photosensitize bipolar cells allowing the retina to sense light again.

Currently, MCO-010 is undergoing two separate clinical trials, STARLIGHT and RESTORE, to find the safety and efficacy of treatment for retinitis pigmentosa and Stargardt's disease. Earlier this year, Nanoscope presented its key results from the latest Phase IIb RESTORE trial of MCO-010 for the treatment of retinitis pigmentosa. In the trial, 18 patients received a single injection of MCO-010 to treat severe vision loss due to RP. Nine other patients were administered a sham intravitreal injection.

Over a one-year time period, researchers measured efficacy using Multi-Luminance Y-Mobility Tests (MLYMT), Multi-Luminance Shape Discrimination Tests (MLSDT), and Best-Corrected Visual Acuity scores. According to the RESTORE trial, a two or more luminance level change for the MLYMT or MLSDT is considered clinically meaningful, and a 0.3 logMar change in BCVA is also considered clinically meaningful. For reference, MLYMT is a vision-guided mobility test and MLSDT is a near object recognition test.

RESTORE trial researchers reported that all MCO-010 patients showed vision improvement in the MLYMT, MLSDT or BCVA compared to five patients in the placebo group. Seventeen of the MCO-010 patients showed vision improvement in the MLYMT or BCVA compared to four patients in the placebo group. Also, 16 MCO-010 patients demonstrated a two or

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ABOUT RICK

Rick Bay served as the publisher of *The Review Group* for more than 20 years.
To those who worked for him, he was a leader whose essence was based in a fierce and boundless loyalty.
To those in the industry and the professions he served, he will be remembered for his unique array of skills and for his dedication to exceeding the expectations of his customers, making many of them fast friends.

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more luminance level improvement in the MLYMT or MLSDT compared to four patients in the placebo group. Researchers noted that these results are consistent with those observed in an earlier Phase I/II trial in which nine MCO-010 patients demonstrated clinically meaningful data in BCVA and the MLYMT or MLSDT measurements.

Recently, Nanoscope presented key results from its Phase II STARLIGHT trial of MCO-010 for the treatment of Stargardt's disease. This trial only recruited six patients with Stargardt's. Researchers measured systemic adverse events along with BCVA scores, MLYMT, MLSDT, and sensitivity measured by Octopus Visual Field Perimetry, which measures patient reaction time. During the trial, patients experienced clinically meaningful improvements in BCVA, they exhibited an approximately 3-dB gain in mean sensitivity, and high baseline MLYMT and MLSDT performances were maintained throughout the study.

Overall, Nanoscope reported that MCO-010 is well tolerated with no severe adverse events when treating retinitis pigmentosa or Stargardt's. Only one severe adverse event was reported in the RESTORE trial from the placebo group.

• ***GS030 (GenSight Biologics).***

> **"There are some simple systems that you find mainly in microbial organisms. These are rudimentary simple systems. Usually, light-gated ion channels that change the polarization of the cells."**
>
> ***— Joseph N. Martel, MD***

GS030-DP is being developed for the treatment of retinitis pigmentosa. The one-year results from the PIONEER Phase I/II clinical trial of GS030-DP were announced earlier in 2023. Nine patients were administered the optogenetic therapy with a follow-up of up to four years. According to GenSight, patients were divided into three cohorts, each receiving a different dose of GS030-DP (5e10 vg; 1.5e11 vg; 5e11 vg) via an intravitreal injection in the worst affected eye. A Data Safety Monitoring Board reviewed the safety data of all the treated patients and based on their findings, recommended selecting the highest dose (5e11 vg) for the expansion cohort in future trials.

Researchers for the PIONEER trial measured the safety and tolerability of the first three completed cohorts. The patients in each cohort reported only mild and moderate ocular adverse events where the most common adverse event was mild intraocular inflammation responses to corticosteroid treatment. According to the trial report, 70 percent of patients experienced inflammation.

"GS030 uses the CrimsonR opsin protein, which requires a higher stimulation threshold than you would find in the ambient light environment," says Dr. Martel. "There has to be a certain intensity of light." GenSight's treatment currently requires GS030-MD, a wearable device, designed as goggles, to assist with stimulating retinal cells.

"These goggles have a camera embedded in them that takes pictures of the visual environment," explains Dr. Martel. "Those pictures are then processed by various AI algorithms that are then translated into a beam of light within the goggles, which is projected through the pupil and onto the surface of the retina after the retina has been treated with the optogenetic therapy.

"That light is pulsed light and it's at the appropriate wavelength and intensity to activate the genetically modified retina that's expressing the photosensitive proteins in the retinal ganglion cells," continues Dr. Martel.

• ***BS01 (Bionic Sight).*** Since March 2020, 12 patients have been participating in the Phase

TABLE 1. CURRENT OPTOGENETIC THERAPIES IN THE FDA PIPELINE

Product	Company	Trial Stage	Notes
MCO-010	Nanoscope Therapeutics	RP: Phase IIb/III Stargardt's: Phase I/IIa	MCO-010 is designated for the treatment of retinitis pigmentosa and Stargardt's disease. It uses the MCO1 opsin with an rAAV2 vector to be intravitreally injected into the retina.
GS030	GenSight Biologics	Completed Phase I/II	GS030-DP is designated for the treatment of retinitis pigmentosa. It uses the ChrimsonR opsin with an rAAV2.7m8 vector to be injected intravitreally into the retina.
BS01	Bionic Sight	Phase I/II	BS01 is designated for the treatment of retinitis pigmentosa. It uses the ChronosFP opsin with an rAAV2 vector to be injected intravitreally into the retina.
RST-001	AbbVie	Phase I/II	RST-001 is designated for the treatment of retinitis pigmentosa. It uses the ChR2 opsin with an rAAV2.7m8 vector to be injected intravitreally into the retina.
KIO-301	Kiora Pharmaceuticals	Phase I/II	KIO-301 is designated for the treatment of retinitis pigmentosa and choroideremia. Top-line results from Phase Ib trial will be announced in November at the annual American Academy of Ophthalmology meeting.

I/II clinical trial for BS01, an optogenetic therapy for the treatment of retinitis pigmentosa. One year after the trial's initial start date, Bionic Sight announced that the first four patients who received BS01 adapted to see light and motion, and, in two cases, developed the ability to detect the direction of motion. Additionally, two patients who received lower doses showed more than a twentyfold increase in light sensitivity compared to their baseline sensitivity, while the other two received a dose three times higher and showed more than a hundredfold increase.

In April 2023, Bionic Sight released an update on the BS01 clinical trials stating that those who've received the highest dose of the therapy had the most vision restored. Patients have been given vision tests throughout the trial, especially after the four top responders gained the ability to identify shapes and objects. Bionic Sight reported that the success rate for identifying objects ranged from 80 to 100 percent for the top responders. Before treatment, patients' success rate was 25 percent when given four choices and 12.5 percent when given eight choices.

BS01 uses a ChronosFP opsin protein with an AAV vector to photosensitize the retinal ganglion cells. Similar to other optogenetic therapies, BS01 requires a device to be worn like a pair of glasses to properly transmit light to the retina. Bionic Sight states that its unique device produces neural impulses, similar to those produced by ganglion cells in a healthy retina, instead of enhancing the shape and intensity of the image.

• ***KIO-301 (Kiora Pharmaceuticals).*** Recently, Kiora announced the completion of the final patient's last endpoint from the ABACUS trial of KIO-301. Topline study results from the Phase Ib clinical trial will be reported in November at the annual American Academy of Ophthalmology meeting.

Prior to the trial, a total of six patients were enrolled, all with late-stage retinitis pigmentosa. Earlier this year, Kiora presented preliminary results from the ABACUS trial. They presented the results from a patient with no light perception and received a low dose injection of KIO-301 in one eye. The patient reported an improvement in the ability to perceive contrast between light and dark at days seven, 14 and 29 of the trial. They also reported an improvement in object identification and a positive impact towards their overall functional vision during everyday activities. Also, it was noted that the patient's initial dose was safe and well tolerated at day 29 without adverse events.

In addition to retinitis pigmentosa, KIO-301 is being considered for the treatment of choroideremia and other rare inherited retinal diseases.

• ***RST-001 (AbbVie).*** According to AbbVie, RST-001 was given Orphan Drug designation in 2014 and began Phase I/II clinical trials for the treatment of retinitis pigmentosa in 2015. This is an ongoing study and it's estimated to complete in September 2024. During the study, 14 participants will be measured, each over a six-month time frame. The primary outcome is measured by the number of participants with any Grade 3 or greater adverse event related to RST-001.

AbbVie says that the study is composed of two parts. The first part is to determine the expansion cohort for future studies. The second part of the study will focus on obtaining additional safety data at the highest tolerated doses as well as provide additional clinical data to aid in the design of future studies.

Other Applications

Although the developing optogenetic therapies are focused on severe forms of vision degradation, there are other applications in ophthalmology. For instance, researchers at Stanford University studied optogenetics as a mechanism to regulate intraocular pressure.

"It starts with a clinical question: What controls pressure in the eye? That's when we discovered this specialized structure called primary cilia," says Yang Sun, MD, PhD, a researcher and professor

A prototype design of GenSight Biologics' GS030-MD goggles. According to GenSight, the front of the product features a camera which captures the natural environment and sends a stream of images to a projector inside the device. A cable runs down the side of the device and connects to a processing unit with software that alters the images to the correct light intensity.

of ophthalmology at Stanford University School of Medicine. "In fact, primary cilia have actually been observed in the body for almost 40-plus years. The initial observation of the cilia in the eye was made in 1976, and then subsequently in 1982 and the 2000s. They were observed in the trabecular meshwork and Schlemm's canal," he continues. Primary cilia can sense aqueous humor flow, therefore this plays an important role in regulating IOP.[7]

"The idea behind the study was to use this optogenetic technique to regulate fluid flow in different parts in the eye," says Dr. Sun. The researchers' study used two modified plant proteins, cryptochrome 2 (CRY2) and CIBN, introduced to inositol polyphosphate 5-phosohatase (OCRL) to modulate IOP.[8] Direct exposure to blue light at a wavelength of 450 nm activated the dimerization of CRY2 and CIBN.[8] Since OCRL is located in the primary cilia and plasma membrane of the trabecular meshwork cells, the activated proteins target and modulate OCRL to increase outflow facility, which correlates with a decrease in IOP.[2]

Optogenetics continues to advance in health care and the future looks bright for the novel technology. "I think a lot of novel therapeutic vehicles may arise from this group of gene therapy approaches," says Dr. Sun. "Optogenetics certainly has great promise, and it will be fantastic to see it in clinical practice." ◀

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What to do with a White Cataract

The challenges to expect and tips for successful management of these complicated cases.

LIZ HUNTER
SENIOR EDITOR

The creation of a continuous circular capsulorhexis is key to any cataract surgery, and although surgeons can master this technique, there are some patient presentations that make it more tricky. White cataracts are one such situation. However, not all white cataracts are created equal, so a thorough understanding of the etiology will influence how to proceed with the surgery. We spoke with some experienced cataract surgeons who shared tips on techniques and tools that could make removal of white cataracts go more smoothly.

Approaching a White Cataract

White cataracts are often age-related and develop due to delayed treatment. They can also be caused by trauma to the eye. Studies have found traumatic white cataracts can contribute to the dysfunction of the epithelium, therefore leading to an increased risk of capsular breaks during surgery.[1]

"The term white cataract by name simply describes what it looks like," says Richard Davidson, MD, a professor of ophthalmology at the University of Colorado Sue Anschutz-Rodgers Eye Center. "It's a very dense lens inside the eye. It could be from a regular age-related cataract becoming too mature over time and therefore becoming more dense. It could be from trauma, prior surgery such as a retinal detachment repair or an injection that accidentally broke the lens capsule—all of those things can lead to white cataracts."

The approach will be a little bit different based on the etiology of the cataract. "You must determine the etiology and properly identify it," says Marjan Farid, MD, the director of cornea, cataract and refractive surgery at the University of California - Irvine School of Medicine. "Ask yourself: Is this a hypermature and centrally dense cataract that's been around a long time? These cataracts appear white and have a significant cortical component and centrally they may be very mature and dense.

> **"Complications can happen anywhere along the way and it starts with the capsulotomy. If you get a bad capsulotomy, the case automatically becomes more difficult."**
>
> ***— Richard Davidson, MD***

"Or is it a young cataract that developed after a trauma?" Dr. Farid continues. "If there was some kind of recent trauma to the eye, those cataracts can turn white very quickly, but those will often be very soft with milky, liquified protein built up within the capsule, forming an intumescent cataract. As the lens doesn't like to be touched, even subtle trauma to the eye or another ocular surgery can cause a rapid whitening of the cataract."

A significant amount of pre-surgical planning is necessary.

"The first thing you want to do is perform a complete eye exam and you really want to get a feel for what caused this cataract and what the vision potential is for the eye," says Dr. Davidson. "Does the eye have the ability to see? Sometimes that involves doing an ultrasound to see if the retina is detached and checking old records to see what the previous vision was just to try and figure out what was their best vision previously, and is there a chance of getting that vision back again."

Dr. Davidson says the surgery planning process should include a conversation with the patient. "I explain that this isn't a routine case and there's likely going to be a longer surgery, it's going to be something that's a little bit more complicated, and there's a chance that we might have to get a retina specialist involved," he says.

Dr. Farid also counsels her patients and tempers their expectations. "Anytime we have one of these very complex cataracts, especially if it's trauma related, I make sure to tell patients that we're going to do our best to remove their cataract safely, however, due to the uncertainty of capsule stability they may require a subsequent surgery," she says.

"Make sure that you've explained to the patient that this isn't what their next-door neighbor or family member had where they're in and out in

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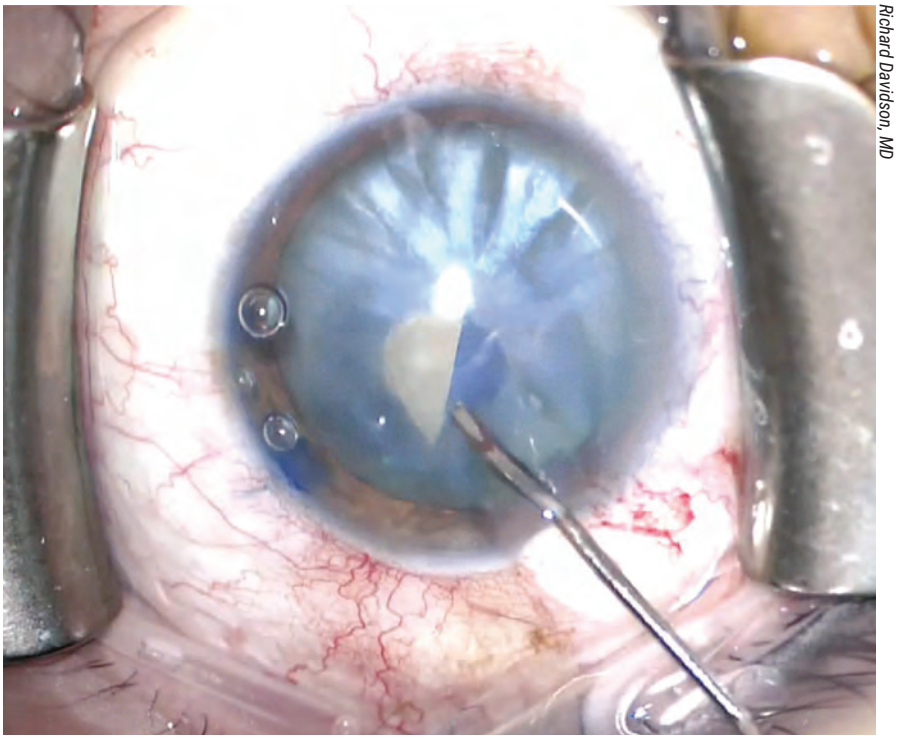
Dr. Chayet is considered a pioneer in refractive and cataract surgery, and is the medical director of the Codet Vision Institute in Tijuana, Mexico. He is a clinical investigator for RxSight, LensGen and ForSight Vision6.



Richard Davidson, MD

Experts say staining the capsule with trypan blue is essential for visualization with white cataracts and will help surgeons through the capsulorhexis step.

10 minutes," adds Dr. Davidson. "It could be 10 minutes, but it could be an hour, so you want to make sure that they understand that the chances of complications are higher. You want to document that conversation because that's really important."

Discussing IOL options takes some additional consideration. "IOL offerings depend on what you think the vision potential is for the eye," says Dr. Davidson. "Believe it or not, when I was a resident white cataracts usually meant poor vision potential—nowadays, there's some patients coming in with white cataracts who actually want multifocal lenses or other 'premium' options. They have good vision potential in the eye and you really have to sit and counsel them carefully, and sometimes it's hard to do because you don't know exactly what that vision is going to be."

Dr. Farid avoids multifocals if the cataract is trauma related and she's worried about zonular stability. "I'll also avoid toric lenses due to concerns about lining up the lens appropriately with the visual axis," she says.

Managing the Surgery

Now that the surgeon is ready to go to the OR, the available resources also play a role in how they proceed, adds Dr. Davidson. "Not every surgeon has a femtosecond laser or a Zepto device. You may be operating in a place that has just you and your hands and some basic instruments," he says.

No matter what's available, achieving a complete capsulotomy matters. "Complications can happen anywhere along the way and it starts with the capsulotomy. If you get a bad capsulotomy the case automatically becomes more difficult for yourself," Dr. Davidson says.

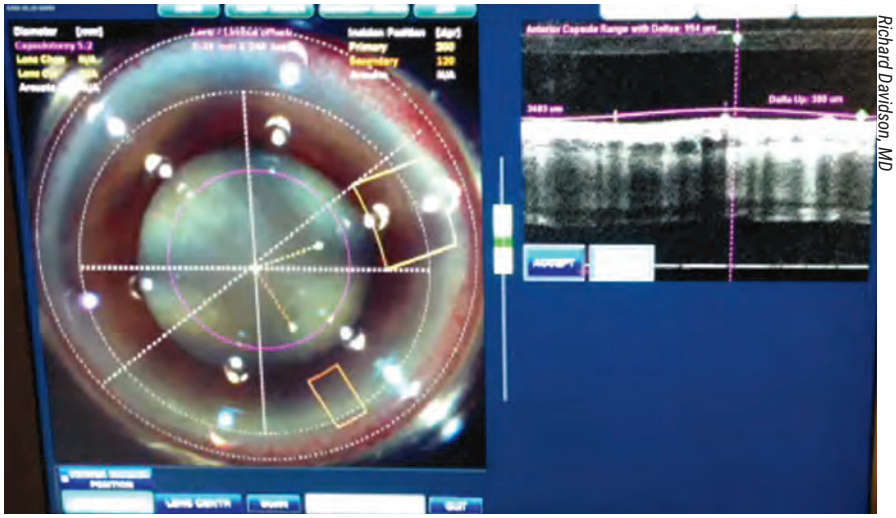
"If it's a white cataract, the longer it takes can be a little bit of a risk," he continues. "A femtosecond laser can be helpful to make the capsulotomy. From a capsulotomy standpoint, I do like the femtosecond laser. The problem is that some femtosecond lasers are faster than others. There are lasers that can do a capsulotomy in one second, and there are some that take four, six, seven seconds."

Dr. Farid says femto can help reduce one of the most notorious complications with white cataracts: the Argentinian flag sign. The Argentinian flag sign was named by Daniel Mario Perrone, MD, upon observation of a radial anterior capsule tear after it had been stained with trypan blue, giving it the appearance of blue and white stripes.[2]

"It's nice to use an ultra-fast laser because you potentially avoid the risk of capsular radialization and an Argentinian flag sign, which a manual capsulotomy can cause," she says. "If approaching the rhexis manually, you want to stain the capsule with trypan blue for better visualization. If it's a hyper-mature cataract and there's a lot of pressurized liquification of the cortical material within, then the original incision into the capsule can create a rapid radialization. To avoid this, you can go in with a needle on a syringe and as you enter into the capsule, you also withdraw the fluid to deflate that pressure rapidly and to prevent the radialization of the capsule. Once you deflate that capsular bag, then you can carry on with your capsulotomy."

Recovery from the Argentinian flag sign is possible, continues Dr. Farid. "If a capsular radialization is encountered, usually the tear doesn't go completely around the lens and therefore a gentle approach to removing the nuclear material is imperative," she says. "A gentle hydrodissection, minimizing any stress on the remaining capsule is critical. Chop techniques become very important. You want to direct all your forces centrally rather than outwardly where you can put stress on the zonules or put more extension on that radialization. If you can keep your forces central and gently bring out those nuclear segments into the anterior chamber and away from that capsular bag, then you can successfully complete a case of an Argentinian flag and even successfully put a three-piece lens into the sulcus."

Technologies continue to evolve to assist with the capsulotomy step of cataract surgery. Dr. Davidson says the Zepto device (Centricity), which



Richard Davidson, MD

Some surgeons favor using a femtosecond laser when presented with a white cataract due to its speed and accuracy in creating a capsulotomy.

creates a 'precision pulse capsulotomy' (PPC) in only 4 milliseconds, can be a helpful tool. "That can be really helpful in white cataracts specifically because the problem with white cataracts is that often the capsule is under pressure from fluid beneath the capsule, and the capsulotomy can be very challenging," he says. "With devices like Zepto, which deliver pretty much instantaneous bursts of energy, you can get a nice capsulotomy very quickly and in a safe manner."

One retrospective study,[3] which was authored by co-founder/consultants for Centricity, compared manual capsulorhexis in 15 cases with white cataract to 20 cases of PPC with white cataract. It showed PPC created a complete capsulotomy without tags or tears in all 20 cases. It also reduced the use of trypan blue and OVD, resulting in shorter overall surgery time.

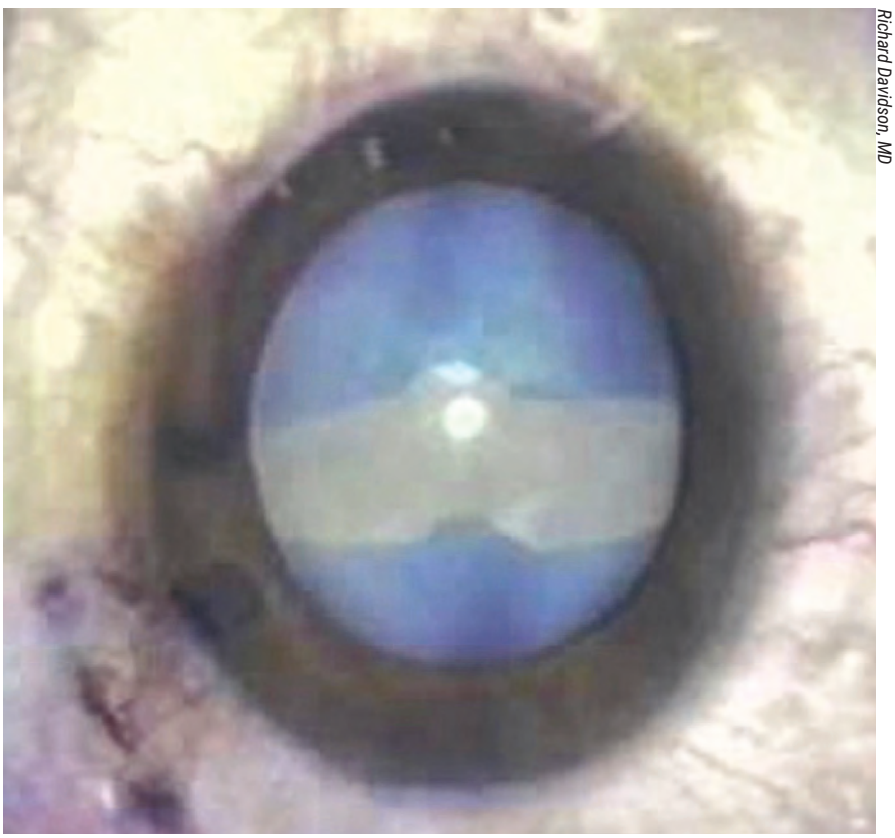
Challenges to Expect

Depending on how dense the lens is, lens disassembly can be challenging. "These lenses tend to be very dense, very fibrotic, and you have to learn how to chop a lens and be very good about breaking up this fibrotic-type lens," says Dr. Davidson.

Both Dr. Farid and Dr. Davidson reference the Zeiss miLoop. "It's a nitinol ring that goes around the lens that then cuts the lens into two or more pieces," Dr. Davidson says. "It saves a lot of energy or phaco time when you're trying to get these lenses out or disassembled because it cuts through and you don't have to exert as much force or use as much phaco to get the lens broken into smaller pieces."

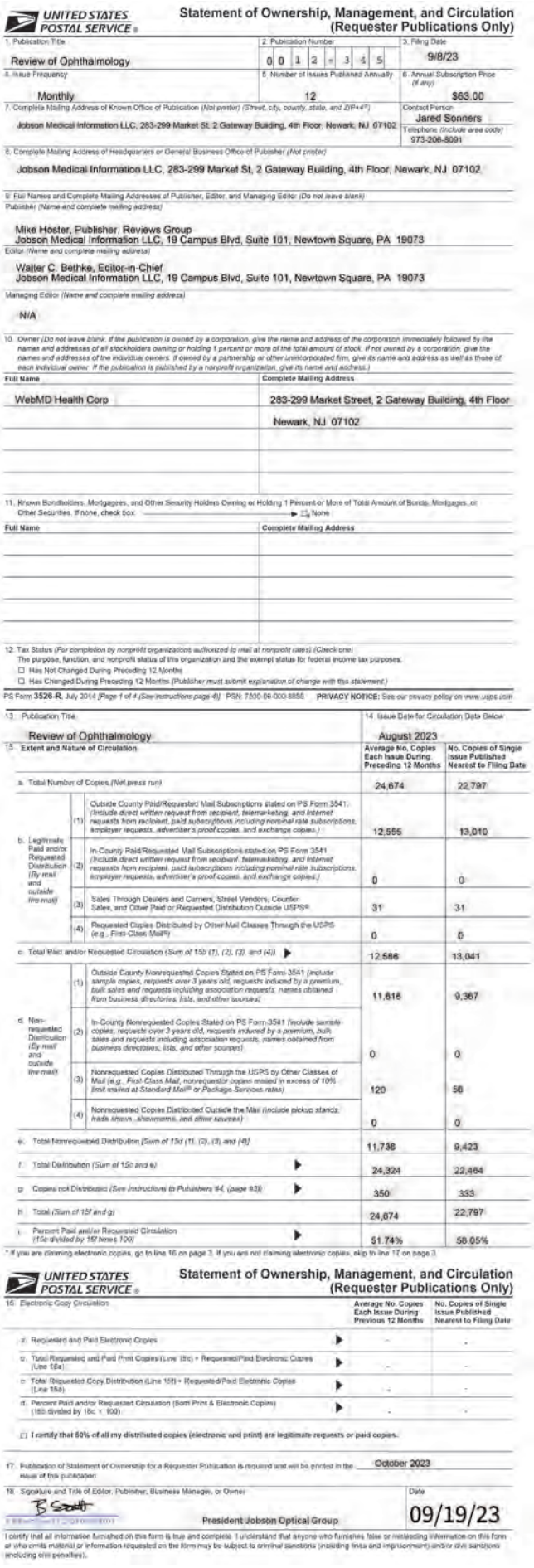
Another thing to keep in mind is that sometimes these lenses are so dense, phaco isn't always the best option, he continues. "Sometimes it's better to do an extracapsular cataract extraction either through MSICS or traditional extracapsular cataract extraction," Dr. Davidson says. "Sometimes in the right hands, that's a better procedure than trying to phaco and use a lot of phaco energy. In these cases you really have to think about your own experience, what you're most comfortable doing and what works best for you because different surgeons are going to have different strengths."

Dr. Farid emphasizes the importance of keeping any forces central. "Directing the manipulative forces central will minimize zonular stress, especially if it's a trauma-related white cataract, is important for stability of



Richard Davidson, MD

The last thing a surgeon wants to see when removing a white cataract is an Argentinian Flag sign. Not to worry, experts say the surgery can be successfully recovered when this happens.



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Statement of Ownership, Management, and Circulation (Requester Publications Only)

1. Publication Title	2. Publication Number	3. Filing Date
Review of Ophthalmology	0012-3455	9/8/23
4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price (If any)
Monthly	12	$63.00

7. Complete Mailing Address of Known Office of Publication (Not printer) (Street, city, county, state, and ZIP+4®): Jobson Medical Information LLC, 283-299 Market St, 2 Gateway Building, 4th Floor, Newark, NJ 07102. Contact Person: Jared Sonners. Telephone (Include area code): 973-206-8091

8. Complete Mailing Address of Headquarters or General Business Office of Publisher (Not printer): Jobson Medical Information LLC, 283-299 Market St, 2 Gateway Building, 4th Floor, Newark, NJ 07102

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor (Do not leave blank)

Publisher (Name and complete mailing address): Mike Hoster, Publisher, Reviews Group, Jobson Medical Information LLC, 19 Campus Blvd, Suite 101, Newtown Square, PA 19073

Editor (Name and complete mailing address): Walter C. Bethke, Editor-in-Chief, Jobson Medical Information LLC, 19 Campus Blvd, Suite 101, Newtown Square, PA 19073

Managing Editor (Name and complete mailing address): N/A

10. Owner (Do not leave blank. If the publication is owned by a corporation, give the name and address of the corporation immediately followed by the names and addresses of all stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, give the names and addresses of the individual owners. If owned by a partnership or other unincorporated firm, give its name and address as well as those of each individual owner. If the publication is published by a nonprofit organization, give its name and address.)

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12. Tax Status (For completion by nonprofit organizations authorized to mail at nonprofit rates) (Check one)
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13. Publication Title	14. Issue Date for Circulation Data Below
Review of Ophthalmology	August 2023

15. Extent and Nature of Circulation			Average No. Copies Each Issue During Preceding 12 Months	No. Copies of Single Issue Published Nearest to Filing Date
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d. Non-requested Distribution (By mail and outside the mail)	(1)	Outside County Nonrequested Copies Stated on PS Form 3541 (include sample copies, requests over 3 years old, requests induced by a premium, bulk sales and requests including association requests, names obtained from business directories, lists, and other sources)	11,618	9,367
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f. Total Distribution (Sum of 15c and e) ▶			24,324	22,464
g. Copies not Distributed (See Instructions to Publishers #4, (page #3)) ▶			350	333
h. Total (Sum of 15f and g)			24,674	22,797
i. Percent Paid and/or Requested Circulation (15c divided by 15f times 100) ▶			51.74%	58.05%

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17. Publication of Statement of Ownership for a Requester Publication is required and will be printed in the October 2023 issue of this publication.

18. Signature and Title of Editor, Publisher, Business Manager, or Owner: President Jobson Optical Group. Date: 09/19/23

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the capsule and zonules," she says.

Zonulopathy is something to be on the lookout for in white cataracts.

"One problem when you're taking out these lenses, is that they can be super mobile in the capsular bag and you can't always tell if it's just mobile or if there's actually zonulopathy, too," Dr. Davidson says. "I personally always assume there's zonulopathy and try to get the lens out of the bag as quickly as possible and work with it out of the bag, assuming the patient has a deep enough anterior chamber. You just don't know what these zonules are like and until you have more of the cataract out and until you can see better, you can't tell very well if there's zonulopathy.

"Once you have more of the lens out it's nice to be able to put a capsular tension ring in if you need to," he continues. "That's really where having experience helps because you can see the subtle things that a more novice surgeon may not be able to notice, such as the way the capsule moves, that may suggest that a zonulopathy is present."

At this stage, capsule stability can influence the IOL selection. "In some cases you may feel more comfortable putting in a three-piece lens," Dr. Davidson says. "If you're not sure about whether there's a hole in the capsule, sometimes people will put a lens in the sulcus and capture the optic. It depends on the integrity of your capsule and how you assess the zonules. We always want to take a step back for a second once the cataract's out and really get a good look. When you put viscoelastic in you can kind of get a feel for how the capsule is holding up—is it collapsing on itself or not—and then make a decision. You don't know exactly what you're going to get until you put the lens in and until the patient heals a bit."

Postop Care

Oftentimes, these patients need more aggressive steroids or nonsteroidals afterwards. "Depending on the length of the surgery and the amount of phacoemulsification energy used, I do put patients on steroids, nonsteroidal anti-inflammatories and antibiotics," says Dr. Farid. "If there's more inflammation in the postop period, we might extend their postoperative drop regimen."

"Certainly once you have the cataract out, you want to get a good look at the retina during the postop period and make sure everything looks good," says Dr. Davidson. ◀

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DISCLOSURES

Dr. Davidson is a consultant for Centricity. **Dr. Farid** reports no relevant disclosures.

Early Responders to Anti-VEGF Treatment in RVO

Macular edema secondary to retinal vein occlusion is the sight-threatening condition clinicians fear. Previous studies have shown that early responders (ERs) who respond well to anti-VEGF injections within three months of treatment have better outcomes as measured by best visual acuity (BVA) and central subfield thickness (CST) at 12 months post injection initiation compared to limited early responders (LERs). This study analyzed whether early responder eyes continue to respond better than limited ER eyes over longer periods. This study also aimed to identify baseline comorbidities associated with response status.

The retrospective cohort study included patients over age 18 with RVO-related macular edema treated with anti-VEGF injections.

Patients were categorized as ERs or LERs. LER eyes were defined as having CST reduction <10 percent, BVA gain <5 ETDRS letters, or both at three-months after anti-VEGF initiation. BVA and CST changes over the 24- and 36-month period following first anti-VEGF treatment were compared between ERs and LERs. Patient characteristics and systemic comorbidities were identified by chart review. Statistical analysis involved Levene test, Welch's t-test and Welch's ANOVA.

Main outcome measures included BVA and CST changes over the initial 24- and 36-month periods following treatment.

The 24-month cohort included 68 ERs and 39 LERs, and the 36-month cohort included 58 ERs and 33 LERs. Here are some of the findings:

- At 24 months, significant differences were found in BVA and CST gains between ER (+19.8 letters, -221. um) and LER (-2.4 letters, -90.1 um) (p<0.0001; p<0.01).
- At 36 months, significant differences were found in BVA and CST gains between ER (+17.7 letters, -229.3 um) and LER (+1.3 letters, -128 um) (p<0.001; p<0.05).
- After controlling for differences in baseline BVA and CST, only the 24-month change in BVA remained significant (p<0.001).
- No significant associations were found between response status and cardiopulmonary, endocrine or oncologic comorbidities.

Investigators found that early-responder eyes with BRVO and CRVO had better functional responses to anti-VEGF injections at 24 months compared to limited early responder eyes even after controlling for baseline differences. They added that early identification of eyes as early responders or limited early responders in BRVO and CRVO may predict long-term functional prognoses.

Ophthalmol Retina 2023; Aug 16. [Epub ahead of print].
Kailar RS, Kuo BL, Perkins SW, et al.

DALK Outcomes in Keratoconus

Scientists investigated the effect of the keratoconus stage using the Amsler-Krumeich classification system and associated parameters on deep anterior lamellar keratoplasty outcomes.

They determined the preoperative KC stage and presence of corneal scarring and recorded the preoperative and postoperative best-corrected visual acuity, refractive error, mean central keratometry (Kmean) readings, topographic astigmatism and minimum corneal thickness (CT) values. They also noted the intraoperative and postoperative complications.

A total of 137 eyes (54 eyes in stage 3 and 83 eyes in stage 4) were included. The mean follow-up period was 42.2 ±24.36 months. Here are some of the findings:

- No statistically significant differences were found between stage 3 and 4 KC groups for postoperative BCVA, Kmean, CT, spherical equivalent and topographic astigmatism values (each p>0.05).
- The effect of preoperative BCVA, Kmean, CT and refractive error values on postoperative BCVA couldn't be demonstrated (p=0.264).
- No statistically significant correlation was found between postoperative and preoperative values (each p>0.05).
- Although intraoperative Descemet's membrane perforation and postoperative early suture loosening were observed more frequently in stage 4 KC than stage 3 KC, the two groups were statistically similar for these and other complications (each p>0.05).

Scientists wrote that preoperative keratoconus stage and parameters used in classification weren't useful in predicting postoperative deep anterior lamellar keratoplasty outcomes. As such, they suggested that the timing of surgery should be planned with the understanding that progression of the disease won't have a negative effect on outcomes.

Cornea 2023; Aug 21. [Epub ahead of print]
Kemer Atik B, Emul M, Kirgiz A, et al.

This article has no commercial sponsorship.

Challenging IOLs

(Continued from page 42)

eyes,especially with the LAL, which allows you to tweak a final refraction after surgery," says Dr. Zhu. "I have found the LAL to be my go-to for post-RK eyes and some of my post-refractive eyes in which they've had large ablations and I'm worried about missing the target by a large magnitude."

"I was very interested in the LAL for post-LASIK patients," says Dr. Fram. "I was very motivated to see if the technology would help us hit our refractive targets. If you have a myopic ablation, then you can end up hyperopic because the cornea is overestimated. If the corneal power is overestimated, you won't put in as powerful of an IOL and you can end up hyperopic. When you work with the LAL, you don't have to worry about that because you can adjust afterward. In hyperopic LASIK, the cornea is underestimated and you can put in a lens that's too powerful because the cornea is steeper than was assumed and so, in that scenario, the patient ends up too myopic. I don't have to worry about that when using the LAL. However, with post-hyperopic LASIK you want to be a little bit careful with the LAL because if you have a lot of negative spherical aberration in the cornea and then you add a negative spherical aberration lens, there can be issues. But, in general, the goal of hitting your target with a post-LASIK patient is the priority."

Dr. Fram cautions surgeons about using the LAL on post-RK eyes. "You can use it but the patient needs to have normal Placido imaging," she says. "If they don't have normal Placido imaging, they're still going to need a lot of help with higher order aberrations and the LAL doesn't correct higher order aberrations. I'll use the iTrace to help me decide, am I going to put a LAL in this patient, or am I going to put an IC-8?"

Although this lens has been doing well, Dr. Zhu says surgeons shouldn't consider it to be the solution to every challenging eye. "I think that we have to acknowledge that the LAL is an extra expense for the patient, as well as quite a bit of extra time that they have to dedicate postoperatively," she says. "We shouldn't neglect all of our preoperative due diligence of having to treat the ocular surface and get multiple measurements whenever possible, because a lot of times people are just relying on the LAL knowing it can be adjusted postoperatively so they're almost abandoning all of the traditional good practices. A lot of patients can still get excellent outcomes by using some of the traditional formulas by doing that preoperative due diligence, and using the modern-day formulas even for complex eyes.

"I don't want people to think that a LAL is the only way to go, especially because it's such a huge financial investment and not a lot of practices or surgeons are able to afford it," Dr. Zhu continues. "This lens also adds a bit of negative spherical aberration so I would caution using it in the eyes that already have a large amount of existing negative spherical aberration, such as post-hyperopic LASIK eyes, because it may affect the visual quality. There have been a few cases of IOL exchanges with a LAL because of visual quality issues, but thankfully it's been rare, and overall, I've had a very positive experience with it."

Dr. Zhu says the Apthera/IC-8 can be considered for eyes with irregular astigmatism, post-RK and keratoconus. "Any eye that's more severe will do well because the pinhole is going to improve the best corrected visual acuity, which the LAL doesn't do," she says. "The LAL only gets you to a more precise refractive outcome, but it's not going to improve the quality of vision. The IC-8 has the advantage of both offering more flexibility in terms of the landing zone so you can be a little bit off and it's still forgiving because of that pinhole, but it also improves the visual quality because of the pinhole effect. I tend to reserve the IC-8 for more irregular eyes and I'll use the LAL for eyes that I think are relatively regular and have good potential for the patient to still be happy with their final outcome."

Dr. Fram says, "We've been very successful using the small aperture IC-8 in RK patients, but I think the key with that lens is to make sure the patient understands that they may have a little bit of dimming because it's a small aperture lens and it's supposed to be in the non-dominant eye and it's off-label for irregular corneas."

A preop pilocarpine test may help determine if the IC-8 is the right way to go, says Dr. Fram. "You don't want to use the IC-8 if you test a patient preoperatively and a pinhole obscures their vision because of a scar or if you put pilocarpine in and they don't see any improvement," she says. "The pilo test will mimic what the IC-8 does with the small aperture. So, how do I target that lens? For an eight-cut RK, which is the most common, I'll aim -0.75 to -1 D using the Barrett True K and the ASCRS calculator on RK because the small aperture lens—when targeted myopic—did best in the clinical trials for mini-monovision. You always want to hedge a little bit more myopic in post-RK eyes because you can get a hyperopic shift over time. Some will do topo-guided PRK after for enhancement. The IC-8 has been a huge advancement for these challenging patients and patients where you want to avoid diffractive technology." ◀

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PRODUCT NEWS

Devices and drugs to improve clinical care and strengthen your practice.

GLAUCOMA THERAPY

Thea Launches Iyuzeh

Thea has launched preservative-free Iyuzeh in the United States. The company says the drug is the first and only preservative-free latanoprost option for patients with primary open-angle glaucoma and ocular hypertension in the nation. According to the company, this will help avoid patients experiencing the moderate to severe signs and symptoms of ocular surface disease associated preservatives.

The company says that, in multiple trials across the United States and Europe, Iyuzeh demonstrated consistent IOP-lowering effects and tolerability. It lowered IOP by 3 to 8 mmHg in patients with OAG or OHT with a mean baseline IOP of 19 to 24 mmHg, compared to the BAK-preserved Xalatan's 4 to 8 mmHg.

The recommended dose of Iyuzeh is one drop in the affected eye(s) once daily in the evening. The company says reduction of the IOP begins three to four hours after administration, with the maximum effect achieved after eight to 12 hours, lasting at least 24 hours. The most frequently reported ocular adverse events in the clinical trials included conjunctival hyperemia and eye irritation.

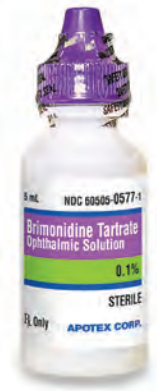
For more information about Iyuzeh, visit theapharmainc.com.

Generic Alphagan-P Now Available

Apotex has released its latest ophthalmic product in the United States: brimonidine tartrate ophthalmic solution, 0.1%.

Brimonidine is an alpha-adrenergic receptor agonist indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

For information, visit www.apotex.com/products/us/downloads/pre/brim_opso_0.1_ins.pdf.



CORNEAL SURGERY

A Corneal Cover-Up

NovaBay Pharmaceuticals recently announced the launch of Avenova Allograft in the United States. The company says this prescription product is the only optic allograft manufactured using BioStem Technologies proprietary process and is intended for use as a protective covering during the repair of ocular surfaces. BioStem will be responsible for manufacturing, packaging, shipping and regulatory compliance.

The Avenova Allograft provides a protective environment or covering for repair of the cornea and conjunctiva, helping the ocular surface to return to a healthier state, the company says. BioStem says the graft uses what the company calls its patented six-step BioRetain process that preserves the natural integrity of the placental tissue. The product consists only of the amnion layer of the placental membrane and measures between 20 to 50 µm thick, which the company says makes it ideal for delicate ophthalmic applications. Avenova Allograft is available in 8 mm, 10 mm and 12 mm diameter sizes.

NovaBay's commercial launch of Avenova Allograft includes outreach programs aimed at educating eye-care specialists on both the clinical benefits of the product, as well as the process for Medicare reimbursement. Clinics can order the product directly on Avenova.com.

EXAM ASSISTANCE

Bring That Pupil Down

Ocuphire Pharma and Viatris recently annouced the FDA approval of their mydriasis-reversal drug Ryzumvi (phentolamine ophthalmic solution, 0.75%). The drug is approved for the treatment of pharmacologically-induced mydriasis produced by adrenergic agonists (e.g., phenylephrine) or parasympatholytic (e.g., tropicamide) agents, which are commonly used during eye exams for dilation.

Ryzumvi was evaluated in the comprehensive MIRA clinical trial program involving more than 600 subjects. In the MIRA-2 and MIRA-3 Phase III trials, a total of 553 subjects aged 12 to 80 years, who had mydriasis induced by instillation of phenylephrine or tropicamide or a combination of hydroxyamphetamine hydrobromide and tropicamide (Paremyd) were randomized. Two drops (study eye) or one drop (fellow eye) of Ryzumvi or placebo (vehicle) were administered one hour after instillation of the mydriatic agent. The percentage of subjects with study eyes returning to ≤0.2 mm from baseline pupil diameter was statistically significantly greater (p<0.01) at all time points measured from 60 minutes through 24 hours in the Ryzumvi group compared with the placebo (vehicle) group across both of the MIRA-2 and MIRA-3 trials, says the company. The efficacy of Ryzumvi was similar for all age ranges including pediatric subjects aged 3 to 17 years. Pediatric subjects aged 12 to 17 years (n=27) were treated in MIRA-2 and MIRA-3 and pediatric subjects, aged 3 to 11 years (n=11) were treated in MIRA-4.

The most common ocular adverse reactions reported in >5 percent of subjects were instillation site discomfort including pain, stinging and burning (16 percent) and conjunctival hyperemia (12 percent). The product is expected to launch in the first half of 2024, the company says.

For more information, visit ryzumvi.com. ◀

A man presents at Wills with pain, redness and decreased vision in his left eye.

SAIF HAMDAN, MD, MARK PYFER, MD, SADEER HANNUSH, MD
PHILADELPHIA

Presentation

A 63-year-old Caucasian male with one week of pain, redness and decreased vision in the left eye initially presented for ophthalmic evaluation with his local ophthalmologist. On examination, he was determined to have a bacterial keratitis with corneal cultures taken and was started on hourly fortified cefazolin and tobramycin topical drops. A thorough ocular/medical history at the time was only remarkable for nocturnal lagophthalmos; the patient denied any soft contact lens use or recent ocular trauma. Culture data at follow-up resulted in pan-sensitive *Pseudomonas* and the patient was transitioned to hourly fortified tobramycin and moxifloxacin drops. Despite culture-guided therapy, the patient continued to develop worsening pain, leading to presentation to the Wills Eye emergency room.

History

Prior ocular history is notable for cataract extraction with intraocular lens placement in both eyes. Past medical history is significant for asthma, hyperlipidemia and Goodpasture syndrome status post failed kidney transplantation now with end-stage renal disease requiring peritoneal dialysis. His family history was noncontributory. He denies any current or previous tobacco or recreational drug use and reports only occasional alcohol intake.

Current medications included oral prednisone 2.5 mg daily, calcium acetate three times per day with meals, Symbicort/albuterol inhalers, Aspirin 81 mg once daily and atorvastatin 40 mg daily.

Examination

The patient's vital signs were stable. He was afebrile. Ocular examination demonstrated best corrected near visual acuity of 20/20 OD and Hand Motion OS. Intraocular pressure by Tonopen was 16 and 12 mmHg in the right and left eyes, respectively. Pupillary exam demonstrated an irregular pupil shape of the left eye though without an afferent pupillary defect. External exam of left eye revealed pronounced periorbital erythema, soft tissue edema and mildly restricted ocular movements (*Figure 1*). The anterior segment was notable for severe diffuse scleral injection, suppurative discharge and a 3 x 3-mm focal whitening of the inferior perilimbal sclera with

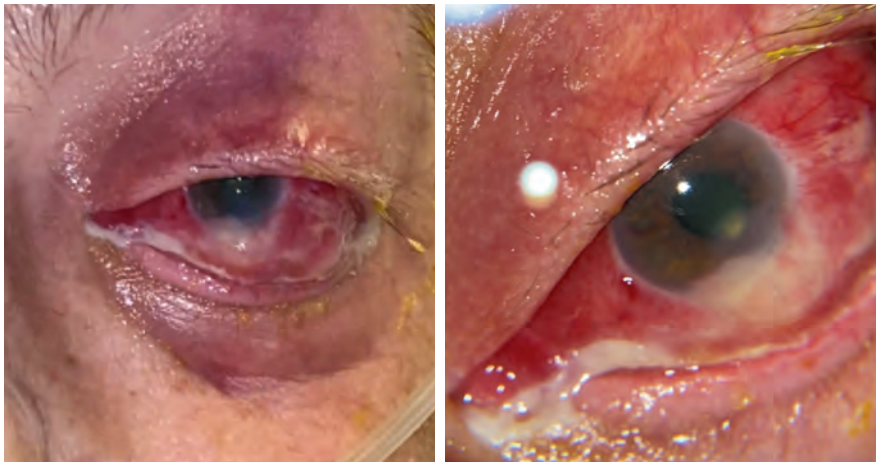


Figure 1 A and B. External photographs of the left eye at initial time of presentation demonstrating severe scleral injection, suppurative discharge and a focal whitening of the inferior perilimbal sclera with thinning and adjacent scleral abscess.

thinning and adjacent scleral abscess at 6 o'clock. A dense white corneal infiltrate with overlying sliver epithelial defect inferiorly was noted; the rest of the cornea showed moderate stromal edema. There was a concurrent 1.5-mm, non-mobile hypopyon and a centered posterior chamber intraocular lens. Dilated fundus exam was limited secondary to media opacity. The anterior and posterior segment examination of the right eye was unremarkable except for a well-positioned PCIOL. B-scan ultrasonography of the left eye revealed moderate anterior vitreous opacities layering inferiorly, underlying inferior scleral abscess and mild posterior scleral thinning. CT orbits with contrast noted left orbital wall thickening with surrounding fatty infiltration and accompanying preseptal inflammation without post-septal extension.

What's your diagnosis? What work-up would you pursue? The diagnosis appears below.

Work-up, Diagnosis and Treatment

The differential diagnosis for this patient presenting with acute onset scleritis includes infectious and inflammatory etiologies. Infectious causes include bacterial (*Pseudomonas* spp, *Staphylococcus* spp, *Streptococcus* spp, and tuberculosis), fungal, protozoan and viral (VZV and HZV). Inflammatory etiologies may be idiopathic or associated with an underlying rheumatologic history. Given the patient's clinical history, particularly a preceding culture-positive bacterial keratitis, the highest consideration was placed on infectious sources.

A repeat corneal scraping and culture of the suppurative discharge was performed, and the patient was started on fortified vancomycin/tobramycin hourly, ciprofloxacin drops hourly, atropine b.i.d. and intravenous ciprofloxacin. Subconjunctival tobramycin was administered, and the patient underwent scleral deroofing in the operating room the next day with additional cultures taken. Bacterial cultures revealed heavy-growth, pan-sensitive *Pseudomonas aeruginosa*. The patient was continued on topical ciprofloxacin and fortified tobramycin drops hourly, ciprofloxacin ointment every four hours (q4h), atropine b.i.d. and systemic IV ciprofloxacin with close daily observation. He additionally received daily subconjunctival tobramycin until ultimately requiring further surgical debridement. On day seven, he underwent sclerectomy and abscess drainage with amniotic membrane scleral patch graft with an intravenous angiocatheter insertion, conjunctivoplasty and punctal occlusion of the left eye. Subsequently, a tobramycin infusion (40 mg/mL) twice daily was administered through the intraoperatively inserted subconjunctival catheter for two days *(Figure 2)*.

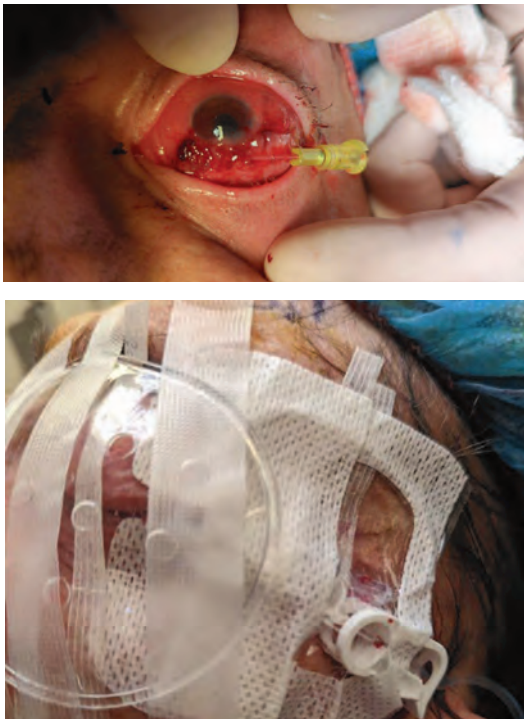


Figure 2 A and B. External photographs of the left eye postoperatively, demonstrating amniotic membrane scleral patch graft with intravenous angiocatheter insertion (A) and subsequent dressing to allow for continuous tobramycin infusions (B).

On evaluation on Day 10 from initial presentation, the visual acuity in the left eye had improved from hand motion to 20/200 with notable improvement of scleral injection, discharge and intraocular inflammation. At this point, the catheter was removed and a temporary tarsorrhaphy was placed; topical therapy was continued with ciprofloxacin and tobramycin ointment q4hr, atropine b.i.d. and topical prednisolone acetate q.i.d. along with oral ciprofloxacin. The patient was eventually discharged with plan for close follow-up in the outpatient cornea clinic.

Discussion

Infectious scleritis is a rare, severe ocular disorder that's often associated with poor prognosis due to its diagnostic challenge and delay in treatment. Characterized by deep inflammation of the sclera, scleritis most commonly occurs secondary to immune-mediated inflammation, though about 5 to 15 percent of all cases are due to infectious etiologies.[1] Inappropriate recognition of IS may lead to use of immunosuppressive therapy, risking exacerbation of active infectious process. Thus, a thorough patient history and evaluation for infectious processes should be considered in cases of severe monocular presentations.

IS can be classified as primary and secondary etiologies—the former occurs as a consequence of preceding scleral surgery or trauma, while the latter typically refers to extension of disease from a primary infection, such as a keratitis as suspected in our case. Preceding ocular surgery is the most common risk factor, particularly pterygium excision, though other cited surgical associations include cataract extraction, vitreoretinal surgery, strabismus surgery and glaucoma filtration surgery.[2] Additional risk factors of IS include trauma, local (ocular) or systemic immunosuppressive agents, radiation therapy, iatrogenic sources (subtenon or intravitreal injections) and immunocompromising disorders (HIV infection, diabetes mellitus).[2,3] Bacterial sources account for the majority of cases with *Pseudomonas* spp being the most common (up to 85 percent).[4] Gram-positive bacteria, specifically *Staphylococcus* spp and *Streptococcus* spp, are also frequently associated, particularly following invasive ocular procedures.[5,6] Additional microbial sources have been implicated, especially in the setting of various environmental factors/exposures, such as *Mycobacterium tuberculosis* in endemic regions (e.g., India) and fungi in developing countries and tropical climates.[2] While much rarer, other sources cited in current literature include spirochetes (e.g., Lyme disease, often with concurrent neuro-ophthalmologic manifestations), protozoa (e.g., *Toxoplasma gondii*-associated posterior scleritis with chorioretinitis, panuveitis), helminths (e.g., toxocariasis) and viruses (*Herpesviridae* family).[1,2,6]

Early recognition and culture-guided antimicrobial therapy are the mainstays of treatment for IS; delayed diagnosis can lead to visually devastating complications including endophthalmitis, perforation and dissemination. Prompt initiation of topical antimicrobial therapy as well as concurrent systemic agents has been associated with improved prognosis; additional prolonged therapy duration even beyond clinical improvement has been associated with better outcomes for IS.[6,8] Despite appropriate initiation of antimicrobials, medical therapy alone is often insufficient for true source control due to scleral avascularity, dense collagen fiber networks and prohibitive biofilms. In fact, up to 80 percent of cases of IS require surgical intervention including surgical debridement, patch graft placement, conjunctival flap, tenonplasty and tarsorrhaphy.[2] In a 10-year consecutive case series of culture-positive *Pseudomonas* scleritis, the authors reinforced that surgical intervention not only aids in confirming diagnosis but also allows for therapeutically reducing microbial load.[9] Additionally, the use of subconjunctival antibiotics in conjunction with surgical therapy has been associated with improved outcomes.[9,10] However, frequent subconjunctival administration of therapy with injections carries many disadvantages.

> **Early recognition and culture-guided antimicrobial therapy are the mainstays of treatment for IS.**

Recognition of this challenge prompted the development of the suprapalpebral lavage, first described in 1966.[11] SPL was originally derived from veterinary medicine allowing for continuous local delivery of antimicrobial therapy and, to date, the technique has undergone many modifications to allow for maximized antibiotic delivery while minimizing surgical complications (e.g., ptosis).[12,13] One report described a case series of six patients with IS and keratitis refractory to topical antibiotic therapy that improved with SPL, citing the ability to reduce bacterial load on the ocular surface and improved antibiotic penetration.[14] In our case, we used a novel variant of a SPL by directly placing an intravenous angiocatheter underneath the amniotic membrane scleral patch graft to allow for twice daily antibiotic infusion. To our knowledge, this is the first case report detailing such an approach and ultimately resulting in a favorable outcome.

In conclusion, IS is a serious ocular disorder associated with poor prognosis, particularly in the setting of delayed diagnosis or misdiagnosis. Successful treatment is dependent on aggressive, culture-guided antimicrobial therapy, often in conjunction with surgical management. While inspiration from veterinary medicine has allowed for breakthrough in treatment of severe cases, ongoing exploration of therapeutic approaches may prove invaluable in managing this challenging and vision-threatening disease. ◀

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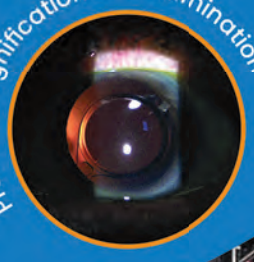

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REFERENCE:

1. Sarkisian SR Jr, Grover DS, Gallardo M, et al; iStent infinite Study Group. Effectiveness and safety of iStent infinite trabecular micro-bypass for uncontrolled glaucoma. *J Glaucoma.* 2023;32(1):9-18.

iStent infinite® IMPORTANT SAFETY INFORMATION

INDICATION FOR USE. The iStent infinite® Trabecular Micro-Bypass System Model iS3 is an implantable device intended to reduce the intraocular pressure (IOP) of the eye. It is indicated for use in adult patients with primary open-angle glaucoma in whom previous medical and surgical treatment has failed. **CONTRAINDICATIONS.** The iStent infinite is contraindicated in eyes with angle-closure glaucoma where the angle has not been surgically opened, acute traumatic, malignant, active uveitic, or active neovascular glaucoma, discernible congenital anomalies of the anterior chamber (AC) angle, retrobulbar tumor, thyroid eye disease, or Sturge-Weber Syndrome or any other type of condition that may cause elevated episcleral venous pressure. **WARNINGS.** Gonioscopy should be performed prior to surgery to exclude congenital anomalies of the angle, PAS, rubeosis, or conditions that would prohibit adequate visualization that could lead to improper placement of the stent and pose a hazard. **MRI INFORMATION.** The iStent infinite is MR-Conditional, i.e., the device is safe for use in a specified MR environment under specified conditions; please see Directions for Use (DFU) label for details. **PRECAUTIONS.** The surgeon should monitor the patient postoperatively for proper maintenance of IOP. Three out of 61 participants (4.9%) in the pivotal clinical trial were phakic. Therefore, there is insufficient evidence to determine whether the clinical performance of the device may be different in those who are phakic versus in those who are pseudophakic. **ADVERSE EVENTS.** The most common postoperative adverse events reported in the iStent infinite pivotal trial included IOP increase ≥ 10 mmHg vs. baseline IOP (8.2%), loss of BSCVA ≥ 2 lines (11.5%), ocular surface disease (11.5%), perioperative inflammation (6.6%) and visual field loss ≥ 2.5 dB (6.6%). **CAUTION**: Federal law restricts this device to sale by, or on the order of, a physician. Please see DFU for a complete list of contraindications, warnings, precautions, and adverse events.

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PM-US-0908

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