Wills Eye Resident Series: A 57-year-old Woman with Interface Haze After DMEK, *p.70*

REVIEW® of OPHTHALMOLOGY

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TIPS FOR SUCCESSFUL IOL EXCHANGE

Surgeons share pearls for ensuring a good lens-exchange outcome—and a happy patient. **P. 52**

ALSO INSIDE:

When patients rely on artificial tears alone, inflammation may persist.
Xiidra can disrupt the chronic inflammatory cycle in dry eye disease.*
It can provide lasting symptom relief in as little as 2 weeks.[1-5]†

*Xiidra blocks LFA-1 on T cells from binding with ICAM-1 that may be overexpressed on the ocular surface in dry eye disease and may prevent formation of an immunologic synapse which, based on in vitro studies, may inhibit T-cell activation, migration of activated T cells to the ocular surface, and reduce cytokine release. The exact mechanism of action of Xiidra in DED is not known.[1,2,5]

†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. The mean age was 59 years (range, 19-97 years). The majority of patients were female (76%). Use of artificial tears was not allowed during the studies. The study end points included assessment of signs (based on Inferior fluorescein Corneal Staining Score [ICSS] on a scale of 0 to 4) and symptoms (based on patient-reported EDS on a visual analogue scale of 0 to 100). 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. Effects on signs of dry eye disease: at day 84, a larger reduction in ICSS favoring Xiidra was observed in 3 out of the 4 studies.[1]

Indication

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

Important Safety Information

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

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

KEN JEONG,
REAL DRY EYE PATIENT.

xiidra® (lifitegrast ophthalmic solution)5%

Dry eyes deserve a change

Important Safety Information (cont)

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

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

References: 1. Xiidra [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; June 2020. **2.** Bron AJ, de Paiva CS, Chauhan SK, et al. TFOS DEWS II Pathophysiology Report. *Ocul Surf*. 2017;15(3):438-510. **3.** US Food and Drug Administration. Code of Federal Regulations, Title 21, Volume 5 (21CFR349). Accessed May 25, 2021. https:/www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=349&showFR=1 **4.** Jones L, Downie LE, Korb D, et al. TFOS DEWS II Management and Therapy Report. *Ocul Surf*. 2017;15(3):575-628. **5.** Pflugfelder SC, Stern M, Zhang S, Shojaei A. LFA-1/ICAM-1 interaction as a therapeutic target in dry eye disease. *J Ocul Pharmacol Ther*. 2017;33(1):5-12.

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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NEWS

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OCTOBER 2021

First Ranibizumab Biosimilar Approved

It was no surprise to those who follow industry and regulatory developments affecting the retina specialty. On September 17, 2021, the U.S. Food and Drug Administration announced the approval of the first ophthalmology biosimilar to ranibizumab (Lucentis, Genentech/Roche), the anti-vascular endothelial growth factor agent Byooviz. But as more biosimilar approvals seem imminent as patents expire, some wonder how this regulatory approach translates to ophthalmology and what impact it could have on community practices and patients downstream.

South-Korea based Samsung Bioepis and U.S. partner Biogen developed Byooviz, or SB11, which has been approved to treat wet age-related macular degeneration, macular edema and myopic choroidal neovascularization, all indications for Lucentis, first FDA-approved in 2006.

Biosimilars are biological products approved based on data showing that they're highly similar to the "reference product," a biological product already approved by the FDA, with no clinically meaningful differences in safety, purity or potency. The concept closely mirrors generic drug approvals following a chemical-based, branded drug patent expiration. The program was implemented to lower costs and increase accessibility to patients.

Neither of these potential benefits are disputed by Timothy G. Murray, MD, MBA, FACS, founding director/CEO of Murray Ocular Oncology and Retina of Miami, president of The Foundation of the American Society of Retina Specialists and immediate past president of ASRS. "If there wasn't a cost issue and there wasn't an access issue, then there really is no benefit to a biosimilar," he says. With branded anti-VEGFs running between $1,800 and $2,000 an injection, many retina specialists have turned to off-label use of bevacizumab (Avastin, Genentech) at roughly $50 per injection, he noted. Thus, short of drug companies lowering their prices, biosimilars are the only option for FDA-approved, affordable anti-VEGF treatments.

While it's helpful to understand biosimilars in the context of generics, Dr. Murray makes a distinction. "I hold biologics to a much higher standard than simple generics," in which "production and manufacturing play only a small role," he says. In the case of biologics, "we have some very good information that how the drug is manufactured, what the biologic process is, and what the standards are, are really critical. I think many of us are very anxious about the approval of biosimilars because there's such a potential for a bad outcome. I think that's the biggest concern." He adds that even branded biologics manufacturers have faced quality issues with some of their lots.

In addition, it may take a larger treatment population for safety issues to emerge. "The most recent example, where we found that with broader use there was a problem with the drug, was brolucizumab," Dr. Murray recalls, recounting the efforts of the American Society of Retina Specialists Research and Safety in Therapeutics Committee, which analyzed clinical and imaging characteristics from submitted reports of retinal vasculitis related to brolucizumab (Beovu, Novartis), prompting a relabeling of the drug.[1] In the case of Byooviz, "have enough patients been evaluated with this drug to believe that it's a very similar drug [to ranibizumab] or not?" Dr. Murray asks.

Approval of Byooviz was based on a randomized, double-masked, parallel group, multicenter Phase III study in which 705 patients were randomized (1:1) to receive SB11 or reference ranibizumab in monthly injections (0.5 mg); 634 patients continued to receive treatment up to week 48. The least squares mean change in best corrected visual acuity from baseline at week 52 was 9.79 letters for SB11, compared with 10.41 letters for reference ranibizumab (difference: -0.62, [90% CI: -2.092, 0.857]). The LS mean change in central subfield thickness was –139.55 µm for SB11 vs –124.46 µm for reference ranibizumab (difference: -15.09, [95% CI, -25.617, -4.563]). Pharmacokinetics, safety

(Continued on p. 9)

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PROLENSA®
(bromfenac ophthalmic solution) 0.07%

ARE YOU PRESCRIBING THE #1 BRANDED OCULAR NSAID*?

THE #1 PRESCRIBED BRANDED OCULAR NSAID*

*IQVIA NPA Monthly. April 2021

DELIVER THE PROLENSA® EFFECT

Achieve powerful corneal penetration with PROLENSA®, the only branded formulation of bromfenac approved for once-daily use[1-3]

INDICATIONS AND USAGE

PROLENSA® (bromfenac ophthalmic solution) 0.07% is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.

IMPORTANT SAFETY INFORMATION

- PROLENSA® contains sodium sulfite, a sulfite that may cause allergic type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.
- All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including bromfenac, may slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including bromfenac. Use with caution in patients who have previously exhibited sensitivities to these drugs.
- There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery. Use with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

IMPORTANT SAFETY INFORMATION (CONT.)

- Use of topical NSAIDs may result in keratitis. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including bromfenac, and should be closely monitored for corneal health. Patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients. Post-marketing experience with topical NSAIDs suggests that use more than 24 hours prior to surgery or use beyond 14 days post-surgery may increase patient risk for the occurrence and severity of corneal adverse events.
- PROLENSA® should not be instilled while wearing contact lenses. The preservative in PROLENSA®, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of PROLENSA®.
- The most commonly reported adverse reactions in 3%-8% of patients were anterior chamber inflammation, foreign body sensation, eye pain, photophobia, and blurred vision.

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

References: 1. PROLENSA Prescribing Information. Bausch & Lomb Incorporated. **2.** Baklayan GA, Patterson HM, Song CK, Gow JA, McNamara TR. 24-hour evaluation of the ocular distribution of (14)C-labeled bromfenac following topical instillation into the eyes of New Zealand white rabbits. *J Ocul Pharmacol Ther.* 2008;24(4):392-398. **3.** Data on file, Bausch & Lomb Incorporated.

BAUSCH + LOMB

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to prescribe Prolensa safely and effectively. See full prescribing information for PROLENSA®.

PROLENSA® (bromfenac ophthalmic solution) 0.07%

Rx only
Initial Rx Approval: 1997

INDICATIONS AND USAGE

PROLENSA® (bromfenac ophthalmic solution) 0.07% is indicated for the treatment of postoperative inflammation and reduction of pain in patients who have undergone cataract surgery.

DOSAGE AND ADMINISTRATION

Recommended Dosing

One drop of PROLENSA ophthalmic solution should be applied to the affected eye once daily beginning 1 day prior to cataract surgery, continued on the day of surgery, and through the first 14 days of the postoperative period.

Use with Other Topical Ophthalmic Medications

PROLENSA ophthalmic solution may be administered in conjunction with other topical ophthalmic medications such as alpha-agonists, beta-blockers, carbonic anhydrase inhibitors, cycloplegics, and mydriatics. Drops should be administered at least 5 minutes apart.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Sulfite Allergic Reactions

Contains sodium sulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

Slow or Delayed Healing

All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including bromfenac, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Potential for Cross-Sensitivity

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including bromfenac. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

Increased Bleeding Time

With some NSAIDs, including bromfenac, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

It is recommended that PROLENSA ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Keratitis and Corneal Reactions

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration, or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including bromfenac, and should be closely monitored for corneal health.

Post-marketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days post-surgery may increase patient risk for the occurrence and severity of corneal adverse events.

Contact Lens Wear

PROLENSA should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of PROLENSA. The preservative in PROLENSA, benzalkonium chloride may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of PROLENSA.

ADVERSE REACTIONS

Clinical Trial 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 clinical practice.

The most commonly reported adverse reactions following use of PROLENSA ophthalmic solution following cataract surgery include: anterior chamber inflammation, foreign body sensation, eye pain, photophobia and vision blurred. These reactions were reported in 3 to 8% of patients.

USE IN SPECIFIC POPULATIONS

Pregnancy

Treatment of rats at oral doses up to 0.9 mg/kg/day (systemic exposure 90 times the systemic exposure predicted from the recommended human ophthalmic dose [RHOD] assuming the human systemic concentration is at the limit of quantification) and rabbits at oral doses up to 7.5 mg/kg/day (150 times the predicted human systemic exposure) produced no treatment-related malformations in reproduction studies. However, embryo-fetal lethality and maternal toxicity were produced in rats and rabbits at 0.9 mg/kg/day and 7.5 mg/kg/day, respectively. In rats, bromfenac treatment caused delayed parturition at 0.3 mg/kg/day (30 times the predicted human exposure), and caused dystocia, increased neonatal mortality, and reduced postnatal growth at 0.9 mg/kg/day.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because of the known effects of prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), the use of PROLENSA ophthalmic solution during late pregnancy should be avoided.

Nursing Mothers

Caution should be exercised when PROLENSA is administered to a nursing woman.

Pediatric Use

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

Geriatric Use

There is no evidence that the efficacy or safety profiles for PROLENSA differ in patients 70 years of age and older compared to younger adult patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (systemic exposure 30 times the systemic exposure predicted from the recommended human ophthalmic dose [RHOD] assuming the human systemic concentration is at the limit of quantification) and 5 mg/kg/day (340 times the predicted human systemic exposure), respectively, revealed no significant increases in tumor incidence.

Bromfenac did not show mutagenic potential in various mutagenicity studies, including the reverse mutation, chromosomal aberration, and micronucleus tests. Bromfenac did not impair fertility when administered orally to male and female rats at doses up to 0.9 mg/kg/day and 0.3 mg/kg/day, respectively (systemic exposure 90 and 30 times the predicted human exposure, respectively).

PATIENT COUNSELING INFORMATION

Slowed or Delayed Healing

Advise patients of the possibility that slow or delayed healing may occur while using NSAIDs.

Sterility of Dropper Tip

Advise patients to replace bottle cap after using and to not touch dropper tip to any surface, as this may contaminate the contents. Advise patients that a single bottle of PROLENSA be used to treat only one eye.

Concomitant Use of Contact Lenses

Advise patients to remove contact lenses prior to instillation of PROLENSA. The preservative in PROLENSA, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of PROLENSA.

Concomitant Topical Ocular Therapy

If more than one topical ophthalmic medication is being used, the medicines should be administered at least 5 minutes apart.

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New Anti-VEGF Biosimilar

(Continued from p. 5)

(including incidence of treatment-emergent adverse events), and the immunogenicity profile of SB11 and reference ranibizumab were comparable at all timepoints up to week 52.

Earlier this year, Cardinal Health, on behalf of The Center for Biosimilars, conducted research via a series of survey questions with U.S.-based community retina specialists (n=37) suggesting a lack of awareness of biosimilars. When asked about their familiarity with biosimilars, 31 percent of physician respondents (out of 29 total responses) said they aren't very familiar with biosimilars, and more than half (55 percent) said they have read research about them but are not familiar with issues such as manufacturing, approval processes, and clinical trial design. Nonetheless, 83 percent of respondents said they could envision biosimilars fitting into their treatment plan, and more than half of respondents said they would consider using a ranibizumab biosimilar or aflibercept biosimilar once they become available.[2]

They're on the way. At least two more companies are developing biosimilars for Lucentis. Samsung Bioepis and Biogen are also working to steer SB15 toward approval as a biosimilar to Eylea (aflibercept, Regeneron), and at least three more companies are following suit with aflibercept biosimilars in clinical trials. Biogen will take the lead to commercialize Byooviz in the United States as of June 2022, based on a licensing agreement with Genentech, Samsung Bioepis and Biogen.

To date, the FDA has approved 31 biosimilars, including one interchangeable biosimilar, meaning that it can be substituted without involvement of the prescriber.

1. Witkin AJ, Hahn P, Murray TG, et al. Occlusive retinal vasculitis following intravitreal brolucizumab. J Vitreoretin Dis. 2020;4:4:269-279.
2. Oskouei ST. Opinion: Is the ophthalmology market ready to embrace biosimilars? Center for Biosimilars website. Posted January 16, 2021. Available at: https://www.centerforbiosimilars.com/view/is-the-ophthalmology-market-ready-to-embrace-biosimilars- Accessed September 27, 2021.

Study Supports Individualized Anti-VEGF Protocols

Developing new injection schedules for patients receiving anti-VEGF agents is always on physicians' minds, due to the high costs of injections; the intense follow-up schedules; the psychological and physical impacts of these schedules; and the threat of geographic atrophy. Studies suggest that individualized treatment is best for wet AMD patients when taking into account treatment costs and scheduling. A new analysis published in *Retina* examined treatment-naïve wet AMD patients who received a single injection of ranibizumab/aflibercept; it reported that a subset of these patients demonstrated resolution of choroidal neovascular membrane-associated exudation that lasted more than two years with a single injection.[1]

The retrospective, observational study included 63 patients with wet AMD who achieved complete resolution of retinal exudation with a single injection. The researchers defined complete resolution as the total disappearance of intraretinal fluid, cysts and subretinal fluid, as well as a return to a retinal thickness <250 µm on SD-OCT. Follow-up visits occurred on days one, seven and 30 postoperatively, and then monthly. Patients had nine mandatory visits per year if the macula remained fluid-free.

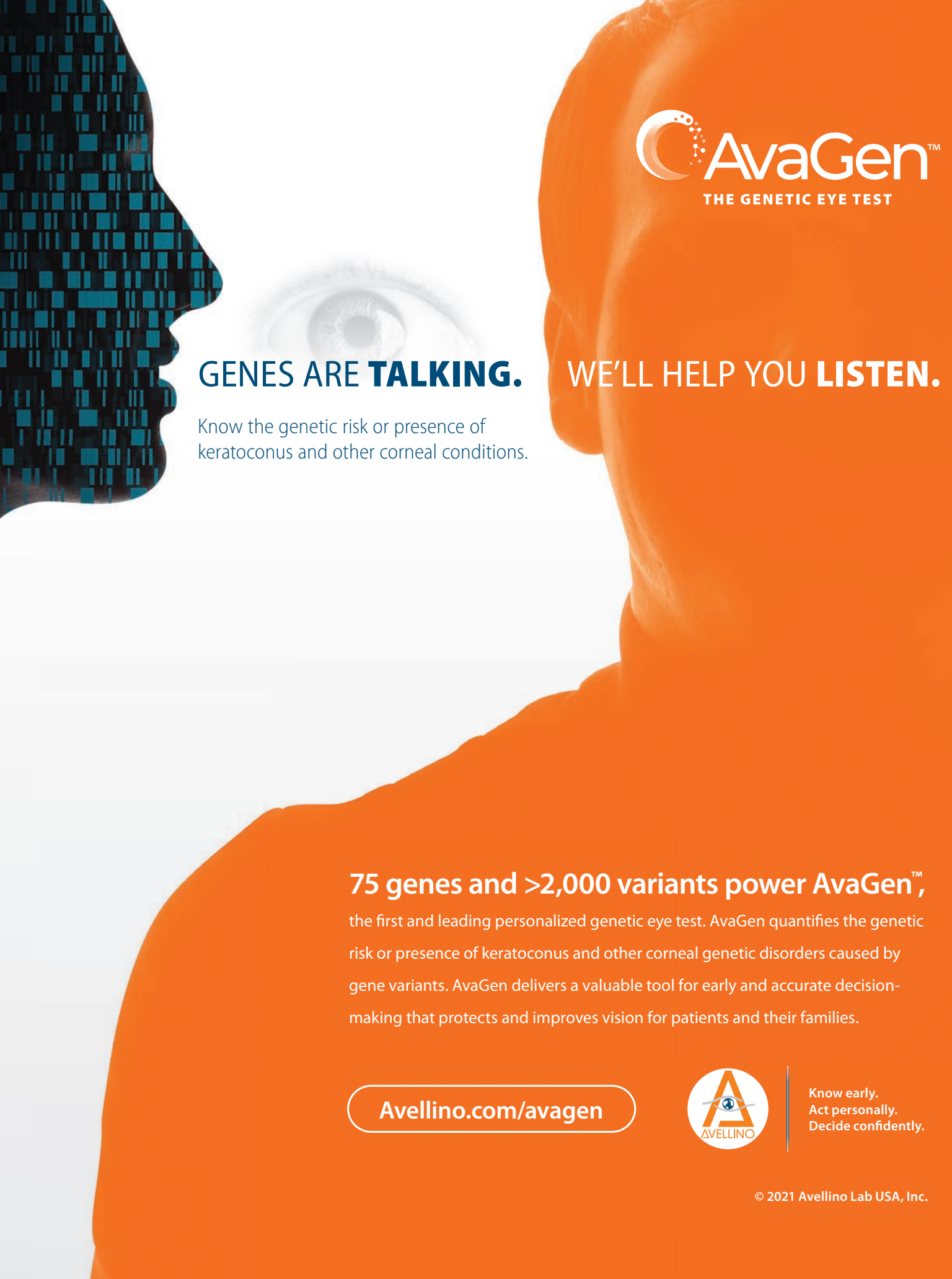
The patients' mean baseline and final-corrected distance VA were 20/160 and 20/45, respectively. They completed an average of 10.9 follow-up visits per year. The authors also noted that smaller choroidal neovascular membranes (<200 µm), early presentation, better presenting corrected distance VA, subfoveal choroidal neovascular membranes, absence of blood/fibrosis and use of aflibercept (2 mg) were factors associated with resolution after one injection.

Overall, the researchers said that a defined subset of patients receiving just one injection had "very good" visual and anatomical outcomes. These patients showed complete resolution of the neovascular membrane, and only seven required multiple injections after a treatment-free interval of at least 24 months. They noted no adverse events during follow-up.

Of these patients, 63 percent demonstrated a 15-letter gain and 47 percent were able to maintain a 10-letter gain at the end of follow-up (at least three years). A lack of continued therapy didn't adversely affect the final visual outcome, the researchers noted. The study indicates that, "The three patients who lost vision showed macular atrophy on SD-OCT—probably a consequence of the natural progression of the disease. Overall, the gains noted in the first months after the injection were reduced by the end of the follow-up period; this reflects a continuing degenerative process in all probability, even if there's no recurrence of the neovascular membrane."

The researchers say that the purpose of the study wasn't to challenge established protocols but to call for more flexibility in their execution and provide thought for future studies that look at larger numbers (modified PRN from baseline). ◀

1. Bilgic A, Kodjikian L, Mathis T, et al. Single injection response to antivascular endothelial growth factor agents in patients with wet age-related macular degeneration: Incidence and characteristics. Retina. 2021;41:1901-10.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Vol. 28, No. 10 • OCTOBER 2021

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OCTOBER 2021

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WALTER C. BETHKE, EDITOR IN CHIEF

EDITOR'S PAGE

The Weight of Expectations

As we hear time and again, from many corners of medicine, patient expectations—or, more specifically, managing patient expectations—play a key role in the perceived success of a surgical procedure.

I was reminded of this while looking over this month's features. Taken together, they're almost like a rogues' gallery of ophthalmic surgeries that revolve around patient expectations. In one, "Cataract/IOL Surgery After RK," you've got the first mass-market refractive surgery, radial keratotomy. When RK was first introduced, you can imagine the grandiosity of the expectations harbored by spectacle wearers. Though the surgery turned out to be successful in many cases, there were of course those that didn't go as well. Also, it turned out that progressive hyperopia was a possible concern. Now, these same patients are coming in for cataract surgery which, ironically, would probably go very smoothly if it weren't for their RK. Once again, as in the 1980s and 1990s when they got their RK, expectations needed to be tempered.

In another of this month's features, we fast-forward to one of today's expectation-laden procedures: premium intraocular lenses ("Responding to Premium IOL Setbacks," p. 42). Though the survey cited in the article notes that patient expectations aren't a leading cause of dissatisfaction after these lenses' implantation, surgeons still spend a good deal of time managing expectations preop. As Baylor's Zaina Al-Mohtaseb, MD, says in the article, "Cataract surgery has become a refractive procedure. High patient expectations and new lens technologies require correction of spherical error, astigmatic error and, in some cases, presbyopia."

This discussion of patient expectations and the need to make them more realistic got me thinking about how we all get our hopes up for all kinds of things, every day. Of course, the biggest example of this, at least recently, is the pandemic. We went from expecting it to be isolated to another country to realizing we'd need to wear masks and social-distance for a year or more. Despite this, we still held on to the expectation that a vaccine would bring everything back to normal again. The vaccines arrived, and have been great for keeping us out of the hospital but, in terms of a complete resolution of the pandemic, we learned that we had to adjust our expectations yet again. A return to normalcy may be coming, but it won't happen as quickly as we'd hoped.

We're going to get through this, but it's going to take more work than we thought to become immunologically "20/Happy."

Speaking of happy, what could make you happier than leaving work behind and spending all of your time with family and friends? Well, this is what Senior Editor, Sean McKinney has to look forward to as he retires this month after 50 years of work, many of it spent making quality contributions to ophthalmic journalism. We wish Sean all the best on a well-deserved retirement. Sean, thanks for your hard work and friendship.

— Walter Bethke
Editor in Chief

Neurotrophic keratitis is a degenerative disease that warrants immediate attention[1]

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OXERVATE is the first FDA-approved pharmacologic treatment that targets the root pathogenesis of neurotrophic keratitis (NK)[2]

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OXERVATE is a recombinant human nerve growth factor indicated for the treatment of neurotrophic keratitis.

Important Safety Information

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

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

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*Study NGF0212 (REPARO): 52 patients per group; European patients with NK in one eye; 72% of patients completely healed; key findings were after 8 weeks of treatment; 6 times daily; vehicle response rate 33.3%.[2] Study NGF0214: 24 patients per group; US patients with NK in one or both eyes; 65.2% completely healed; vehicle response rate 16.7%.[2,7]
†Complete corneal healing was defined as the absence of staining of the corneal lesion and no persistent staining in the rest of the cornea after 8 weeks of OXERVATE treatment.[2]

References: 1. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol.* 2014;8:571-579. **2.** OXERVATE (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL) [US package insert]. Boston, MA: Dompé U.S. Inc.; 2019. **3.** Voelker R. New drug treats rare, debilitating neurotrophic keratitis. *JAMA*. 2018;320:1309. **4.** Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol*. 2017;232:717-724. **5.** Muzi S, Colafrancesco V, Sornelli F, et al. Nerve growth factor in the developing and adult lacrimal glands of rat with and without inherited retinitis pigmentosa. *Cornea*. 2010;29:1163-1168. **6.** Data on file. Dompé U.S. Inc.; 2021. NGF0212. **7.** Pflugfelder SC, Massaro-Giordano M, Perez VL, Hamrah P, Deng SX, Espandar L, et al. Topical recombinant human nerve growth factor (cenegermin) for neurotrophic keratopathy. *Ophthalmology*. 2020;127:14-26.

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

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

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

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

Recommended Dosage and Dose Administration

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

ADVERSE REACTIONS

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

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

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

Animal Data

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

Lactation

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

Pediatric Use

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

Geriatric Use

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

NONCLINICAL TOXICOLOGY

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

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

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Mastering Iris Defect Suturing Techniques

Solutions for anatomical challenges that too many surgeons aren't willing to meet during cataract surgery.

BY STEVEN B. SIEPSER, MD, FACS
WAYNE, PA.

Why master iris defect suturing for cataract surgery? Why even try? I know at least some of my colleagues will ask themselves these questions when starting to read this article. By the time even the most dubious among us finish it, however, I hope more will give it at least some consideration.

Although not indicated for every iris defect, suturing significant defects has evolved into an increasingly viable way to spare patients debilitating visual disruptions—before or after cataract surgery—as well as troubling life-long cosmetic abnormalities.

Exactly what is a significant iris defect? This depends on what patients report to us. The Challenging and Complex Sub-Committee of the Cataract Committee of ASCRS members now emphasizes that we shouldn't dismiss any patient's concerns solely based on the size of a defect.[1] Remember that the potential effects of these defects on visual function are widespread and can include glare, light scatter, photophobia, monocular diplopia and reduced visual acuity and contrast sensitivity. Symptoms can range from evoked patient observations to life-altering distractions and disabilities.

These repairs are especially helpful in cataract surgery—most especially premium cataract surgery—to help us achieve the refractive outcomes that today's patients expect. I've had the pleasure of introducing new suturing techniques and then seeing other surgeons refine these techniques through the years. (Imitation, I've learned, can be the highest form of flattery.)

Best of all, suturing an iris defect is often something you can do yourself. In this review, I'll discuss congenital and traumatic iris defects, as well as iatrogenic defects caused by our surgical maneuvers. I'll also go over indications for suturing, suggest suturing techniques and recommend when to rule out suturing. Risks and contraindications for intraoperative repair of iris defects and pupillary reconstruction will also be covered.

Good Reasons for Saying No?

Through the years, I've heard colleagues offer many reasons why iris defects are best left alone. Below are a few:

- Iris defects don't significantly affect vision.
- Repairing an iris defect isn't the number one priority during cataract surgery.
- Repairing or reconstructing an iris doesn't make much of a difference to the patient.
- Going to this trouble doesn't really work or help—so why do it?
- We've always done surgery without fixing iris defects. Why change now?
- The iris tears like wet tissue paper.

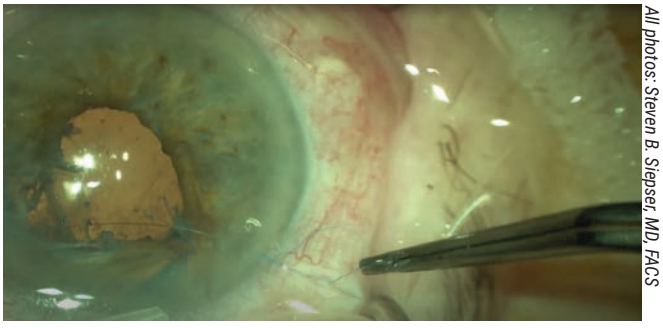
The reality is that iris defects can cause a broad spectrum of problems for our patients. The defects may be congenital, traumatic, intraoperative or idiopathic. (*See Risks to the Iris During Cataract Surgery on page 20.*) Acquired conditions, such as traumatic mydriasis and iridodialysis, may also play a role.

Suturing to Reconstruct an Iris

When reconstructing an iris, we typically seek to achieve one of three objectives:

1. correcting functional impairment;
2. securing the integrity of the anterior segment; or
3. addressing patients' cosmetic concerns.

We need to customize treatment to address the problems at hand.



All photos: Steven B. Siepser, MD, FACS

Figure 1. The sliding knot repair is created outside of eye during the Siepser slide-knot iris repair.

This article has no commercial sponsorship.

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

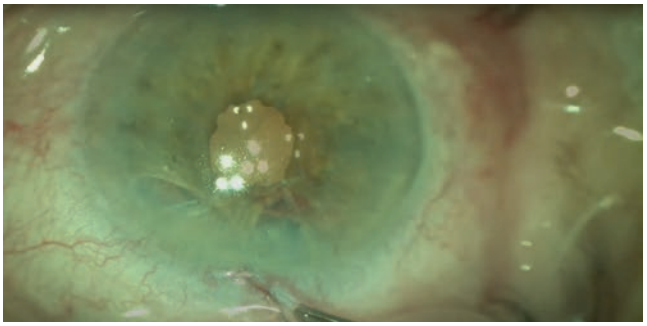


Figure 2. The sliding knot is internalized to close a portion of the iris defect.

Although I'll focus primarily on suturing repairs, other needed interventions may be necessary to respond to large iris defects in cataract surgery patients, such as corneal tattooing and placement of an artificial iris.

In small-pupil cases, it may be helpful for you to counsel patients and their families regarding the possibility of prolonged surgical time. If the reconstruction involves the potential use of a pupil expansion device, for example, it will pose a greater risk of iris damage, possibly giving rise to functional or cosmetic problems after surgery. If you've prepared the family and your OR staff for a potentially complicated procedure, you won't have to contend with arbitrary time pressures challenging your desire to do what's best. Avoid being led down an unproductive primrose path. It's far easier to tell a family that you spent some extra time getting things just perfect than to explain why another intervention is needed.

Each of us is at risk for panicking when things go south. At such a moment, take several deep breaths and count to 10. A case may seem to spiral into an emergency, putting you at risk for a phenomenon called time compression, which will interfere with your judgment. A short moment of meditation will give you the time to come up with an alternative plan.

Like many of us, I often struggle to complete my share of challenging iris repairs without losing concentration and focus. Earlier in my career, when operating on aphakic patients who required thick, high-plus glasses or contact lenses, I was always able to improve their vision, but unable to fix terrible sector iridectomies. I often found no safe and effective way to repair these defects.

The McCannel technique, introduced in 1976, provided us with an open-chamber direct method of iris suturing. To perform the technique, we needed to bring the defect to the corneal opening to pass a 10-0 nylon suture into the edge of the defect. In 1994, I was able to advance this technique by using a closed chamber "sliding knot" approach I had borrowed from a fly-tying technique used in fly fishing.

How to Use the Sliding Knot

My approach relies on the use of the two paracenteses, which keep the anterior chamber formed with the aid of viscoelastic. Here's how it works: Initiate your proximal paracentesis with a 15-degree blade, creating a 1.2-mm incision that's 0.5 mm anterior to the limbus. Make a 6 o'clock incision and lubricate the cornea. You can line up your approach to the incisions by positioning a Sinskey hook over the defect.

As you know, when an iris is damaged or sections of the iris are cut, it retracts, much like a long garden worm that shrinks down to almost nothing when cut. Polypropylene suture with a CIF-4 needle, often present in the OR, can be used for these situations. Once the paracenteses are in place, with an additional incision 90 degrees away, you can begin the procedure, usually using grasping, 25-gauge coaxial microforceps to tease and unfurl the retracted iris. (You'll be impressed by the amount of iris that can be stretched to fill fairly large defects.)

Next, identify the end of the posterior pigment of the iris, locate the collarette for alignment, then pull and stretch the collarette to stabilize it. Once you've confirmed the location of the pigment margins, you can use a Luer-locked syringe and 27-gauge cannula to express viscoelastic and drive the needle point into the cannula. Pierce both sides of the iris with this technique. Next, dock the tip of the needle in the cannula and back it out of the distal paracentesis.

With the suture ends now externalized through each side of the paracentesis, insert a Bonn's hook or Condon snare. After introducing the hook or snare, pass over the defect to grasp the suture that's between the incision and the far side of the iris defect. Draw the grasped suture toward the proximal incision, thus making it into a loop, and then draw the loop out of the proximal incision. You can externalize this distal loop on the proximal side while the suture remains threaded through both sides of the iris defect. Then you can tie various sliding knots outside of the eye that can be slid into the eye and into position over the iris defect. Before I explain how this is done, consider what constitutes a sliding knot.

A sliding knot can be formed by using one, two, three or four throws,

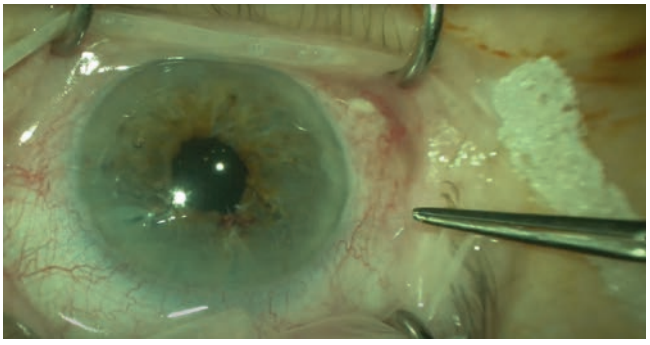


Figure 3. By continuing to create sliding knots and internalizing them, the surgeon is progressively able to completely close a significant iris defect.

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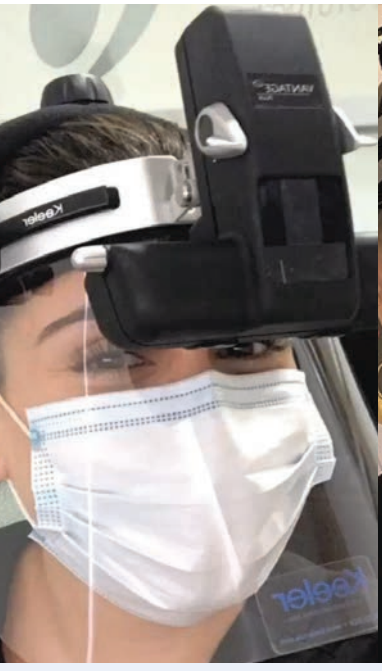

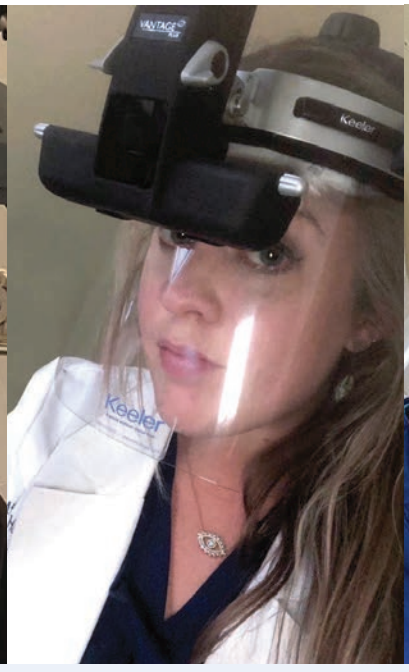

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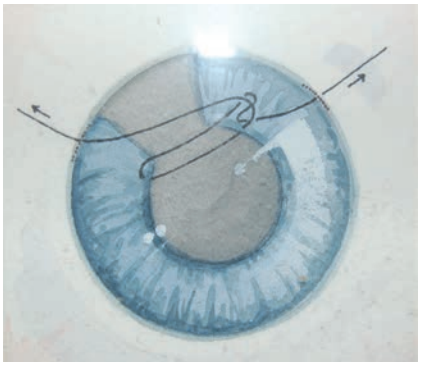

Figure 4. In this illustration, the sliding knot is created outside the eye and then drawn over the defect.

depending on the desired knot configuration. Keep in mind that it's not the final configuration of the knot but the process of sliding it into position that makes this knot unique and effective. After making one of these sliding knots outside of the eye, grasp and pull on the suture end that's extending from the knot through the eye and out the distal side of the eye, while maintaining your grasp on the suture end extending from the proximal side. By balancing these competing, pulling forces, you'll be able to navigate the knot into the eye and park it atop the defect. Pulling on the suture ends from each side of the eye will enable you to tighten the knot, closing the defect while maintaining a closed chamber, without having to enter the eye. This doesn't deform the iris, and it allows for a tight anatomic closure.

As you know, some irises have multiple defects. The process I've just described can be repeated as many times as needed to close every defect, making repairs possible in all medians during the same procedure.

Through the years, a number of modified suturing techniques have been introduced, many addressing the shortcomings of the original techniques, such as a steep learning curve or sutures protruding into the anterior chamber. Some modified suturing techniques have been used to respond to complex ocular pathology. Several of the innovations are described below. (The numbers associated with them represent the number of wraps used for each throw, meaning, for example, that a 2-1-1 square knot involves two wraps on the first throw and one wrap on the second and third throws.)

- ***Osher, Cionni, Snyder Siepser variant.*** Throws are created by threading a suture end through the loop. The 2-1-1 square-knot configuration distinguishes this technique from the 2-1 throws of my original technique.
- ***Condon Siepser variant.*** Throws are created by wrapping the side of the suture loop attached to the iris around forceps before grasping the other suture end. This also features 2-1-1 square-knot-configured throws.
- ***Ahmed Siepser variant.*** Throws are created by wrapping the side of a suture loop that's not attached to the iris around the forceps before grasping the other suture end. This variant features 3-1-1 square-knot-configured throws.
- ***Narang, Argarwal Siepser variant.*** A single throw of four wraps is completed as part of my original maneuver.
- ***Ogawa Ahmed variant.*** This technique relies on an instrument inside the eye to act as a pulley to hold the knot in place until it's taut. The Ahmed component relies on coaxial forceps inside the eye to stabilize and tighten the knot.

Additional Suturing Techniques

Iris cerclage is another proven suturing technique, best used to help us control persistent mydriasis caused by diffuse iris sphincter dysfunction.[2,3] We can use this approach to rescue a pupil from permanent disfigurement, achieving excellent control of the patient's final pupil size. The technique is an ideal way to treat mydriasis following trauma, providing the patient with good functional and cosmetic results.

You begin performing iris cerclage by making 1-mm stab incisions at 9, 5, and 1 o'clock over the limbus or the clear cornea. Next, fill the anterior chamber with viscoelastic and insert

RISKS TO THE IRIS DURING CATARACT SURGERY

Think of the risks to the iris that can arise during cataract surgery. Small pupils, for example, predispose patients to iatrogenic damage because the pupils can be easily damaged by phaco, aspiration ports and surgical instruments.

Meanwhile, the iris of a pupil of any size can be inadvertently aspirated by the phaco or irrigation/aspiration tip. Repeated mechanical contact with the iris by a chopper or even large, dense nuclear fragments can lead to pigment loss, chaffing of the iris constriction and pupillary distortion, a situation found more often in patients with uveitis and glaucoma. Other risks include inadequate pupillary dilation, associated with insufficient response to mydriatics, senile miosis and surgeons hurrying to do surgery before full dilation takes hold.

Fibrosed pupillary margins, pseudoexfoliation, iris synechiae and medication-related floppy iris syndrome may also be implicated during surgery. In addition, of course, we know that we should always guard against thermal damage, excessive tissue manipulation and prolapse. Stretching or distorting pupillary sphincter muscles can injure the midperipheral sphincter or iris root and can be associated with iridodialysis.

Preventive measures include administration of non-steroidal anti-inflammatory drugs and mannitol to lower pressure in the eye. Of course, a careful history is always important to assess patients for past usage of systemic alpha-adrenergic receptor antagonists and other miosis-causing medications. Iris rings and pupil expanders should be used judiciously; try to rely more on OVDs to achieve viscomydriasis.

Concentrations of eyedrops, such as those containing 10% phenylephrine, may be indicated, if safe for the patient. Some surgeons recommend using atropine preoperatively in patients with IFIS.[8]

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- EYSUVIS is formulated with AMPPLIFY® Drug Delivery Technology, designed to ***ENHANCE OCULAR SURFACE TISSUE DISTRIBUTION AND PENETRATION***[2,3]
- EYSUVIS had a ***LOW INCIDENCE OF INTRAOCULAR PRESSURE ELEVATION*** (similar to vehicle) and was well-tolerated in clinical trials[4] —Please see Warning on Intraocular Pressure Increase below

*The safety and efficacy of EYSUVIS was assessed in 4 multicentered, randomized, double-masked, placebo-controlled trials in 2871 patients with documented Dry Eye. Patients received either EYSUVIS or vehicle 4 times a day for at least 2 weeks. Patients taking EYSUVIS showed significant reduction in the symptoms of Dry Eye (ocular discomfort) as early as Day 4 after starting treatment (versus vehicle). Symptoms continued to improve up to the end of the treatment period (Day 15). Patients taking EYSUVIS also showed significant reduction in signs of Dry Eye (conjunctival hyperemia) at Day 15 versus vehicle.

EYSUVIS®
(loteprednol etabonate ophthalmic suspension) 0.25%
THE FAST FLARE FIGHTER

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 Prescribing Information for EYSUVIS on the next 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**. Korenfeld M, Nichols KK, Goldberg D, et al. Safety of KPI-121 ophthalmic suspension 0.25% in patients with dry eye disease: a pooled analysis of 4 multicenter, randomized, vehicle-controlled studies. *Cornea*. 2020. In press.

kala PHARMACEUTICALS

US-EYS-2100022 www.EYSUVIS.com

EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%, for topical ophthalmic use

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.com.

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

Part # 2026R02

October 2020
Kala®

US-EYS-2000115

forceps through the 1 o'clock port while you're inserting a needle that conveys a 10-0 polypropylene suture through the 9 o'clock incision. Use your forceps to grasp and stabilize the iris. Make three to four bites peripheral to the pupillary edge before removing the forceps from the anterior chamber.

You'll then need to use a blunt instrument to guide the needle out of the incisions or to dock the needle in a cannula to back it out. This cycle should be repeated three or more times. The result of the repeated efforts will be continuous bites encircling the pupillary margin, with both suture ends exiting the 9 o'clock port. The suture ends can then be pulled to create the appropriate pupil size and tied externally or by using a slipknot approach.

The cerclage—or purse string technique, as it's also known—provides your patient with a substantial aesthetic advantage when you've repaired a mydriatic pupil. The bottom line: Unlike the other methods I've discussed, this suture technique lets you create a round pupillary aperture.

Over time, surgeons have innovated with other novel approaches to surgically manage the effects that complex ocular pathologies have on the iris. One is the use of the modified sewing machine technique for iridodialysis repair—so named because it replicates the action of a sewing machine by using a pre-threaded 26G/30G needle with a prolene suture to achieve a minimally invasive repair.

Another suturing technique for iris repair is done with the mattress suture.[5] The mattress suture—which is also included in the technique used to improve cosmetic outcomes in the repair of sectoral iris defects—has been used to help surgeons succeed with iridodialysis repair. Additionally, this bowstring suturing technique has been employed to treat traumatic aphakia that involves a large iris defect. The technique combines tangential and radial suturing loops that are used to center and reconstruct much of the pupil. The remainder of the procedure involves an iris-claw implant and the implantation of custom-made sectoral iris prostheses.

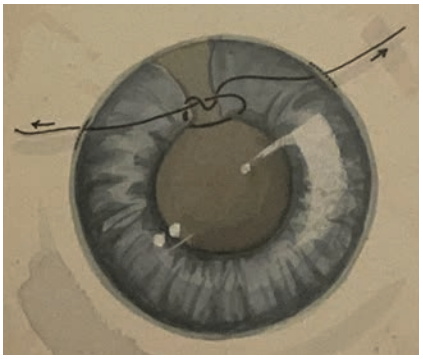

Figure 5. The sliding knot has been internalized, placed over the iris defect and tightened by adjusting the tension from outside each paracentesis.

For Large Defects

In some patients, such as those with aniridia or large sectoral defects, iris suturing isn't feasible. Surgical alternatives to suturing in iris reconstruction in these cases include the implantation of iris prosthetic devices and corneal tattooing. Each of these alternatives has benefits and drawbacks. (I'm leaving out cautery, used by some surgeons, because more study of cautery is needed.)

Let's first review the use of prosthetics. Some prosthetic devices are designed for capsular bag placement. Others are intended for scleral fixation or passive sulcus fixation. These devices can be essential in the treatment of aniridia and can also be used for albinism and large pupillary defects. Currently, three general types of prosthetic irises are available:

- an iris-lens diaphragm;
- a device that's based on an endocapsular capsular tension ring; and
- a customized artificial iris.[6]

An iris-lens diaphragm can correct both aniridia and aphakia. However, it requires large incisions for implantation and can be difficult to position. You can insert an endocapsular CTR-based device through much smaller incisions. However, some models are brittle and prone to fracture, requiring an intact capsular bag.

A customized artificial iris is a personalized silicone implant that resembles the fellow eye.[7] The implant is foldable, allowing insertion through a small incision, but it has no central optic, requiring an accompanying IOL implant, if one is indicated. Insertion options for the artificial iris include implantation in the sulcus with transscleral suture fixation or with capsular support and with endocapsular implantation. Only one prosthetic iris, CustomFlex Artificial Iris (HumanOptics), has been approved by the U.S. FDA.

Why Do Nothing?

As you can see, iris suturing and alternative approaches have greatly expanded our repertoire of interventions that we can use to help patients with a variety of iris defects and related issues. The time to leave well enough alone has passed. I hope more of us explore these options to optimize patients' experiences and improve their vision in the years ahead. ◀

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2. Behndig A., Small incision single-suture-loop pupilloplasty for postoperative atonic pupil. J Cataract Refract Surg 1998: 24:11: 1429-1431.
3. Ogawa GS. The iris cerclage suture for permanent mydriasis: A running suture technique. Ophthalmic Surgery, Lasers and Imaging Retina 1998;29:12:1001-1009.
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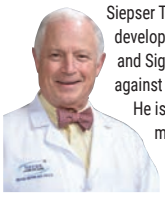
6. Srinivasan S, Ting DS, Snyder ME, et al. Prosthetic iris devices. Canadian Journal of Ophthalmology/Journal Canadien d'Ophtalmologie 2014;49:1:6-17.
7. Voelker R. First Artificial Iris Ok'd. JAMA 2018;320:1:23.
8. Bendel RE, Phillips MB. Preoperative use of atropine to prevent intraoperative floppy-iris syndrome in patients taking tamsulosin. J Cataract Refract Surg 2006;32:10:1603-5.

DISCLOSURES

Dr. Siepser, an anterior segment surgeon and the medical director of Siepser Eye Care in Wayne, Pennsylvania, is the inventor of the sliding knot approach to iris defect repair and has been involved in the development of other surgical techniques through the years. **Dr. Siepser** is the owner of Siepser Technologies, LLC, focused on development of ophthalmic-related products, and SightAssure, offering patients insurance against inadequate surgical outcomes. He is also a consultant for instrument-maker Gulden Ophthalmics (Elkins Park, Pennsylvania) and IOL-maker Rayner Surgical (New York, New York).



WHAT COULD SHE SEE THIS YEAR?

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

Inspired by a real patient with DME.

375 MATH TESTS

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- EYLEA is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

REGENERON

EYLEA ACHIEVED RAPID, SUSTAINED OUTCOMES IN DME

Demonstrated efficacy outcomes in VISTA and VIVID, phase 3 anti-VEGF trials in DME (N=862)[1]

Mean change in BCVA (ETDRS letters) at Year 1 from baseline[1-5,*]

	Initial Gains (Month 5)		Primary Endpoint (Year 1)		Prespecified Exploratory Endpoint (Year 3)	
	VISTA	VIVID	VISTA	VIVID	VISTA	VIVID
EYLEA Q4	+10.3 (n=154)	+9.3 (n=136)	+12.5 (n=154)	+10.5 (n=136)	+10.4 (n=154)	+10.3 (n=136)
EYLEA Q8†	+9.9 (n=151)	+9.3 (n=135)	+10.7 (n=151)	+10.7 (n=135)	+10.5 (n=151)	+11.7 (n=135)
Control	+1.8 (n=154)	+1.8 (n=132)	+0.2 (n=154)	+1.2 (n=132)	+1.4 (n=154)	+1.6 (n=132)

P<0.01 vs control at Year 1.

The analyses of these exploratory endpoints were not multiplicity protected and are descriptive only.

Year 2 data was consistent with results seen in Year 1.[5]

VISTA and VIVID study designs: Two randomized, multicenter, double-masked, controlled clinical studies in which patients with DME (N=862; age range: 23-87 years, with a mean of 63 years) were randomized and received: 1) EYLEA 2 mg Q8 following 5 initial monthly doses; 2) EYLEA 2 mg Q4; or 3) macular laser photocoagulation (control) at baseline and then as needed. From Week 100, laser control patients who had not received EYLEA rescue treatment received EYLEA as needed per re-treatment criteria. Protocol-specified visits occurred every 28 (±7) days.[1]

In both clinical studies, the primary efficacy endpoint was the mean change from baseline in BCVA at Week 52, as measured by ETDRS letter score.[1]

*Last observation carried forward; full analysis set.
†Following 5 initial monthly doses.

SEE WHAT EYLEA COULD DO FOR YOUR PATIENTS WITH DME AT HCP.EYLEA.US

anti-VEGF, anti–vascular endothelial growth factor; BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; Q4, every 4 weeks; Q8, every 8 weeks.

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.
- Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

INDICATIONS

EYLEA® (aflibercept) Injection 2 mg (0.05 mL) is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2019. **2.** Korobelnik JF, Do DV, Schmidt-Erfurth U, et al. Intravitreal aflibercept for diabetic macular edema. *Ophthalmology.* 2014;121(11):2247-2254. doi:10.1016/j.ophtha.2014.05.006 **3.** Brown DM, Schmidt-Erfurth U, Do DV, et al. Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies. *Ophthalmology.* 2015;122(10):2044-2052. doi:10.1016/j.ophtha.2015.06.017 **4.** Data on file. Regeneron Pharmaceuticals, Inc. **5.** Heier JS, Korobelnik JF, Brown DM, et al. Intravitreal aflibercept for diabetic macular edema: 148-week results from the VISTA and VIVID studies. *Ophthalmology.* 2016;123(11):2376-2385. doi:10.1016/j.ophtha.2016.07.032

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

04/2021
EYL.21.03.0211

EYLEA® (aflibercept) Injection
For Intravitreal Injection

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

1 INDICATIONS AND USAGE
EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of patients with:

Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema Following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), Diabetic Retinopathy (DR).

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections
EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation
EYLEA is contraindicated in patients with active intraocular inflammation.

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

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

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

5.3 Thromboembolic Events
There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS
The following potentially serious adverse reactions are described elsewhere in the labeling:
- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.
A total of 2980 patients treated with EYLEA constituted the safety population in eight phase 3 studies. Among those, 2379 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, controlled clinical studies (VIEW1 and VIEW2) for 24 months (with active control in year 1).
Safety data observed in the EYLEA group in a 52-week, double-masked, Phase 2 study were consistent with these results.

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

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

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

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

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

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

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

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

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

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

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.
Safety data observed in 269 patients with nonproliferative diabetic retinopathy (NPDR) through week 52 in the PANORAMA trial were consistent with those seen in the phase 3 VIVID and VISTA trials (see Table 3 above).

6.2 Immunogenicity
As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.
In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose [*see Animal Data*].
Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept, treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

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

8.2 Lactation
Risk Summary
There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, EYLEA is not recommended during breastfeeding.
The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA and any potential adverse effects on the breastfed child from EYLEA.

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

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

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

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

17 PATIENT COUNSELING INFORMATION
In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].
Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

REGENERON

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

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

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

EYL.20.09.0052

Inmates Running The Asylum

Musings on life, ophthalmology and the practice of medicine.

MARK H. BLECHER
CHIEF MEDICAL EDITOR

The basic premise of being a physician is to use your knowledge and expertise to help patients be healthier and enjoy life by preventing, diagnosing and treating disease. In order to do that, our patients need to trust what we say and do, and join with us in implementing our suggestions. It's a voluntary contract, one which requires both sides to execute their part of the deal. All too often though, patients don't go along with the plan. "Noncompliance" is the buzzword of the decade, and even more so in the time of COVID. It's been an issue forever, of course, but it's become a bigger issue as trust has broken down between Americans and the health-care system.

But let's take a few steps back. Noncompliance occurs because patients can't physically do, understand, afford, and/or don't agree with what we want them to do. And in this last item, we have patients who think we're wrong, and those who simply think they know better. There's a difference, however, between thinking your doctor isn't correct and thinking that you know better than your doctor.

All this isn't to say that physicians are always right. We're not. But it's rare that a patient is more correct. This didn't used to be much of an issue. We can thank the internet of course, and the generally more suspicious mood of the country toward anything that seems institutional. I'm afraid medical school seems to be included in that. We can do better to educate our patients, to talk with them in a manner that includes them and relates on a level they are comfortable with. But how do we respond to those who openly contradict our advice, who accuse us of not dealing with them in good faith with regard to medical issues? This problem goes beyond the standard teachings on how to deal with noncompliance. We'd just started to get our arms around patients who consult Dr. Google and find either incorrect information or information not in the proper context for their issue. This led to productive conversations. But patients coming in with their own idea, however obtained, on how to deal with their health issue, isn't so easily dealt with.


Getty

Everything is real if it's on the internet, and everything is fake—it just depends on what outcome you want or how you feel about the source. Research confirms that patients seek out validation for their preconceived or desired facts. The scary part is that we as a society have many fewer shared facts. And therein lies the root of the problem and the serious danger that lies ahead. In a very prescient and sobering book, "The Death of Expertise and Why it Matters," Tom Nichols uncovers the insidious process that's been creeping into society and undercutting our shared respect and acknowledgement that there are actually people who do know best, and that there are incontrovertible facts.

And, while there will always be 'experts' who are motivated by other than altruistic motives, at the end of the day there exist absolute truths. We just have to acknowledge them. A T-shirt I saw recently sums up this idea nicely: "Science doesn't care what you believe." And like the laws of physics, without some basis of absolute truths, our world will fall apart.

At the risk of being depressing, I don't have an answer, only a caution: If we don't stand up for what is verifiably correct and denounce falsehoods, we deserve the increasingly frequent opprobrium we get. ◀

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

THE EPIC FUTURE OF EPI-ON

A look at what's coming to cross-linking, both in and out of the FDA pipeline.

CHRISTINE LEONARD
SENIOR ASSOCIATE EDITOR

New cross-linking protocols are attempting to circumvent the shortcomings of the Dresden protocol, in particular by aiming to decrease treatment time and reduce postop pain, while producing comparable results.

"I'm excited by the latest developments in epi-on cross-linking," says Farhad Hafezi, MD, PhD, chief medical officer of the ELZA Institute, Dietikon, Switzerland. "Given everything we've learned about cross-linking over the years, we're now approaching a point where we can leverage that knowledge and combine it with molecules that act as penetration enhancers (to get riboflavin across the epithelium and into the stroma in clinically effective levels), pulsed UV light (that lets oxygen diffuse back into the cornea) and smart, individualized cross-linking protocols to get corneal stiffening effects on the same level as the epi-off gold standard Dresden protocol. At my institute, we've already moved over to epi-on cross-linking."

Neera Singal, MD, FRCS(C), an assistant professor, chief of cornea and the head of the collagen cross-linking program in the department of ophthalmology and vision sciences at the University of Toronto, is also eager for epi-on cross-linking to come to the fore. "Dr. Stulting and colleagues recently reported the results of an epi-on technique with a new riboflavin formulation and UV light, which seems promising but isn't available yet for prime time,"[1] she says. "With an efficacious epi-on technique, we'd virtually eliminate the risk of haze and have a significant improvement in postoperative pain. It'd also allow us to perform CXL on thinner corneas."

Long-term studies are still needed to understand how all of these new protocols may affect corneal stability down the line,[2] but epi-on, accelerated and pulsed protocols show promise. Here, we'll look at some epi-on treatments in the FDA pipeline, and other cross-linking protocols in use outside the United States.

iLink

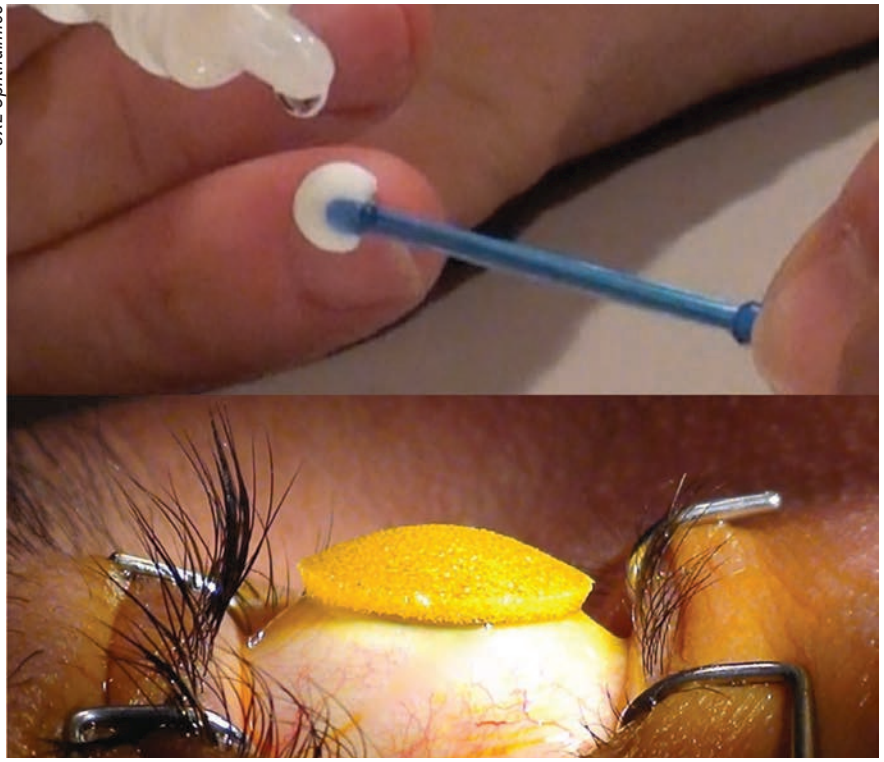
Glaukos' epi-off iLink procedure is currently the only FDA-approved protocol for collagen cross-linking. The epithelium-off treatment involves a 30-minute riboflavin instillation (Photrexa Viscous, 0.146% riboflavin 5'-phosphate in 20% dextran ophthalmic solution) followed by a 30-minute, 3-mW/cm^2 UVA irradiation.

As an epi-off procedure, iLink entails an epithelial defect. Because of this, patients often complain about slow healing and discomfort, says Brandon Ayres, MD, of Ophthalmic Partners in Bala Cynwyd, Pennsylvania. "Most patients feel discomfort for about three days, and during this time, they can't go to work or do much of anything," he says. "There's also a risk of infection. However, if you don't make some form of epithelial defect, you're likely not doing the best for the patient because the CXL won't be as successful."

This article has no commercial sponsorship.

Dr. Ayres is a consultant for Glaukos. **Dr. Hafezi** is a shareholder of EMAGine AG and holds patents for a corneal CXL apparatus and a chromophore for CXL application. **Dr. Singal** has no relevant financial disclosures.

CXL Ophthalmics



The Epismart system uses a disposable wand to remove the mucin layer and promote epithelial permeability (top). A loading sponge is then placed on the cornea to maintain optimal drug concentration (bottom).

Glaukos' next venture into cross-linking treatment is an epithelium-on procedure. The company announced positive Phase III trial results earlier this year. The epi-on procedure achieved its primary endpoint of demonstrating a Kmax treatment effect of -1 D at six months vs. placebo (p=0.0004). This included a 0.2-D improvement in Kmax in the treated arm and a 0.8-D worsening in Kmax in the placebo-controlled arm. Glaukos says this means that the epi-on treatment is effective at halting or slowing keratoconus disease progression. The company plans to submit an NDA in 2022.

Dr. Ayres, one of the doctors participating in the trial, says he's excited about the approval of an epi-on cross-linking treatment. "Patients will experience less discomfort and faster recovery times," he says. "Without having an epithelial defect, the risk of infection is much lower as well."

The new epi-on version is different from iLink. This treatment involves two different proprietary riboflavin formulations. "We were masked to the two types of riboflavin in the study," Dr. Ayres says. "Formulation A is likely a pretreatment meant for sensitizing the epithelium to allow for better penetration, and the addition of Formulation B may be meant to get further into the stroma."

Dr. Ayres adds that the cross-linking is aided by a pair of special goggles that concentrate oxygen around the cornea. "Oxygen, riboflavin and UV light are required for cross-linking to work," he explains. "If we can supply more oxygen, the thought is that we can more rapidly and effectively perform the CXL procedure. In the trial, we were able to do an entire CXL procedure in a little less than half the time we do it now, with significantly less discomfort and fewer healing issues because it's not an epi-off procedure."

The trial also used a new UV light device in a pulsatile fashion to give the oxygen levels in the cornea time to rise between light exposures. Pulsed light treatments aren't approved in the U.S. yet, but many of these new protocols are making use of it to promote oxygen availability to the cornea. "The oxygen concentration must be at least 94 percent to cross-link," Dr. Ayres says. "In the trial, we used a higher fluence of light, and therefore needed more oxygen. That's where the hyperbaric goggles come in.

"I was impressed by the depth of the treatment we were able to get into the cornea," he continues. "One of the major issues of epi-on cross-linking is that the riboflavin doesn't penetrate as deeply, but we had good results in the trial. As a clinician, I felt like I was doing good. Deeper penetrance into the cornea means a better cross-linking treatment and a more stable cornea. We're looking forward to seeing the compiled trial data soon, and hopefully in a few years, the FDA will green-light this new procedure. We really want epi-on treatments to be as effective or even more effective than epi-off treatments."

Epismart

EpiSmart (CXL Ophthalmics), an epi-on procedure developed by Roy S. Rubinfeld, MD, MA, is scheduled to begin Phase III trials in a few months. The treatment uses a proprietary riboflavin formulation that contains sodium iodide as its key active ingredient.[3] "Sodium iodide enhances the penetration of riboflavin and helps to achieve homogeneous stromal loading," explains Michael D. Webb, MA, MBA, president and CEO of EpiSmart. "It also scavenges hydrogen peroxide and converts it into oxygen. We apply the riboflavin solution, known as RiboStat, once at the initial outset of the procedure, rather than continually dropping riboflavin into the patient's eyes."

The EpiSmart procedure takes approximately 50 minutes from start

FIRST AND ONLY
FDA-APPROVED TREATMENT FOR THYROID EYE DISEASE

In the treatment of Thyroid Eye Disease (TED),

IT'S TIME FOR A BREAKTHROUGH
IT'S TIME FOR TEPEZZA

TEPEZZA is proven to[1-4]:

- **Decrease proptosis[1]**
- **Improve diplopia[1]**
- **Reduce orbital pain, redness, and swelling[2,3]**
- **Improve functional vision and patient appearance[2,3]**

...in patients with TED, without concomitant steroids (vs placebo at Week 24).[2-4]

INDICATION

TEPEZZA is indicated for the treatment of Thyroid Eye Disease.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

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

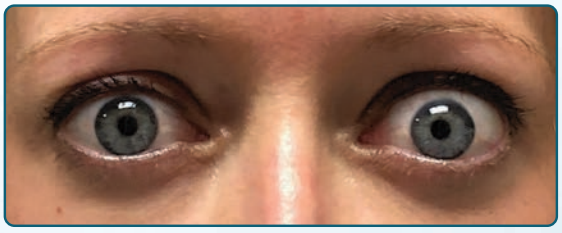
Preexisting Inflammatory Bowel Disease: TEPEZZA may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

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

TEPEZZA®
teprotumumab-trbw

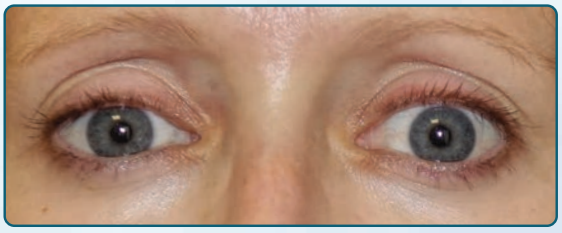
TEPEZZA significantly decreased proptosis, one of the most disfiguring symptoms of TED[1,2,5,6]

SEE THE TEPEZZA DIFFERENCE[7]*



BASELINE
Proptosis: 19 mm OD, 20.5 mm OS

OD, oculus dexter; OS, oculus sinister.



WEEK 21: ON DAY OF 8TH INFUSION
Proptosis: 17 mm OD, 18 mm OS

*Real patient treated with TEPEZZA. Individual results may vary for patients treated with TEPEZZA.

Significantly greater proptosis responder rate† (Study 2)[1,2]

TEPEZZA
83%
TEPEZZA (n=41)
P<0.001 at Week 24

vs

Placebo
10%
Placebo (n=42)

†Both the safety and efficacy of TEPEZZA were evaluated in 2 randomized, double-masked, placebo-controlled clinical trials (Studies 1 and 2) consisting of 171 patients with TED (84 were randomized to TEPEZZA and 87 to placebo). The primary endpoint in Studies 1 and 2 was proptosis responder rate, defined as having a ≥2-mm reduction from baseline in proptosis in the study eye at Week 24 without deterioration (≥2-mm increase in proptosis) in the non-study eye.[1]

» See more before and after photos

Adverse Reactions

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

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

References: 1. TEPEZZA (teprotumumab-trbw) [prescribing information] Horizon. **2.** Douglas RS, Kahaly GJ, Patel A, et al. Teprotumumab for the treatment of active thyroid eye disease. *N Engl J Med*. 2020;382(4):341-352. **3.** Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for thyroid-associated ophthalmopathy. *N Engl J Med*. 2017;376(18):1748-1761. **4.** Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for thyroid-associated ophthalmopathy. *N Engl J Med*. 2017;376(18)(suppl):1748-1761. https://www.nejm.org/doi/suppl/10.1056/NEJMoa1614949/suppl_file/nejmoa1614949_appendix.pdf. **5.** Data on File. Horizon, December 2019. **6.** Bruscolini A, Sacchetti M, La Cava M, et al. Quality of life and neuropsychiatric disorders in patients with Graves' orbitopathy: current concepts. *Autoimmun Rev*. 2018;17(7):639-643. **7.** Data on File. Horizon, December 2020.

HORIZON

TEPEZZA™
teprotumumab-trbw

For injection, for intravenous use

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

INDICATIONS AND USAGE

TEPEZZA is indicated for the treatment of Thyroid Eye Disease.

WARNINGS AND PRECAUTIONS

Infusion Reactions

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

Exacerbation of Preexisting Inflammatory Bowel Disease

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

Hyperglycemia

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

Monitor patients for elevated blood glucose and symptoms of hyperglycemia while on treatment with TEPEZZA. Patients with preexisting diabetes should be under appropriate glycemic control before receiving TEPEZZA.

ADVERSE REACTIONS

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

- Infusion Reactions [see Warnings and Precautions]
- Exacerbation of Inflammatory Bowel Disease [see Warnings and Precautions]
- Hyperglycemia [see Warnings and Precautions]

Clinical Trials Experience

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

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

The most common adverse reactions (≥5%) that occurred at greater incidence in the TEPEZZA group than in the control group during the treatment period of Studies 1 and 2 are summarized in Table 1.

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

Adverse Reactions	TEPEZZA N=84 N (%)	Placebo N=86 N (%)
Muscle spasms	21 (25%)	6 (7%)
Nausea	14 (17%)	8 (9%)
Alopecia	11 (13%)	7 (8%)
Diarrhea	10 (12%)	7 (8%)
Fatigue[a]	10 (12%)	6 (7%)
Hyperglycemia[b]	8 (10%)	1 (1%)
Hearing impairment[c]	8 (10%)	0
Dysgeusia	7 (8%)	0
Headache	7 (8%)	6 (7%)
Dry skin	7 (8%)	0

a - Fatigue includes asthenia
b - Hyperglycemia includes blood glucose increase
c - Hearing impairment (includes deafness, eustachian tube dysfunction, hyperacusis, hypoacusis and autophony)

Immunogenicity

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

If the patient becomes pregnant during treatment, TEPEZZA should be discontinued and the patient advised of the potential risk to the fetus.

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

Data

Animal Data

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

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

Contraception

Females

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

Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

Geriatric Use

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

OVERDOSAGE

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

PATIENT COUNSELING INFORMATION

Embryo-Fetal Toxicity

Advise females of reproductive potential that TEPEZZA can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy.

Educate and counsel females of reproductive potential about the need to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

Infusion-Related Reactions

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

Exacerbation of Inflammatory Bowel Disease

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

Hyperglycemia

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

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HORIZON

to finish, with a 20-minute UVA exposure, and consists of three parts. First, a small wand-shaped tool is used to remove the mucin layer from the surface of the cornea. Next, the riboflavin solution is applied to a loading sponge that helps maintain drug concentration during stromal loading. Epismart uses a pulsing UVA device with two arms for bilateral treatment. It includes a fixation light and modulated compensating light to maintain the eye's target focus.

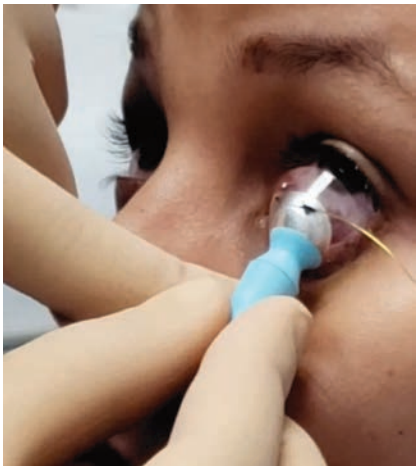
"This is a true epi-on procedure," Mr. Webb explains. "Generally, our patients go back to school or work the next afternoon with both eyes treated. We hope EpiSmart will help to move cross-linking toward a treatment paradigm that allows for treatment upon initial diagnosis, rather than waiting for significant vision loss."

On-Eye Cross-linking

"An operating room in a contact lens" is how Roy S. Chuck, MD, PhD, the Paul Henkind Chair and a professor in the department of ophthalmology and visual sciences at Montefiore-Einstein, and chairman and cofounder of TECLens, describes the CXLens. The scleral lens-based device is connected via a thin fiber optic cable to a small, portable UV delivery device. No speculum is involved. The developers say that the familiar contact lens form helps to reduce patients' fear of the procedure.

CXLens is meant to be a comfortable procedure. "Patients can move their head, eyes, and even close the treated eye during therapy, all without interrupting or displacing the UV beam," says Dr. Chuck. "The scleral lens tracks eye movement, so when the eye moves, the device moves. This increases the accuracy of UV targeting. With conventional cross-linking, if the eye moves out of the field of the light, you get no effect."

Before the procedure, a reservoir contact lens filled with riboflavin is placed on the eye to hold the riboflavin against the cornea for absorption. The riboflavin doesn't have to be re-administered during the treatment, nor does the treatment require additional oxygen. "We preload the cornea with perfluorocarbon, which can carry three times as much oxygen as is in the air," explains Patrick D. Lopath, MBA, MS, a biomedical engineer, COO and co-founder of TECLens.


TECLens

The CXLens is a scleral lens-based device that emits UV light to cross-link the cornea. This image shows lens insertion.

A small pilot study of the CXLens with Juan Batlle Logroño, MD, in the Dominican Republic demonstrated successful results, says Mr. Lopath. Nine corneal transplant candidates with advanced keratoconus received a scleral contact lens reservoir containing 0.007% benzalkonium chloride preserved with 0.25% riboflavin-monophosphate for 30 minutes. The reservoir lens was then replaced with the CXLens UVA light-emitting contact lens, and the eye was irradiated with 375-nm UVA light at 4 mW/cm^2 intensity for 30 minutes for a dose of 7.2 J/cm^2.[4]

After six months, the treated eyes had an average of -1 ±1.6 D decrease in maximum keratometry (p=0.049), a nonsignificant 2.3 ±7.5-letter improvement in BCDVA (p=0.19), a nonsignificant -17 ±14-µm decrease in thinnest corneal thickness (p<0.01), and a nonsignificant -86 ±266-cells/mm^2 decrease in endothelial cell density (p=0.2). The authors concluded that the device has the potential to perform efficient, high-throughput transepithelial corneal cross-linking and is ready for larger-scale studies. (You can view a video of the procedure in the online version of this article at reviewofophthalmology.com.)

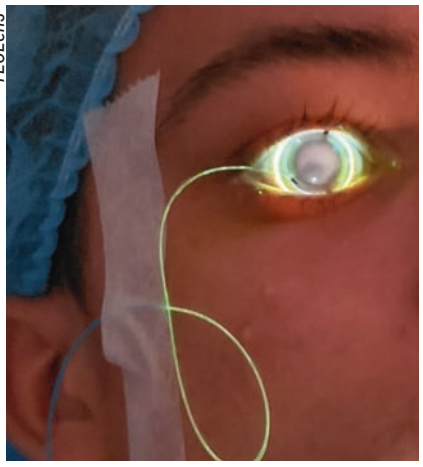
Biomechanics in Real Time

In addition to patient comfort and eye tracking, the CXLens' on-eye treatment enables real-time sensing of the cross-linking-induced biomechanical changes without interrupting treatment. "We can measure this with our real-time biomechanical modeling feedback system," says Mr. Lopath. "We measure how the ultrasound interacts with the eye and can deduce from that how much we've increased the tensile modulus of the corneal tissue."

They say that CXLens also has the potential to be a noninvasive vision-correction technology, because it can alter corneal biomechanics and thus change the eye's refractive shape. "We refer to the procedure as 'quantitative cross-linking,' " says Mr. Lopath. "We use computational modeling to optimize a refractive treatment, since we know the changes that cross-linking makes to the eye."

Reshaping while strengthening the cornea with UV light is a hot topic, says Dr. Ayres. "The UV lights we have in the States have 8-mm beams, which are too broad for targeted reshaping, but with a more focused beam of light applied to only certain parts of the cornea, we could predictably reshape it."

To perform a refractive procedure using the CXLens, Mr. Lopath says the patient's corneal topography is mapped with any standard topographer; then, that data is mapped onto a digital biomechanical framework built with data from healthy eyes with similar refractive error.


TECLens

A fiber optic cable connects the CXLens to the UV delivery device. Patients can blink, close their eyes and turn their heads during the treatment because of the on-eye configuration and the device's built-in eye tracker.

"TECLens' initial approach will use this population-based model because the equipment needed for measuring corneal biomechanics isn't ubiquitous in ophthalmology practices today," says Mr. Lopath. "For example, presbyopic treatment plans use a dataset of baseline biomechanics from presbyopic eyes.

"A computational model then iterates through different cross-linking treatments 'in silico' until the parameters for the best refractive outcome for a specific patient are determined," he continues. "This treatment plan consists of a simple set of parameters such as UV pattern, intensity and time, allowing the physician to simply apply the appropriate CXLens and engage the control console to execute the plan. The control system uses the ultrasound feedback to stop the therapy when the baseline corneal stiffness has changed by the amount the digital model calculated for the optimum outcome."

"As a refractive surgeon, I find that lower myopes and presbyopes are always the most hesitant to undergo ablative vision correction," says Dr. Chuck. "We hope that this non-ablative, familiar contact lens-based procedure will open up a lot of eyes, if you will."

Treating the Underlying Cause

Bala Ambati, MD, PhD, MBA, of Pacific Clear Vision Institute in Eugene, Oregon, a professor and the director of ophthalmology and visual science at the University of Oregon's Knight Campus, and iVeena Delivery Systems' president, began looking into the underlying causes of keratoconus when he felt unsatisfied by conventional cross-linking.

"In 2015, we did an experiment in my lab, then at the University of Utah, and found that we could use copper to increase lysyl oxidase," he says. "In keratoconic patients, there's a deficiency of lysyl oxidase, which leads to a deficiency of natural collagen cross-links. I felt that treating the underlying pathophysiology of the disease by enhancing the activity of this critical enzyme would be a great pharmacologic approach.

"Lysyl oxidase is a cuproenzyme," he explains. "It's dependent on copper ions for its function, and interestingly enough, keratoconic corneas have been described as being deficient in copper. There's a variety of reasons for that, especially in places like the Middle East, where there's a lot of exposure to alkaline sand, which can affect copper transport throughout the cornea."

He went on to develop IVMED-80, currently an orphan drug candidate for keratoconus. "A pharmacologic approach can avoid surgery and the risks and pain associated with it," he says. IVMED-80 is a prescription aqueous soluble drop. In clinical trials, there were no reports of irritation or effects on vision. Patients can instill the drops themselves, just like glaucoma drops.

Treatment duration will likely depend on disease severity and age at onset. "We know from surgical CXL studies that teenagers and adults who undergo surgical cross-linking have a fairly significant rate of relapse and need retreatment with repeat surgical CXL within five years. I suspect IVMED-80 will be patient-dependent, where patients who present with KCN in their 30s may only need it for a year. Patients who present when they're teenagers might need it for a very long time."

The Phase I/IIa study was conducted in Mexico and included 31 patients who had completed a course of IVMED-80, administered twice daily. Three subarms received placebo (artificial tears), IVMED-80 for six weeks or IVMED-80 for 16 weeks. All patients were followed for 26 weeks to determine the impact of duration of therapy, as well as the effects of therapy cessation.

"As expected, the placebo group progressed by about 0.2 D over the course of the six months," says Dr. Ambati. "The patients who received IVMED-80 for six weeks had no benefit; they pretty much wound up where they started, in terms of Kmax. The patients who received IVMED-80 for 16 weeks improved. Their corneas flattened by about 0.8 D over the follow-up period. We're very pleased with these results. We had 1 D of reduction relative to placebo over the follow-up period and there were no adverse events. In addition to Kmax flattening, we observed a reduction in corneal astigmatism, as measured by Pentacam, by about 0.5 D as well. That was an unexpected benefit."

At the end of the six months of follow-up, the IVMED-80 group receiving drops for 16 weeks had an 11.3-letter improvement, relative to baseline. The placebo patients had an eight-letter improvement relative to baseline. "The reason both groups improved is because patients memorize the ETDRS eye charts," says Dr. Ambati. "But the treated patients improved more than the placebo patients, and the amount of improvement we saw with IVMED-80 was slightly higher than what was published in the U.S. clinical trial with Photrexa, the surgi-

cal CXL product, so we were encouraged by that and by the anatomical improvement as well."

Dr. Ambati says he hopes patients with mild, moderate and even advanced keratoconus will benefit from this drop. "If the keratoconus is very severe or the patient has corneal scarring, they'll need a transplant, of course, but as long as that's not the case, and we can provide pharmacologic benefit at minimal risk, I think that would be a tremendous advance in our care of keratoconus patients."

An at-home prescription drop could benefit clinicians as well. "Surgical cross-linking is a challenge to clinician workflow, to put it charitably, because of how long it takes to load riboflavin," says Dr. Ambati. "It's a challenge in terms of the number of postop visits, and it's also a challenge to get insurance approval. If we can conserve physician time and energy and move away from a surgical paradigm to a pharmacologic paradigm, I think it's a win for physicians, who would prefer not to have surgical risks and complications in patients that need to be managed, and who frankly have better uses for their time than putting in eye drops every two minutes for 45 minutes to load a patient's cornea."

CXL at the Slit Lamp

Though it's a novel approach outside the United States, cross-linking at the slit lamp doesn't differ practically from cross-linking in the OR. What makes cross-linking possible at the slit lamp is the photochemical reaction between UV light and riboflavin, which kills pathogens,[5] explains Dr. Hafezi. "The patient's position doesn't matter when it comes to UV irradiation, and riboflavin doesn't redistribute in the cornea for at least an hour when the patient is sitting upright,[6] which is long enough to not only perform Dresden protocol cross-linking (30 mins UV irradiation) but greatly in excess of what's required to perform accelerated cross-linking protocols, which are on the order of 10 minutes, not 30. Patients are comfortable sitting in a chair for this time, and they also have the advantage of being able to fixate their fellow eye on the slit lamp's red fixation light."

The main advantages of cross-linking at the slit lamp are cost and accessibility. Performing the procedure in-office removes the costs of running the OR, as well as the administrative burden of booking in competition with other surgeons, explains Dr. Hafezi. "It's been hard to ignore the cost and efficiency benefits that have been seen with in-office cataract surgery and the move from performing intravitreal anti-VEGF injections from the OR into a procedure room, and we haven't seen any additional safety issues associated with those transitions," he points out. "It enables surgeons to be more flexible regarding when they can perform cross-linking, since they don't have to wait for an OR slot to become available."

Farhad Hafezi, MD, PhD

Performing cross-linking at the slit lamp is possible, in part, due to the photochemical reaction between UV light and riboflavin, which kills pathogens. Because it can be done outside the OR, experts say this approach will help to bring cross-linking to regions of the world that lack large hospital centers.

Using a slit lamp will also open up cross-linking to more remote regions. Dr. Hafezi says that, given that most ORs are in big hospitals in large population centers, if you don't need an OR, and just need a slit lamp, then you can perform cross-linking just as easily in remote parts of low-to-middle income countries as you can in a large hospital in a high-income country.

Currently, only one cross-linking device can be used at the slit lamp—the C-eye (EMAGine AG, Zug, Switzerland). C-eye is a portable, battery-powered device that can be charged with a USB-C cable. It automatically calibrates UV output and fits a range of slit lamps. The device includes eight keratoconus protocols, including the Dresden protocol, pulsed and high fluence protocols, and the sub400 thin-cornea protocol;[7] a refractive cross-linking protocol for LASIK, SMILE and PRK; and two infectious keratitis treatment protocols.

"My go-to protocol for many years was 9 mW/cm^2 for 10 minutes," Dr. Hafezi says. "It doesn't provide the same biomechanical strength as the Dresden protocol, but clinically, it's sufficient for most forms of keratoconus in adults. I reserve the classic 30-minute Dresden protocol for the most aggressive forms of keratoconus (in children), but this will change in the near future. Our latest research, which is in press with TVST, identified an accelerated protocol using very high fluence that rivals the stability of the Dresden protocol but takes a fraction of the time. This protocol will be implemented clinically in the next one to two years. In patients with corneas thinner than 400 µm, I regularly perform our sub400 protocol epi-off CXL."

Branching into Thin Corneas

Conventional cross-linking is limited to eyes with a corneal thickness greater than 400 µm, but there are several techniques in use for thin corneas such as using hypo-osmolaric riboflavin to swell the cornea,[8] a riboflavin-soaked contact lens[9] and leaving epithelial cells in "islands" above the thinnest points.[10]

In 2014, Dr. Hafezi and his group began looking into a different approach, one that would alter the amount of light delivered to the eye, rather than altering the thickness of the cornea, which may be unpredictable. "When CXL was introduced, we didn't have a complete understanding of the UV-riboflavin reaction," he says. "We didn't know, until our research group showed five years ago, that oxygen diffusion into the cornea was an essential component of the cross-linking reaction and that it gets consumed rapidly once the UV irradiation begins.[11]

"Once we understood that, this enabled us to develop a cross-linking algorithm that accounted for corneal thickness, UV intensity and duration of irradiation, and predicted the depth of the cross-linking effect.[12] We then validated this algorithm, later called sub400, first in laboratory experiments and then in a clinical trial.[7] This means that once we measure a cornea's thickness, we can individualize the amount of UV irradiation to the cornea to cross-link a 'safe' amount of cornea, and leave a 70-µm safety margin of un-cross-linked cornea above the corneal endothelium. All of this can be performed at the slit lamp. I perform sub400 cross-linking at the slit lamp almost every time I spend a day performing surgery."

Accelerated CXL

Proponents say that accelerated CXL addresses many of the problems found with conventional CXL such as the standard treatment's long procedure duration, stromal damage, patient discomfort and risk of corneal haze.

"Accelerated cross-linking has really changed the way the procedure is offered to patients with keratoconus," says Dr. Singal. "Most of the modifications that have been applied since cross-linking's inception in 2003 are related to modifications in fluence and time, per the Bunsen-Roscoe law of reciprocity, so the total irradiation remains constant. The gold standard of CXL is the Dresden protocol, which is based on supplying the cornea with a total irradiation of 5.4 J/cm^2. Accelerated CXL can decrease the procedure time by increasing the fluence, while keeping the total irradiation amount constant at 5.4 J/cm^2."

Dr. Singal says that because the treatment duration is much shorter, the procedure is more efficient and comfortable for the patient. "The

OTHER APPROACHES TO AND USES FOR CROSS-LINKING

Here are two more off-label ways cross-linking is being used:

• ***Oral riboflavin.*** John S. Jarstad, MD, FAAO, of the University of South Florida-Tampa, proposed a walking protocol for cross-linking that involves taking 400 mg/day of riboflavin and walking vigorously toward the sun for 15 minutes each day without wearing sunglasses or UV-blocking contact lenses. In his clinical trial, all patients following this protocol achieved an average 1.2 D of corneal flattening and their keratoconus didn't progress, while the control group taking 100 mg/day stabilized but saw less flattening. (To read more about this, see "Crosslinking 2020: Closer to the Holy Grail" from the October 2020 issue of *Review*.)

• ***PACK-CXL.*** As Dr. Hafezi points out, the photochemical reaction between UVA light and riboflavin during cross-linking has the beneficial side effect of killing pathogens, making cross-linking a safe procedure to perform in an office setting. Photo-activated chromophore for infectious keratitis, or PACK-CXL, has been studied for the management of infectious keratitis and may also serve as an adjunctive therapy for treating fungal keratitis.[14]

A 2013 meta-analysis reported that cross-linking's effectiveness in reducing corneal melt was in the following order, from most to least effective: Gram-negative bacteria, Gram-positive bacteria, *Acanthamoeba* and fungus.[15] Researchers believe that its low effectiveness in fungal infections may be due to the fact that fungal infections penetrate deeper into the cornea than most bacteria. One case study in 2019 demonstrated resolution of a fungal infiltrate at the site of a phaco-tunnel.[16] The cross-linking procedure used 0.1% riboflavin with the Dresden protocol. Rashmi Deshmukh, MD, of Queens Medical Centre, University of Nottingham, says it's possible that PACK-CXL had a synergistic effect with the already administered antifungal medical treatment.

—CL

shorter time also reduces corneal dehydration, and less keratocyte exposure time potentially results in less haze," she adds.

However, simply following the Bunsen-Roscoe law of reciprocity for accelerated CXL protocols doesn't lead to the same outcomes as in the standard Dresden protocol. "This is because we're shortening the time that oxygen is available to the cornea during the CXL process," Dr. Singal says. "Recent studies have shown that pulsed delivery of the UVA light to the cornea is important for accelerated CXL because it allows for more oxygenation during treatment. This results in enhanced release of singlet oxygen, allowing for more effective cross-linking of the collagen molecules."

Dr. Singal's 2020 study on accelerated epi-off cross-linking prospectively studied efficacy, risk of progression and characteristics affecting outcomes in 612 eyes.[13] "Our study is the largest prospective study looking at accelerated CXL in keratoconus patients," she notes. "It was reassuring to see that our study supported many of the smaller studies, regarding efficacy. We found that our cohort showed stabilization of the disease at one year, which we defined as a change of less than 1 D in Kmax from baseline."

When determining progression risk in the study, she says age and preop Kmax values were important. "The risk of progression for our entire cohort was 17.9 percent, which is consistent with previously reported studies using the accelerated protocol," she says. "However, when we looked at our subset of patients that had a preop Kmax value greater than 58 (191 eyes, approximately 30 percent of the total group), we found that about 20 percent progressed at one year. Among our subset of pediatric patients (14 to 18 years old, 53 eyes), we noticed a very high risk of progression at 32 percent." Dr. Singal says it's important to counsel these patients preoperatively about the increased risks and closely monitor them after the procedure. ◀

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CATARACT/IOL SURGERY AFTER RK

Surgeons need to manage inaccurate IOL calculations, an extended postop recovery time and patient expectations.

MICHELLE STEPHENSON
CONTRIBUTING EDITOR

Eyes that have undergone radial keratotomy have irregular corneas, which can present unique challenges for cataract surgeons. Lens calculations, the surgical procedure itself and the postoperative healing period are not routine in these eyes.

Lens Calculations

According to Daniel Chang, MD, who is in practice in Bakersfield, California, the challenge with lens calculations is that these patients have irregular and fluctuating corneas. "You have a target that's hard to hit and that's moving," he says. "When it comes to biometry, it's a challenge trying to figure out what to do with the information that you get, because every machine is going to give you something potentially very different, particularly when it comes to astigmatism."

Los Angeles surgeon Uday Devgan, MD, agrees. "Lens calculations after RK are challenging because RK changes the cornea," he says. "It's different from LASIK, because LASIK just changes the front curvature of the cornea. In RK, both the front and the back of the cornea are changed. The RK cuts that are made change the whole structure. In other words, in LASIK or PRK, the laser is taking away some tissue; in RK, no tissue is taken away. We are just changing its configuration. By making those radial cuts, you flatten the center of the cornea."

Because of the RK cuts, when the cornea is measured, surgeons are overestimating its power. "As a result, the typical lens calculation formulas will indicate too low of an IOL power," Dr. Devgan says. "The key is to adjust the IOL power calculations based on the RK that was done, and there are many different ways of doing this. Probably the easiest is to go to the ASCRS website, where you can just type in all of the data you have."

Dr. Devgan notes that the amount to add to the lens power depends on how many cuts were made with the RK. "These aren't as exact as a lens calculator, but are a general rule of thumb," he says. "If you have a four-cut RK, add 0.5 to 1 D of IOL power. If it's an eight-cut RK, add maybe 1 to 1.5 D of IOL power. If it's 12-cut and beyond, add at least 2 D of power. It's not quite as accurate as doing all of the fancy calculations and special measurements, but it works."

Richard Hoffman, MD, who is in practice in Eugene, Oregon, uses the ASCRS calculator, as well as the Holladay 2, which has a box to check for post-RK eyes. "When all else fails, you can just use the effective corneal refractive power on your corneal topography," he says. "That will usually get you close, but the Holladay 2 formula takes into account the corneal topography and the previous RK. I've been pretty successful with those two methods in getting people close to where they should be."

Limitations of RK

Because RK causes the cornea to be irregular, Dr. Devgan recommends not placing a multifocal lens in a post-RK eye. "With RK, the cornea is basically multifocal already," he explains. "RK isn't a smooth, clean

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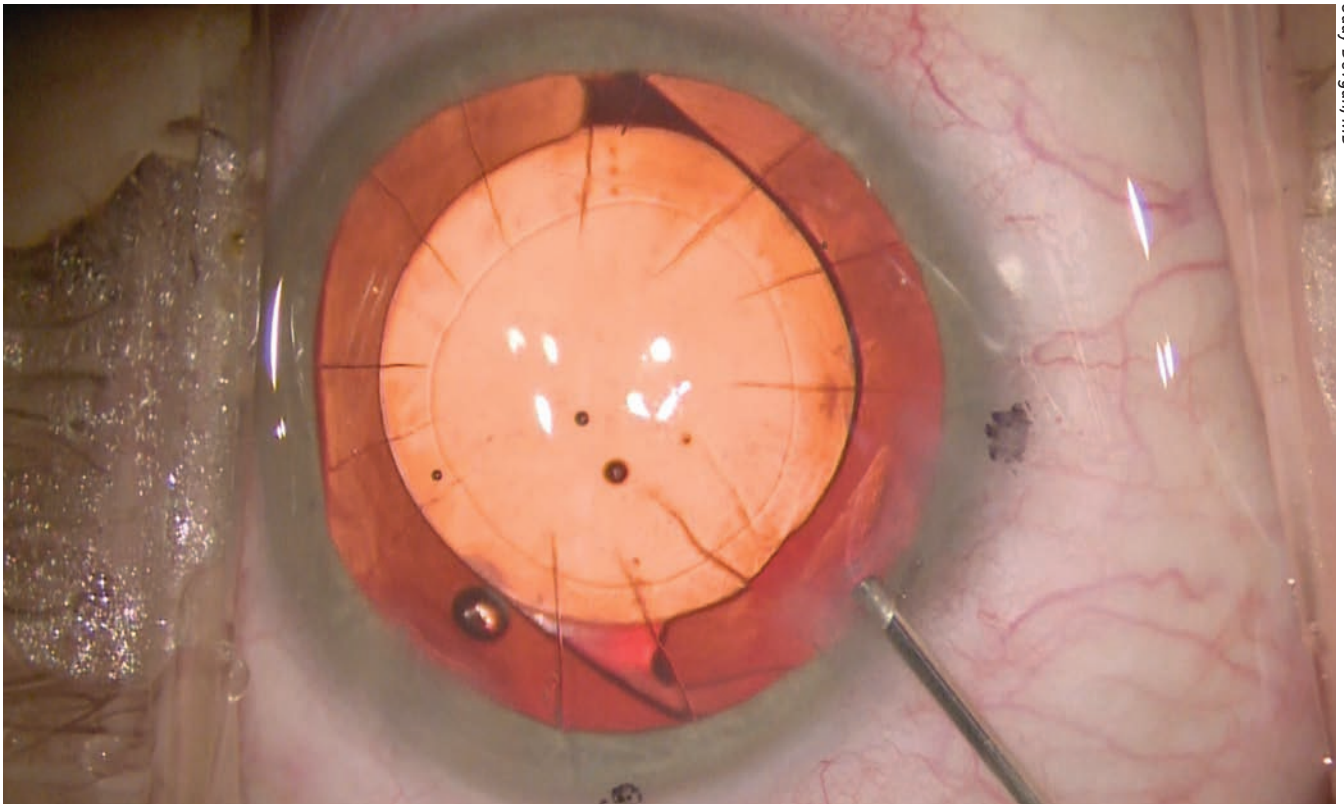

Uday Devgan, MD

An eye with a toric IOL and many RK cuts. Surgeons say that, in some RK eyes, you can put the entry wound between two of these cuts.

treatment like LASIK. As a result, RK patients don't do well with multifocal lenses. I prefer to stick with a monofocal lens in these eyes. RK patients can do very well with a monofocal toric lens if they have a consistent degree of astigmatism."

Dr. Hoffman agrees that multifocal IOLs shouldn't be used in these patients; however, he says that surgeons have had success with extended depth-of-focus lenses. "The safest thing is just to implant a standard monofocal lens, but, if you have the right patient who understands all the limitations, an extended depth-of-focus lens is a possible option for them," he says.

Another limitation of RK is that the radial cuts often result in a very small optical zone. "These cuts are often within a couple of millimeters of the central visual axis, which can cause these patients to see starbursts around lights at night," Dr. Devgan explains. "This will continue after cataract surgery. Patients must understand that, while the lens in their eye is changed during cataract surgery, they're still living with the same cornea and the aberrations, distortions and dysphotopsias they've experienced since undergoing RK."

Additionally, corneas in patients who have undergone RK change throughout the day. Some patients have better reading vision in the morning, so they will do all of their close-up work in the morning hours. Other patients experience the opposite. "This diurnal fluctuation is very consistent in these patients, and they are used to living with it," says Dr. Devgan. "When you measure them, make sure to ask about whether they're having their best near vision or not at the time."

Surgery

When contemplating surgery, it's important to remember that RK cuts are typically 90 percent or more of the corneal depth. If the surgeon inadvertently intersects the existing RK incisions when making the cataract surgery incisions, the RK incisions can unzip. "You never want to intersect a pre-existing RK incision," Dr. Devgan advises. "If you have an eight-cut-or-fewer RK incision, you can usually slip your phaco incisions in between two of the RK cuts. However, once you get to 12-cut or more, you're probably not going to be able to make your incision in the cornea. In these cases, you may have to revert to making a scleral tunnel incision."

Dr. Hoffman uses a bimanual technique in these patients. "It's nice, especially in RK eyes, because you can fit your 1-mm bimanual incisions in between the RK incisions, even if the eye had a 16-cut RK, because usually there's a space between some of the RK incisions that's wider than the space between others," he explains. "Most RK patients have eight-cut RKs, so just a standard coaxial technique can be

done. If a patient has many incisions and you don't do a bimanual technique, then you usually have to cut down the conjunctiva and do a scleral tunnel incision. By having the sclera in the roof of your tunnel, you can go through those RK incisions without them splitting open. If a patient has 24 RK incisions, I can do the entire bimanual procedure through two 1-mm incisions that are fit in between the RK incisions. When it's time to place the implant, I'll just do a 2.2-mm stab incision that's through the conjunctiva and the sclera, so I don't really have to cut down the conjunctiva."

According to Dr. Devgan, it's important not to use too high of an infusion pressure intraoperatively because that can put stress on the RK incisions. "At the end of cataract surgery, I not only check my cataract surgery incisions to make sure they're sealed and watertight, I also check all the pre-existing RK incisions, too," he says. "You can do this very easily by using a fluorescein dye strip and painting the whole anterior surface of the eye with the dye. Then, you can see if there's a leak anywhere."

In the postoperative period, surgeons and patients should be prepared for swelling of the RK incisions. "Even the gentlest and most beautiful cataract surgery is going to cause the RK incisions to temporarily swell," says Dr. Devgan. "Sometimes, surgeons will perform a cataract surgery on an RK patient, and on postop day one, the patient—instead of being plano—is +1.5. The surgeon is distraught, but this is actually OK. Here's how you tell: Look at the patient's preoperative K measurements. For a simple example, let's say the K reading was 36 D. On postop day one, just put the patient back in that same machine and do K measurements. Instead of 36, let's say it's 34.50. This means that the peripheral RK incisions swelled up after the surgery and made the central cornea even flatter, but that's temporary. The patient will typically be 35.50 a week later. Then, two weeks or a month out, the postop K value is back to 36, the swelling has resolved and the patient is plano. So, when you check the patient's prescription postop, make sure you also compare the keratometry values from before and after surgery."

> **"[RK patients] are not like LASIK patients who expect everything to be perfect, so you have an easier population to deal with in that regard."**
>
> ***—Daniel Chang, MD***

Additionally, Dr. Devgan recommends always choosing the higher lens power if you're choosing between two powers. "RK has been called the gift that keeps on giving, meaning if you make the patient a perfect plano prescription postop, he or she will only stay that way for a couple of years," Dr. Devgan says. "After a few years, he or she will be +0.5, and then in 5 or 10 years, he or she can be +1 again. The cornea is never fully stable throughout the patient's life. Always choose the higher lens power, and let the patient end up -0.5 D postop instead of a perfect 0. It will only stay -0.5 D for maybe a year or two, then it's going to be a perfect plano."

Managing Patient Expectations

Dr. Hoffman adds that there is a greater chance for refractive surprises in post-RK eyes, so he encourages patients to have realistic expectations. "This is actually not difficult in most RK patients, because, most of the time, these patients have fluctuating vision, and they might have had a hyperopic shift post-RK. They are willing to accept a less-than-perfect result. I tell them that, in a normal patient, there's a normal bell curve that's somewhat narrow. In an RK patient, the bell curve is widened, so a patient could end up farsighted or nearsighted enough where he or she would need glasses to fine-tune vision," he adds.

Dr. Chang recommends asking patients how they felt about the quality of vision they had after RK but before the cataract formed. "The saving grace with these patients is that they were all early adopters," he says. "They're not like LASIK patients who expect everything to be perfect, so you have an easier population to deal with in that regard. From a counseling standpoint, you have some advantages there."

Dr. Hoffman prepares patients to expect a longer period for stabilization of the refraction postoperatively. "For the first few days or weeks, the patient should be farsighted, about a +2," he explains. "Sometimes, patients will be a +4 or +5 on the first day depending on the number of RK incisions they have, and they will slowly lose that farsightedness. Depending on how many incisions they have, it might take two or three months for their refraction to stabilize, so they have to be patient postoperatively. Many of them experience fluctuating vision throughout the day, and they had that before their cataract surgery. Cataract surgery doesn't get rid of that, unfortunately, so they can still have fluctuating vision after their cataract surgery."

Dr. Hoffman also mentions the possibility of the RK incisions opening up during surgery, which would require suturing. "In the worst-case scenario, surgeons will need to suture and glue the incisions," he says. "This is rare in patients with eight- or 16-cut RK, but I see a lot of patients with 20-cut, 24-cut and 32-cut RKs. In these patients, there's a greater chance of those incisions splitting open at the time of surgery or toward the end of the procedure. Luckily, I haven't seen many cases of that lately." ◀

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RESPONDING TO PREMIUM IOL SETBACKS

What to do when you miss the mark—and how to ensure you don't next time.

SEAN KAVANAUGH MCKINNEY
SENIOR EDITOR

By now, most surgeons are well-versed on how to use preop diagnostics, treatments and patient counseling to optimize premium IOL results. But few discuss what to do when a case doesn't go as planned. Postop problems—so familiar in this age of targeting perfect vision—may include exacerbations of dry eye, residual refractive error and astigmatism, other forms of ocular surface disease, unexpected retinal issues and dysphotopsias—to name a few. In this review, surgeons explain how they've overcome many of these challenges and how they now safeguard against repeat episodes.

FIGURE 1. PREMIUM IOL PATIENT COMPLAINTS

REASON FOR DISSATISFACTION	EYES (N = 74)
Residual refractive error	42 (57%)
Dry eye	26 (35%)
Visual Disturbance	19 (26%) Waxy vision, ghosting
Pre-existing condition	15 (20%) Fuchs', ERM, CME, dry AMD, ABMD, strabismus
Intraoperative complication (vitreous loss)	6 (8%) Sulcus IOL
Postoperative complication (uveitis, RD, lens dislocation)	3 (4%)
Unreasonable expectations	6 (8%)

Kendall E. Donaldson, MD, MS

Residual refractive error after premium cataract surgery was surprisingly high, at 57 percent, in this study.
Gibbons A, Ali TK, Waren DP, Donaldson KE. Causes and correction of dissatisfaction after implantation of presbyopia-correcting intraocular lenses. Clin Ophthalmol 2016;10:1965-1970.

Not What You Think?

A study of 74 eyes of patients after the implantation of presbyopia-correcting intraocular lenses found that unreasonable expectations as a cause of postop dissatisfaction was a factor in only 8 percent of the surgeries evaluated.[1] So much for the notion that patients are often dissatisfied with the results of premium cataract surgery because they have unreasonable expectations before reaching your table. The study was a retrospective review of the clinical records of patients who had reported one or more sources of postop dissatisfaction between January 2009 and December 2013 at the Bascom Palmer Eye Institute. A total of 57 percent of all cases involved residual refractive errors and 35 percent, dry eye, according to the study. (*For other leading causes of dissatisfaction found in this study, see Figure 1 above.*)

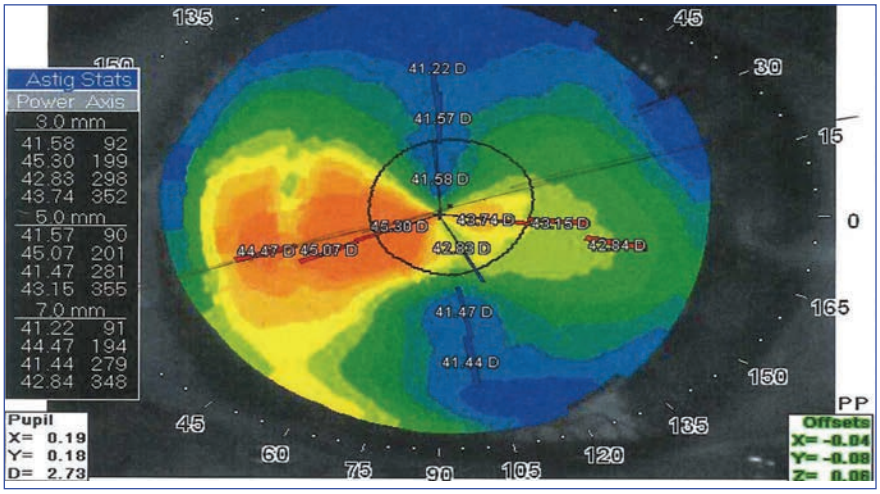
The most common symptom underlying all complaints was blurry or foggy vision, both for distance and near vision. A single treating physi-

This article has no commercial sponsorship.

Dr. Donaldson discloses financial relationships with Alcon, Johnson & Johnson Vision and Bausch + Lomb. **Dr. Raviv** reports financial relationships with Cassini Technologies, Johnson & Johnson Vision, Ocular Therapeutix and Zeiss. **Dr. Al-Mohtaseb** reports financial relationships with Alcon, Bausch + Lomb, Johnson &Johnson Vision, Ocular Therapeutix, Zeiss, CorneaGen and Allergan.

cian determined probable causes of dissatisfaction and provided remedies that included glasses, contact lenses, dry-eye therapy, laser vision correction and IOL exchanges. Significantly, 23 percent of treated patients were only partially satisfied with their final results and 32 percent remained completely dissatisfied. The findings suggest a need for a deeper search for causes of patient unhappiness after implantation of premium IOLs, refinement of postop treatments and, of course, increased diagnostic vigilance before surgery to ensure that potential causes of dissatisfaction are identified and successfully resolved before they create postop problems, according to Kendall Donaldson, MD, MS, one of the authors of the study.

"We can do a better job of getting these patients to 20-happy," says Dr. Donaldson, a professor of clinical ophthalmology at Bascom Palmer in Miami, Florida. "Our objective should be to end up within 0.5 D of our refractive target. How can we make sure we achieve this every time? That's the key question that we must try to answer. Equally important is the emergent question we face in the context of this report: What can we do to reverse—or at least significantly mitigate—a negative patient outcome?"



Kendall E. Donaldson, MD, MS

Figure 2. Significant residual astigmatism can seem like a devastating result for a postop patient who has paid a premium price for premium vision.

Fixing Residual Refractive Errors

If the problem for your unhappy patient is a residual refractive error, Dr. Donaldson, also a professor of cornea/external disease, cataract and refractive surgery at Bascom Palmer, emphasizes the importance of identifying the cause and extent of the error.

"Is it the wrong IOL for that eye?" she asks. "Does the patient have an underlying condition that was missed, such as ocular surface disease, anterior basement membrane dystrophy, Salzmann's nodular degeneration or an irregular eye that's perhaps too long, short, or presenting with staphyloma? Was the problem anticipated and discussed with the patient preoperatively? Does the patient have a history of LASIK, PRK or RK that's playing a role in his or her unexpected outcome? Is irregular astigmatism a factor?"

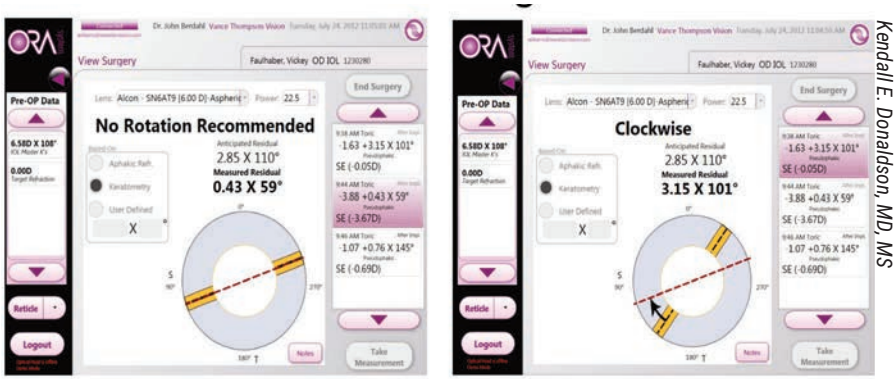
Other possibilities to consider, she continues, include less-than-adequate effective lens position, posterior corneal astigmatism and, sometimes, unknown reasons (when all testing appears normal but the patient is unhappy with the quality of vision).

"In all of these cases, we always check for ocular surface disease that might have been missed preoperatively and, if present, promptly treat it," Dr. Donaldson says. "We can adequately treat some of these other conditions, such as AMBD with a superficial keratectomy, but some ocular surface conditions are chronic and can only be improved, not cured. Remember, though, that we sometimes need to wait for patients to neuroadapt to their new vision. When the time is right, providing laser vision correction as an enhancement can often be a good solution in many of these cases. If the residual refractive error is large, I'll consider an IOL exchange, implantation of a piggyback IOL or again, if appropriate, laser vision correction."

Of course, how you address a residual refractive error will be determined by the type of correction needed, Dr. Donaldson continues. "Myopes are typically easy to treat with LASIK, which the patient will usually find tolerable," notes Dr. Donaldson. "Hyperopes can be more challenging to treat with LASIK or PRK and, as an alternative, may require an IOL exchange."

Dr. Donaldson notes that patients with low amounts of astigmatism are good candidates for almost any type of follow-up procedure. However, she points out that significant residual astigmatism can seem like a devastating result for a postop patient who has paid a premium price for premium vision. (*See Figure 2, above.*) "It's important to zero in on the causes of residual astigmatism," she says. "Surgically induced astigmatism can be related to poor preop measurements, poor calculations, posterior corneal irregularities that weren't detected by keratometry, IOL rotation or poor IOL placement. Other factors could be related to the implantation of a wrong lens, which, of course, may also have resulted from poor measurements and inaccurate calculations. Additional considerations in this area: Could a rotational error of a toric IOL be a factor, either in multifocal or monofocal situations?"

By pinpointing sources of postop astigmatic surprise, Dr. Donaldson continues, you can sometimes address causative factors with more precision than you might have been able



Kendall E. Donaldson, MD, MS

Figure 3. Intraoperative aberrometry can help determine if an IOL needs to be rotated.

to—for one reason or another—when planning the surgery. "As we know, specific technologies and formulas can be used to turn things around for these patients," she says. "Formulas that can reveal the need for postop correction and alignment include Astigmatismfix.com and the Barrett Rx Formula [ascrs.org/tools/barrett-rx-formula]." She adds that Optiwave Refractive Analysis aberrometry (ORA, Alcon) and iTrace Visual Analyzer (Tracey Technologies, Houston, Texas), another wavefront aberrometer, can help guide alignment and realignment of a toric IOL—or even a non-toric IOL, such as an accommodating lens, in some cases.[2] (*See Figure 3 above.*)

In postop cases requiring an IOL rotation or adjustment, intraoperative aberrometers use Fourier calculations to determine the real-time readings of sphere, cylinder, axis, refractive error and IOL power.[3] (*See figure 4 to the right for an example of a successful postop rotation.*) "Don't forget that we can also use this technology during the initial surgery to make final selections of toric IOL powers and refine an IOL's alignment, reducing the incidence of residual astigmatism," she adds.

A Systematic Approach

Tal Raviv, MD, founder and medical director of the Eye Center of New York in New York City, has organized a systematic approach to treating and preventing patient unhappiness after premium cataract surgery. "We're focused on what we see as the top reasons for dissatisfaction, even among patients whose postop UCVA is 20/20," says Dr. Raviv, who's also an associate clinical professor of ophthalmology at Icahn School of Medicine at Mount Sinai. The top reasons for dissatisfaction that he cites include the following:

- glare, halos, starbursts;
- not enough near vision;
- poor distance vision and/or quality of vision; and
- generic IOL problems, such as negative dysphotopsias and dry eye.

Dr. Raviv says he responds to these forms of patient unhappiness with the following types of interventions:

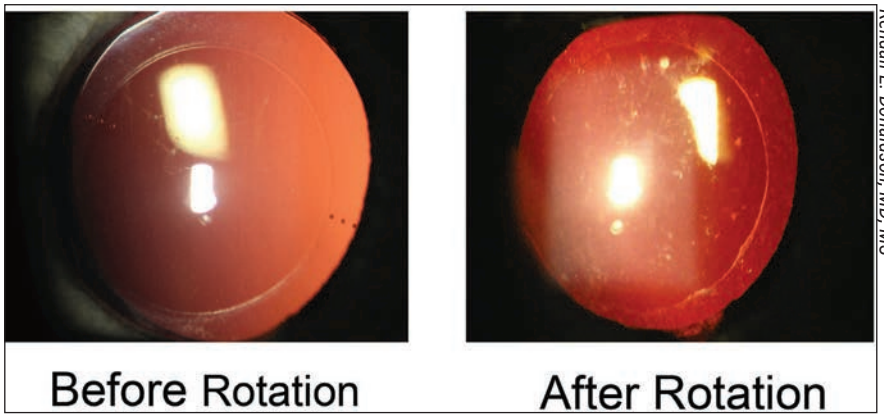
- ***Non-surgical.*** His objectives include optimizing the ocular surface (with drops, dry-eye procedures and superficial keratectomy), performing a YAG capsulotomy, actively monitoring the patient and offering glasses or contact lenses.
- ***Surgical.*** The goal here, in the face of demonstrated need, is to provide PRK or LASIK, rotate IOLs and perform IOL exchanges that may involve monofocals, extended depth of focus lenses or multifocals. Rarely, he says, he needs to provide a piggyback IOL or recenter an IOL via a lasso suture.
- ***Refer for retinal surgery.*** These referrals could be for a pars plana vitrectomy with membrane peel for an epiretinal membrane or a PPV for floaters.

Another approach to postop unhappiness that Dr. Raviv will sometimes take is to defer possible follow-up treatment until after he implants an IOL in the unhappy patient's second eye. He uses alternative IOLs in some cases. "I don't automatically double down on the same technology for the second eye," he says. "Many times, the second-eye surgery can compensate for the perceived deficiency of the first surgery. If that doesn't prove to be the case, then an IOL exchange can be carried out."

To ensure consistent delivery of care, Dr. Raviv follows what he calls the "Raviv Getting to Happy Post-IOL Algorithm." (*For a copy of the algorithm that you can use in your practice, see page 47.*) The algorithm, informed by Dr. Raviv's surgical experience, maps out responses to a variety of premium IOL postop challenges.

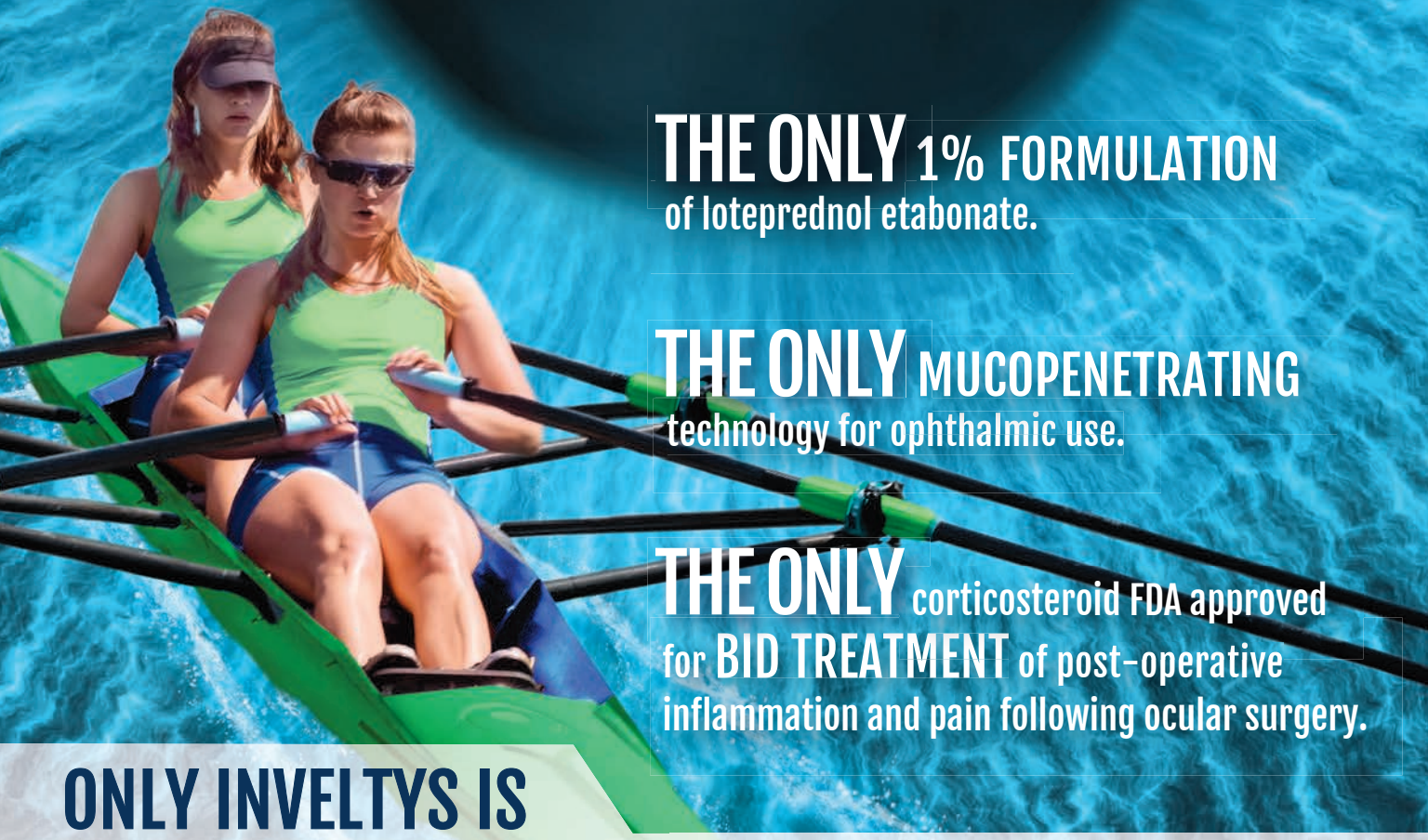
Considering Follow-up Surgery

Dr. Donaldson recommends the following strategies when deciding whether to offer follow-up surgery to unhappy premium IOL patients. "First, determine if the patient can



Kendall E. Donaldson, MD, MS

Figure 4. Postop rotation of torics, made possible by today's technology, can turn things around for some unhappy patients.



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Use of corticosteroids may result in posterior subcapsular cataract formation.

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

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

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

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

In clinical trials, the most common adverse drug reactions were eye pain (1%) and posterior capsular opacification (1%). These reactions may have been the consequence of the surgical procedure.

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

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

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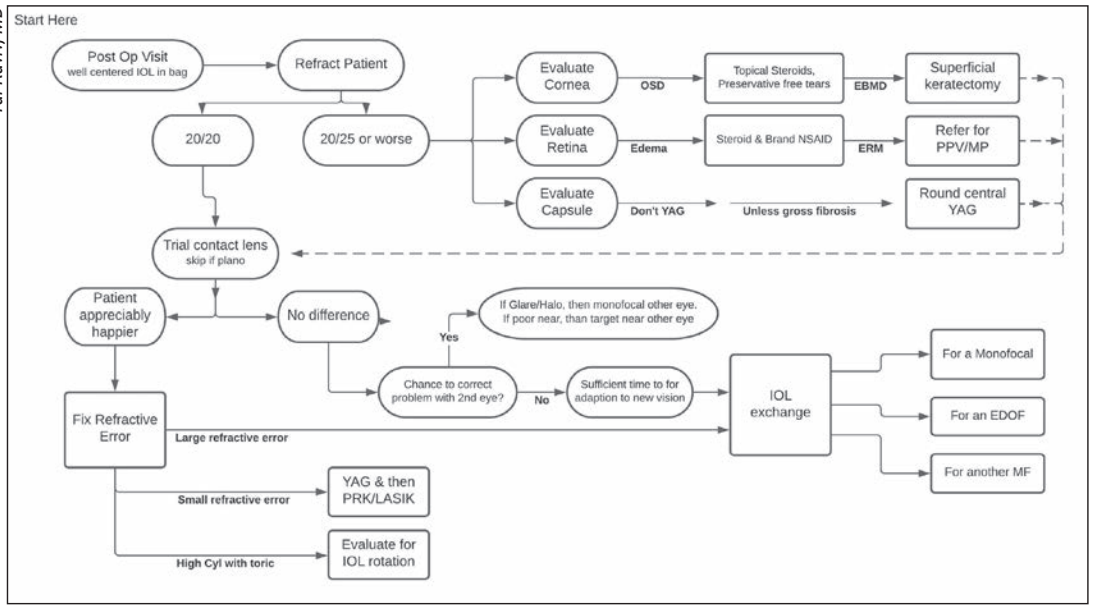
Tal Raviv, MD



tolerate waiting to see if his or her vision improves," he says. "If not, exhaust less-invasive options and potentially seek a consultation with a colleague, when appropriate. If you become convinced a second surgery on the same eye is necessary, present a clear plan to the patient and make sure the patient understands your plan 100 percent, including the timing and possible outcomes of the intervention." The next question is when to do the follow-up surgery. Generally, according to Dr. Donaldson, the following considerations should apply:

• Perform follow-up surgery sooner if a toric IOL is clearly off axis and needs to be repositioned, or if you find you've created an identifiable error in your original measurements that has led to an incorrect power calculation.

• Delay surgery (as long as it seems prudent for each patient), if:

– the patient has a small refractive error and may still neuroadapt; and

– the patient wants to wait. "I recommend three months before enhancing the postop patient who has a history of LASIK surgery, to avoid the suction effect on the cataract surgery wound," says Dr. Donaldson. "A three-month wait is also best for a patient with a history of RK, due to postoperative refractive shifts."

When debating which surgical modality to use on an unhappy postop premium IOL patient, Dr. Donaldson recommends avoiding laser vision correction if ocular surface disease has significantly contributed to the patient's dissatisfaction. "I'd choose a repeat of intraocular surgery for these patients, when possible," she adds. "In some cases, laser vision correction risks making the patient's negative experience worse, even if you've moved them fairly far along on a diagnostic and treatment regimen for the dry eye. In patients without dry eye, laser vision correction is a great option for correction of residual refractive error. For correction of astigmatism, use the tools and formulas I mentioned earlier. If the need for correction is significant enough, I would, on a case-by-case basis, consider doing a lens exchange."

Dr. Donaldson emphasizes that the overriding priority when providing premium cataract surgery should always be effective communication with patients. "Take the time to get to know your patient," she says. "Set accurate expectations before surgery. Discuss the potential need for enhancements before surgery. Remember that insufficient or outright lack of treatment of residual refractive error is the number one reason for dissatisfaction among our patients after these types of procedures. I recommend taking every measure to correct errors resulting from the initial procedure. We have many options we can use to improve disappointing postop outcomes. Every step in the process is crucial to ensuring that we achieve our very best for the patient, starting long before surgery with accurate measurements, and effective management of patients to ensure that their expectations are realistic."

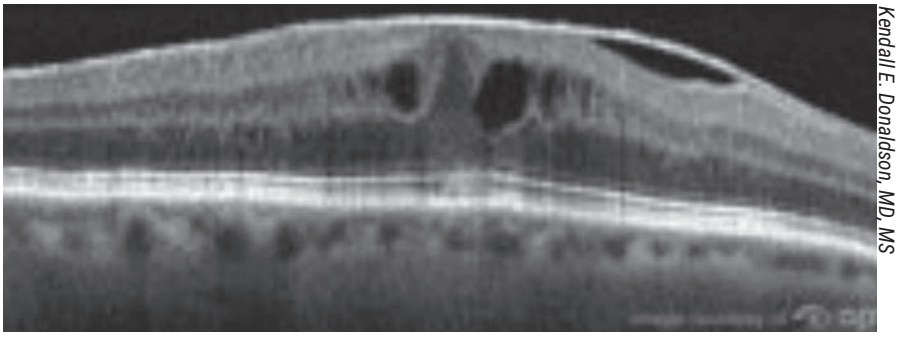
Eye on Refractive Enhancement

Zaina Al-Mohtaseb, MD, an associate professor and the associate residency director of the Cullen Eye Institute of the Baylor College of Medicine, discusses refractive enhancements when following up on unhappy premium IOL patients.

"Cataract surgery has become a refractive procedure," she says. "High patient expectations and new lens technologies require correction of spherical error, astigmatic error and, in some cases, presbyopia."

One of Dr. Al-Mohtaseb's most important goals before even considering a refractive enhancement is to optimize the ocular surface. "Preexisting dry eye is asymptomatic in many patients and it worsens after cataract surgery," she says. "Besides increased dryness, the patient experiences decreased visual acuity and contrast sensitivity. That's why diagnosing and treating any sign of ocular surface disease before cataract surgery is critical to achieving optimal surgical outcomes."

She notes that the disease can negatively affect topography and biometry and, ultimately, surgical outcomes. "These negative effects decrease goblet cell density, tear breakup time and corneal sensitivity," she says. "The



Kendall E. Donaldson, MD, MS

Figure 5. Many surgeons planning premium IOL surgery now rely on preop OCT scans to rule out retinal disorders.

end result is decreased quality of vision, fluctuating vision and decreased refractive outcomes."[4]

Before determining if a post-cataract surgery patient is a refractive surgery candidate, Dr. Al-Mohtaseb waits on IOL stabilization and resolution of postop corneal edema. "The rate of refractive stabilization is proportional to incision size and may take longer in patients with prior keratorefractive surgery, such as radial keratotomy," she points out. "We also want to make sure that the patient has enough tissue for a refractive enhancement and that we've considered all alternative treatment options."

Finally, she says, she rules out other causes of patient dissatisfaction besides the premium IOLs, such as PCO or retinal pathology. In cases of residual astigmatism, Dr. Al-Mohtaseb says that:

- toric IOL repositioning is best performed in the early postop period;
- limbal relaxing incisions are effective in treating low amounts of residual astigmatism, especially in patients whose spherical equivalent is plano; and
- IOL-based surgery is best in the early postop period for poor corneal laser refractive candidates, high refractive errors and hyperopic errors.

"Furthermore," she says, "lens-based enhancements appear superior for treating hyperopic errors because corneal-based hyperopic corrections require larger treatment zones, are less accurate and may regress over time. IOL exchange is indicated for correcting significant residual refractive error as well as IOL dislocation, malposition and multifocal IOL dissatisfaction."

She adds: "Early exchange via the original wound is also ideal to avoid complications due to late capsular bag fibrosis. Late removal of an IOL may require cutting the IOL haptics or viscodissection to free the haptics and remove the IOL as one piece. Wound enlargement can also cause or worsen astigmatism after IOL exchange." (*For an in-depth look at IOL exchange, see this month's cover story on p. 52.*)

New Kind of Partnership

Some surgeons say prevention of premium IOL surgery disappointment creates the need for a new kind of partnership between them and their patients. What's envisioned, and practiced by some surgeons, is a relationship based on shared planning, rather than one that's limited to boundaries imposed by informed consent and risk management. A successful, communicative relationship can provide the best means for identifying patients who aren't good candidates for premium IOL surgery, these surgeons argue.

"Refractive cataract surgery is a transformational journey patients take with their surgeons," says Dr. Raviv. "It's the art and science of planning a customized visual solution, executing it perfectly and enhancing it as needed—and enhancing it is the critical part—during the postoperative period."

Why, he asks, do premium IOLs represent less than 10 percent of the IOL market, even after 20 years into the development of high-technology lenses? "Today's sixth- and seventh-generation PC-IOLs are more forgiving, have less photic effects and provide excellent ranges of vision," he says. "We should be using a lot more of these. There are practices in the United States, successful refractive practices, that use these lenses on 40 to 50 percent or more of their patients. We certainly use a lot of them in my practice. But the reality is that if you have a budding refractive cataract practice, one unhappy multifocal IOL patient can really deflate your penchant for putting one in. So I posit that a refractive cataract surgeon have specific tools and techniques at the ready and know how to use them to treat unhappy multifocal IOL patients."

Among the essential tools, he continues, is a contact lens trial set that includes torics. The contact lenses, available in many small steps away from plano, are superior to a manifest refraction and glasses when it comes to confirming the precise correction that will maximally satisfy an unhappy postop premium IOL patient, he says. "You also need the skill to perform IOL exchanges, and you need to have access to and the skilled ability to use an excimer laser for PRK, at the least. If you don't offer these, you need to partner with someone in your practice or elsewhere who does." He adds that you also need to establish a payment plan that frees patients of any obligations to shell out more cash for postop services that may be needed.

Dr. Raviv says managing patient expectations is essential for offering premium IOL services. "Add these seven words to your electronic health records—'Discussed photic phenom, LVC, IOL exchange, glasses'—and briefly review each of these possibilities with every prospective multifocal IOL patient," he says. "I tell my patients, 'I'm not just going to correct the optical clarity of your eye. I'm also going to clear the focus of your eye. To accomplish that, we may also need to do a touch-up—if you heal out of focus, for example.'"

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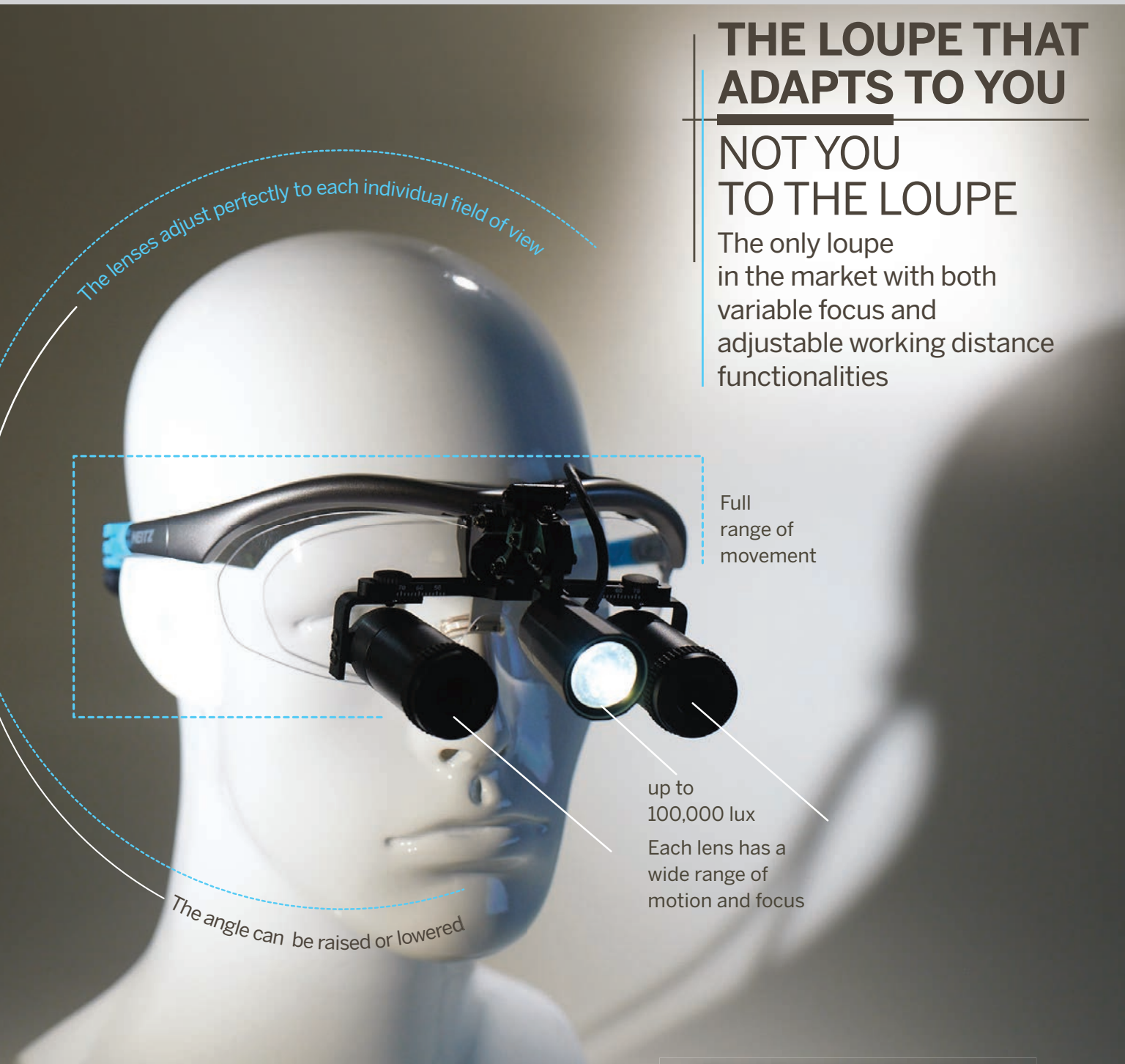

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Under the terms of the payment agreement that waives additional fees, he explains the possible need for follow-up laser vision correction, a possible IOL exchange and, occasionally, the need to wear glasses for near vision. These situations crop up "less than 5 percent of the time, but this is something patients need to know," he adds. "It's critical because some patients say, 'I don't want another surgery.' If they have absolute zero tolerance for a second procedure, then they're really not candidates for a multifocal lens, in my book."

Meanwhile, part of establishing realistic patient expectations means customizing patient education, providing your own brochures and video content to replace industry materials that make some information "a little too rosy," according to Dr. Raviv. He discusses the possibility and likelihood of unwanted visual symptoms that are specific to each brand of IOL. These symptoms may include glare, halos, starbursts, occasional decreased BCVA, blurry near vision and refractive errors.

Identifying Pre-Existing Conditions

Some surgeons are finding they can improve outcomes by increasing their testing and screening efforts before surgery. Many now rely on preop OCT scans to screen for retinal disorders and preop topography to help detect ocular surface disease, corneal dystrophies and degenerations.

"As we institute treatment (before surgery), we track patients' progress, and we have found tear osmolarity (TearLab Osmolarity System) to be a very helpful tool in doing this when used in conjunction with a thorough slit lamp exam and symptom assessment," says Dr. Donaldson. "We've always used the OSDI (Ocular Surface Disease Index) because, of course, we want to know how the patient is feeling." Another helpful screening tool is Inflammadry (Quidel), which aids in detection of inflammation that may need to be treated preoperatively to ensure more accurate preop measurements and a better visual outcome.

WHEN DYSPHOTOPSIAS OCCUR

Dr. Donaldson recommends you consider the following treatment strategies for dysphotopsias:

- Positive (glare, arcs, streaks, halos)
  - pupil modulation - constriction
  - IOL exchange – for material with lower index of refraction
  - optic with round anterior edge (not available in U.S.)
- Negative (shadows, dark spots and crescents)
  - reverse optic capture
  - sulcus IOL placement
  - YAG anterior capsule
  - glasses with solid rim/sidepiece

Hyperosmolarity is also associated with variability in K measurements, a situation that requires increased diagnostic vigilance when evaluating patients for premium IOL surgery.[5] "If the patient's topography is less than optimal, we determine if the tear film needs to be addressed," says Dr. Donaldson. "If necessary, we postpone surgery and reassess the patient at a later date. I recommend that you not operate until you're certain all symptoms are controlled. Measure before any eye drops are administered and repeat on eyes with unusual and inconsistent findings.

"If we determine the postop error has resulted from preop measurements, we need to determine if it was our fault, possibly based a technician's error, or perhaps an instrument error," Dr. Donaldson adds, saying that she typically obtains keratometry readings on several devices and compares her findings to identify potential inconsistencies. She'll also rely on a select few technicians for this testing to ensure more consistency.

One other important issue is a patient's history of having LASIK surgery.

"We know that patients with a history of LASIK surgery have already lost some contrast sensitivity, so we need to be mindful of that when deciding if a patient is a good candidate for premium lens technology," Dr. Donaldson says.

Traits of Challenge, Togetherness

Patient personality has also emerged as a consideration in premium IOL surgery. In 2020, a study found that multifocal IOLs helped ensure better postop visual acuity, but that some patients were also unhappy with their outcomes.[6] Patients with a dominant personality trait of neuroticism were the least happy with their postop outcomes, the research found. Conscientious and agreeable patients were the most satisfied with their postop outcomes. The study suggested that a preop psychological exam and a careful surgical selection process may be in order for patients with neurotic personality traits. Dr. Donaldson also emphasizes always ensuring that you keep patient expectations realistic. "Offer available options but don't promise perfect outcomes," she adds.

Above all, according to Dr. Raviv, the right kind of doctor-patient relationship must be maintained to ensure success for all. "To take our patients through this journey, we must offer empathy, availability and compassion," he says. "Patients need to know that we're there for them—and committed to taking every step with them that's needed." ◀

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OUT WITH THE OLD: SUCCESSFUL IOL EXCHANGE

Surgeons share pearls for ensuring a good lens-exchange outcome—and a happy patient.

CHRISTOPHER KENT
SENIOR EDITOR

Part of the reality of cataract surgery is that a small percentage of implanted monofocal intraocular lenses and presbyopia-correcting intraocular lenses eventually require an IOL exchange. Those exchanges are necessitated by numerous problems, including pathology, surgical error and patient dissatisfaction with refractive outcomes or visual phenomena.

A recent study conducted at Duke University Eye Center explored the causes of lens exchange and the success of different methods used to perform the exchange. The study involved a retrospective review of 91 eyes of 83 patients who underwent IOL exchange between January 2015 and April 2019; lenses explanted included 66 monofocal IOLs and 25 presbyopia-correcting IOLs. (Fifty-six percent of patients with monofocal IOLs and 40 percent of patients with presbyopia-correcting IOLs had had other prior ocular surgeries.)

The study (presented at the 2020 meeting of the American Society of Cataract and Refractive Surgery) found:

- Sixty-three percent of the exchanges were for dislocation; 8.8 percent were done to address uveitis-glaucoma-hyphema (UGH) syndrome.
- Eighty percent of presbyopia-correcting lens exchanges were done to address lens-induced visual disturbance.
- Monofocal IOLs were most often replaced with an anterior chamber IOL; presbyopia-correcting lenses were most often replaced with a ciliary sulcus posterior chamber IOL.
- Patients with both monofocal and presbyopia-correcting lenses had improved UCVA and BCVA following IOL exchange.
- Prior ocular surgery may be a risk factor for IOL exchange.

Here, surgeons share their insights and pearls for deciding when an exchange is appropriate and how to make sure it leads to the best possible outcome.

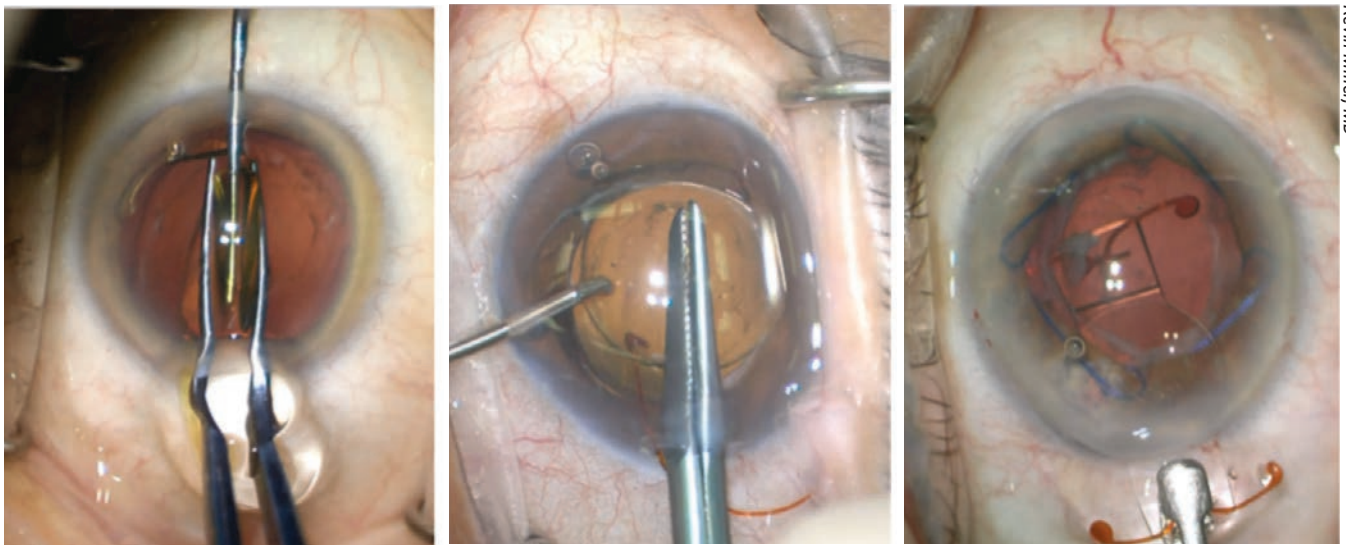
Deciding How to Proceed

"When you're doing an IOL exchange you have to have a plan A, plan B and sometimes a plan C," notes Kevin M. Miller, MD, chief of the Cataract and Refractive Surgery Division of the David Geffen School of Medicine at UCLA. "Very infrequently, you'll have a situation where everything is perfect except the power of the lens. Then you can stick with plan A and swap out the off-lens for an appropriately powered lens. But that only happens 5 percent of the time in my practice. Most cases are much more complicated.

"Once you've established the need for a lens exchange, there are multiple scenarios to consider," he continues. "There are basically three places inside the eye where you can put a lens: the capsular bag, the ciliary sulcus and the anterior chamber. A lens exchange can involve removing a lens from any one of these three spaces and then placing a new lens into any one of them. Capsular bag to capsular bag is common for addressing lens-power errors. If

This article has no commercial sponsorship.

Dr. Miller is a consultant for Alcon, BVI, Johnson & Johnson Surgical Vision, Long Bridge Medical and Oculus USA. **Dr. Rosenthal** is a consultant/KOL for Johnson & Johnson Vision. **Drs. Grayson** and **Daluvoy** report no financial ties to anything discussed in this article.



Kevin Miller, MD

There are three ways to explant a problematic lens: fold it to reduce its size; cut it partially or completely; or remove it in one piece.

the capsule is torn, and the lens is decentering because it's in the torn bag, you might take it out of the bag and put it in the ciliary sulcus. If the entire capsular bag is dropping onto the macula, you might take the lens out and put the new one into the anterior chamber or suture it to the sclera. In some cases, the lens you're removing may be outside the bag as well.

"Of course, you can subdivide these three locations further," he continues. "The lens can be inside the capsular bag or partly captured in the bag, as when the optic is captured in the capsulorhexis or even the posterior capsule, and the haptics are in the sulcus. A lens can be passively placed in the sulcus between the iris and anterior lens capsule, or it can be actively fixated in the sulcus—sutured to the iris or sclera, for example. Or, the haptics can be fixated in the sclera using Amar Agarwal's glued-IOL technique or by putting them through the sclera, as in the Yamane technique.

"Needless to say," he adds, "if you have to remove a lens that's already in one of these other locations, the process will be very different from an in-the-bag exchange."

Does research suggest that one technique is more successful than another? "One of the purposes of our study was to compare the different techniques used for secondary IOLs and IOL exchanges, to see if one technique stood out as better or worse," explains Melissa B. Daluvoy, MD, an assistant professor at the Duke Eye Center in Raleigh, North Carolina, and fellowship director of the Cornea/Anterior Segment Division, who coauthored the study described earlier. "Our study found that the tried-and-true methods we've used for many years—such as anterior chamber IOLs—were just as good as some of the new scleral-fixated techniques. There was no statistically significant difference in outcomes, in terms of visual outcomes or complications. The conclusion we've drawn is that whatever you're good at doing is probably the technique you should use for secondary or replacement IOLs."

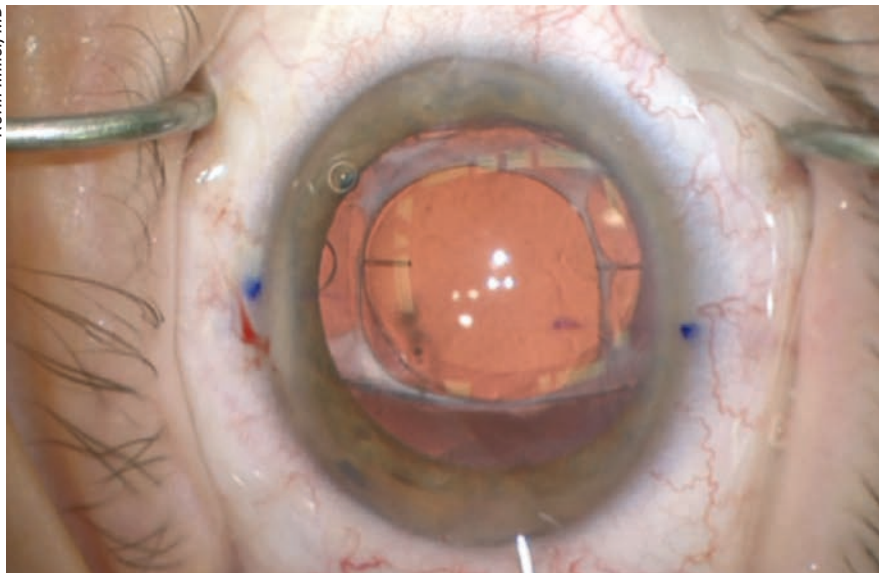
Reposition or Exchange?

Kenneth J. Rosenthal, MD, FACS, an associate professor of ophthalmology at the John A Moran Eye Center, University of Utah, and surgeon director at Fifth Avenue Eye Care and Surgery / Rosenthal Eye Surgery in New York, notes that the decision about whether to exchange or reposition a wayward lens depends on a number of factors. "If I'm dealing with a younger patient who's had the lens in their eye for more than eight or 10 years, I almost always take out the old lens," he says. "I do that for a couple of reasons. Number one is that today's lenses don't last forever. When we first started doing lens implants, most were made of PMMA, which lasts for a very long time. But most lenses today are made out of acrylic—or less commonly, silicone. Those lenses are more perishable, meaning that over time, various things happen to them that affect the clarity of the optic, and even more commonly, the integrity of the haptics.

"For example," he continues, "glistenings and opacification of the lens occur over time. In addition, many of the three-piece lenses have haptics made of polypropylene that become brittle over time. As a result, these lenses can have limited longevity in some patients. Furthermore, when we do surgery on these patients we manipulate the lens, and we may actually cause micro-damage. If you're repositioning the lens rather than replacing it, that damage can ultimately cause the lens to fail.

"For that reason, if I have a 50-year-old patient who may live another 30 to 50 years, I'd rather put a new lens in," he says. "It's kind of like putting a new tire on your car

Kevin Miller, MD



This patient had a STARR silicone toric plate haptic lens—the first toric lens ever made available. (Note the axis marks and one of the positioning holes, partially visibile to the left.) Asymmetric capsular fibrosis decentered the lens, causing the patient to have double vision when sufficiently dilated. Rather than risk a recurrence following lens repositioning, the surgeon broke up the fibrosis, explanted the lens, placed a monofocal lens in the bag and performed corneal relaxing incisions to address the astigmatism.

rather than plugging the old tire. Besides, in an otherwise healthy eye, the amount of surgical manipulation that's involved in removing a lens and exchanging it for a new one isn't substantially greater than just repositioning the existing lens, given modern techniques employing viscoelastics, thorough pars plana vitrectomy and small-incision surgery."

Dr. Rosenthal notes, however, that there are exceptions to this. "I'd consider repositioning rather than exchanging the IOL in a patient who has a lot of retinal pathology," he says. "Another exception is patients who have decreased corneal endothelial cell counts, where you want to get in and out stealthily with the least amount of surgical manipulation. A third exception would be a very elderly patient who can't tolerate a longer procedure, and where the expected lifespan may be shorter."

One situation in which the decision about whether to reposition or explant a lens can be tricky is when dealing with a subluxed lens. "Usually that's a decision I make on the fly," says Doug Grayson, MD, a surgeon at Omni Ophthalmic Management Consultants in Iselin, New Jersey. "I prepare to do either option. However, if it's a one-piece lens, that's coming out."

Dr. Daluvoy agrees. "If the problematic lens is a single-piece lens, I think you should take it out," she says. "Most of the scleral-fixated or iris-fixated techniques only work with a three-piece IOL."

"If you have a subluxed three-piece lens, then you have options," Dr. Grayson continues. "Those lenses are always still in the bag, and the bag is kind of a mess around the lens. You may be able to localize the haptic that's visible on the three-piece, throw a suture under the haptic, pass it through the iris and do a McCannel-style fixation. But sometimes that's not easy to do, especially if the lens is almost falling.

"Keeping the lens in there and doing a Yamane fixation can be a little tricky too," he says. "You have to get all of the old capsule off of the lens, and then do your Yamane externalization of the haptics. Unfortunately, the existing lens won't be a CT Lucia lens, which is best-suited to the Yamane technique because it can withstand a lot of manipulation without the haptic cracking off—although the Tecnis lenses are pretty durable for using the Yamane technique as well.

"The other issue is time in the OR," he adds. "It takes a fair amount of time to clean off the existing lens and suture it in place. Other options, like doing a vitrectomy, putting in a well-fitting AC-IOL and doing an iridotomy take far less time. And, the patient will see great the next day."

Placing a Lens Outside the Bag

Other options besides placing the lens in the bag or fixating it may be worth considering.

"Everybody is currently Yamane-happy," notes Dr. Grayson, "but an AC-IOL is fine. No study has shown that there's a long-term difference in vision between a well-fit AC-IOL and any of the fixated IOLs. In fact, with an AC-IOL you won't have problems with lens tilt, and in my experience you'll have a lower risk of CME. If the anterior chamber is deep and the lens fits right and is well-placed, you won't have a risk of corneal-endothelial compromise. Sometimes you simply don't have enough space in the orbit to do a fixated lens, so I'm prepared to do Yamane or an AC-IOL, and I explain this to the patient as well.

"If I'm dealing with an older patient and the cornea looks relatively healthy, I think an AC-IOL is a reasonable approach," says Dr. Daluvoy. "I tend to avoid an AC-IOL in younger patients because it can cause some endothelial cell loss as time goes on. For the younger patients I typically prefer to put the lens scleral fixated behind the iris, if that's an option."

"Some surgeons like to implant a piggyback lens," Dr. Grayson adds. "There are situations in which this may be a good alternative, such as

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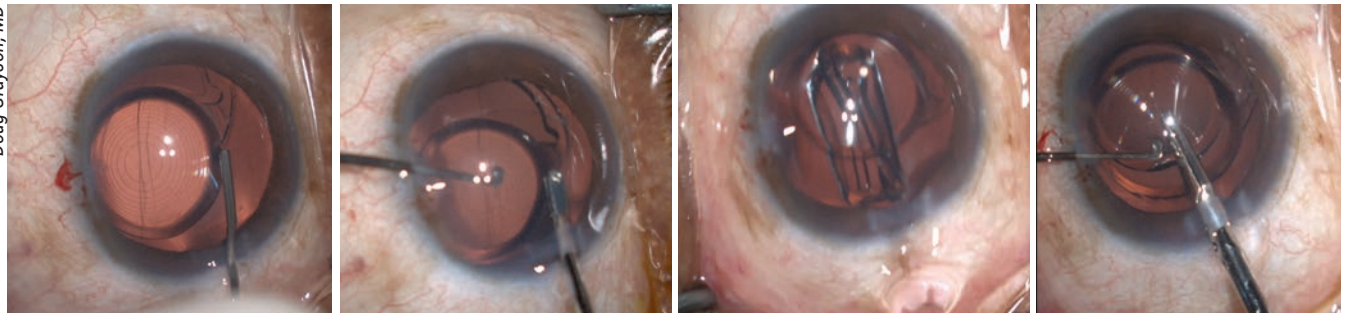


One popular technique used in lens exchange involves placing the new lens in the bag before removing the old lens from the eye, as a way to protect the bag from being damaged during the removal process. A) The existing IOL is mobilized using viscoelastic. B) The existing lens is maneuvered out of the capsular bag. (Note the minimal fibrotic adhesions associated with the Symfony IOL.) C) The replacement IOL is placed in the capsular bag below the old lens. D) The old lens is cut in preparation for removal.

when a corneal refractive fix is off-limits and there's no way to easily remove the existing lens from the bag. I tried implanting piggyback lenses for a while. It's great until you get some kind of posterior iris surface chafing and secondary pigment-dispersion glaucoma."

Dr. Grayson says one of the situations in which a piggyback lens might make sense is when a high myope or astigmatic patient is out of range for any available toric or multifocal lens, but still wants multifocal or astigmatic correction (and has a lot of room between the iris and the IOL). "Basically, you put in the lowest power toric or multifocal lens you have," he explains. "Then you see where the patient is visually, and compensate with a piggyback monofocal. Some surgeons using this approach will put both lenses in at the same time, but I feel more comfortable waiting to see what the exact refraction is with the first lens, six weeks later. Then I put in the appropriate piggyback IOL."

Dr. Rosenthal says he doesn't implant piggyback lenses much anymore. "I've done some in the past, but today the optic range of the lenses that are available off the shelf is pretty large. I do use a piggyback IOL to correct IOL power errors, on rare occasions. If you to decide to use a piggyback lens, the lens in front should always be a three-piece lens, never a one-piece lens. And always use a lens made of a different material from the existing lens, such as silicone on top of acrylic. In particular, avoid ending up with two acrylic lenses, because they tend to form intralenticular opacities."

Getting the Lens Out

"There are basically three different ways to get a lens out of the eye," explains Dr. Miller. "You can fold it; you can cut it; or you can take it out whole. My preference is to refold the lens, which is easiest. This won't work with every lens; PMMA and silicone lenses can't be folded. However, you can refold acrylic lenses because they're soft and malleable inside the eye. Collamer lenses can be folded, although it's sometimes a little tough to do. Silicone lenses are too slippery and thick in the center, so they resist being folded.

"The size of the incision you need to remove a lens changes depending on how you remove it," he continues. "When you refold a lens to remove it, you'll need a larger incision than you needed to inject the same lens. However, the incision can be a little smaller if you bisect the lens. I'd say the typical incision is about 3.5 mm when I'm folding a lens; when I cut the lens, the average is about 3 mm.

"Once a lens is removed, I place a suture in the corneal incision in about half of my cases—the ones that don't seal well," Dr. Miller says. "If I put a suture in, I usually take it out about a week later, and then do a final refraction two weeks later. If it's a large incision, such as the incision you'd make to remove an intact lens that can't be folded, I place multiple sutures. Then I wait two weeks after the final suture is out before doing a refraction for glasses.

"Sometimes," he adds, "when I try to fold a lens the iris starts looking like it might come out through the incision. If that happens, I stop. Instead, I'll just cut the lens and remove it."

"If I decide to cut the lens, I prefer to cut about two-thirds to seven-eighths of the way across and then pull the lens out—essentially in one piece, but pulling out half at a time," says Dr. Rosenthal. "Folding most lenses is easy; you use an old-fashioned cross-action lens folder. A cyclodialysis spatula goes under the lens; the folder goes over the lens. You fold the lens down over the spatula, then turn the lens 90 degrees and explant it. Removing a folded lens does require a slightly larger incision than you may need if you cut the lens. But folding the lens avoids the potential problem of the sharp edges of a cut lens shredding tissue on the way out."

Dr. Grayson sometimes makes a cut about one-third of the way through the optic and then rotates the lens out using wound-assist folding. "If you pull it out slowly enough you won't rip the lens, but you do need that cut to pull it out easily," he explains. "You can do this

under topical anesthesia; it's pretty straightforward and safe."

In the Presence of Capsulotomy

"If the patient has already had a YAG capsulotomy, then the likelihood of the vitreous coming forward is a lot higher," notes Dr. Daluvoy. "If that's the case, you have to be ready with multiple options, because things may not go exactly the way you've planned. Initially, I might plan on a sulcus-fixated IOL, if the anterior rhexis is still good. But if for some reason you lose the bag or there's another problem, then you have to have a plan B, whether that be implanting an AC-IOL or a scleral-fixated IOL. I wouldn't necessarily start with a pars plana vitrectomy in that situation, but I'd be ready either to go pars plana and do a vitrectomy or an anterior vitrectomy, if I encounter vitreous."

"If the patient has already had a capsulotomy, the bag is no longer stable," notes Dr. Grayson. "That means we can't put a new lens into the bag, which eliminates our ability to do a good multifocal lens exchange. We can replace an existing multifocal with a monofocal, but in that situation I'd put a three-piece monofocal in the sulcus with optic capture through the capsulorhexis.

"In these cases I believe a vitrectomy is necessary," he continues. "It's almost impossible to exchange a lens without having some vitreous prolapse after a YAG capsulotomy, because the YAG doesn't just affect the capsule; there's no longer any anterior hyaloid protecting the vitreous. In that scenario you're just asking for trouble if you're not planning a vitrectomy at the time of the exchange. I like to put in pars plana trocars and do a core pars plana vitrectomy. Then I leave the trocars in—they're self-sealing. After that I do the lens exchange. If there's any vitreous left floating around at the end, I'll just get rid of it."

"A small- to moderate-size posterior capsulotomy, like those most surgeons would make, is not a contraindication to lens exchange," says Dr. Rosenthal. "However, doing a lens exchange in those circumstances does require some specialized surgical techniques and more expertise than when dealing with an intact capsule. In many of these cases you'll want to do a limited, pars-plana-approach vitrectomy, to remove the vitreous immediately behind the capsular opening before you elevate the IOL out of the bag. Also, when you dissect the lens free, be very gentle. Be aware of the anterior-posterior force you're applying."

"At the very least," Dr. Daluvoy adds, "if I'm trying to exchange a lens because of quality-of-vision issues—meaning I want to change the power, or the patient is unhappy with a multifocal IOL—the presence of a capsulotomy changes my conversation with the patient and plays a lot into my preop decision-making."

One thing everyone agrees on: When a patient has complaints after the primary surgery has implanted a multifocal, surgeons should never reflexively do a YAG capsulotomy. "Sometimes after you put in a multifocal, the patient will complain of glare and haloes and difficulty seeing at night," notes Dr. Grayson. "That's probably attributable to the multifocal optics. Don't just do a YAG in hopes it will solve the problem, because if you do, you'll have a patient with a multifocal lens and non-adaptation issues who will now need a vitrectomy."

Dr. Rosenthal agrees. "When surgeons have difficulty with a lens implant after the primary surgery, the last thing they should be doing is a YAG capsulotomy," he says. "Always explore other options first, and only do a YAG when you're sure the patient doesn't need a lens exchange."

Removing Different Lens Types

Surgeons agree that lens exchange can be a very different proposition depending on which type of lens you're hoping to remove. "Some popular lenses are made of injection-molded acrylic, which sticks more

WHAT ABOUT CORRECTING A REFRACTIVE ERROR ON THE CORNEA?

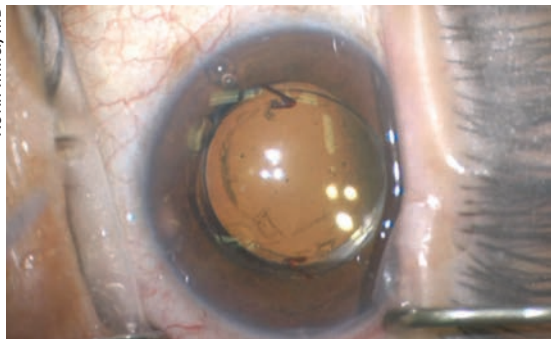
Kevin M. Miller, MD, chief of the Cataract and Refractive Surgery Division of the David Geffen School of Medicine at UCLA, notes that when deciding whether an exchange is necessary, lasering the cornea is sometimes an option. "If it's just a refractive error, it might be possible to perform laser vision correction instead," he says. "With patients in the cataract age range, it's not going to be LASIK in my practice because of the high likelihood of dry eye; it will probably be PRK. However, if a patient has a hyperopic error of +2 or +3, I won't get a very good result doing a hyperopic corneal treatment. In that case, I'll swap out the lens. If it's a myopic error such as -2 or -3 D, I might consider doing laser vision correction.

"In reality," he adds, "exchanging lenses because of a power error is one of the least-common procedures I do, however. It's much more common for me to exchange because of an UGH syndrome, decentration or dislocation into the back of the eye."

Dr. Miller points out a practical issue that comes into play regarding corneal laser refractive-power correction. "Unless you've talked to the patient ahead of time about the possibility of doing laser vision correction," he explains, "it's going to be a hard sell after the surgery's done and the patient finds out you put a lens with the 'wrong' power lens in. Now when you tell the patient, 'We're going to leave the lens in and fix the problem by operating on a different part of your eye,' the patient will say, 'Absolutely not! Put the right lens in!' If you didn't have that conversation ahead of time, the patient will believe you did something wrong. Thinking you made a mistake, the patient will want you to fix the mistake. At that point the patient will have zero interest in laser vision correction."

—CK

tightly to the capsule," explains Dr. Grayson. "In addition, the haptics have a bulge at the end. Because the lens is more adherent, it causes a more aggressive capsular fibrosis; then, once it's scarred into position, the bulge at the end of the haptics prevents you from rotating the haptics out easily. As a result, if you're exchanging one of these lenses five or six weeks out—depending on the amount of scarring—sometimes you have to decapitate the haptics and leave them in place. That's OK if you're implanting another lens and you can orient the new haptics 90 degrees away from the old ones. But if it's a power miss, or an axis miss with a toric lens, you can't always put the new lens where it should be.



Kevin Miller, MD

Every case is unique. Here, a piggyback lens had been placed above an in-the-bag lens to try and resolve dysphotopsias. (It didn't work.) Both lenses had to be removed, followed by a vitrectomy because the capsule had been opened. A new lens was placed in the sulcus, finally resolving the dysphotopsia problem.

"In contrast, some other lenses are tumbled acrylic that's lathed down and polished rather than molded," he continues. "In this case the acrylic is much less adhesive and the haptics don't have that bulge at the end. As a result, it's much easier to exchange them a couple of months after the surgery. That's great, because occasionally you need more time for the refraction to stabilize, whether the patient has epithelial membrane dystrophy, dry eye or is post-LASIK or post-RK."

Dr. Miller agrees that the geometry of the lens makes a difference in terms of how difficult the lens will be to remove. "Loop-haptic lenses are generally very easy to get out of the bag," he notes. "You can usually just dial the lens and the haptics will come right out, even if you have significant fibrosis of the anterior capsule. However, some popular lenses are very difficult to remove. Some have a terminal bulb at the end of the haptic, and you can get a ring of fibrosis around the neck of the haptic just proximal to that bulb. It's usually impossible to pull the haptic through the ring of fibrosis—and the haptic is difficult to see, because it's hidden behind the iris.

"The hardest lens to get out is the Crystalens, because it generates fibrosis around the four polyamide haptics," he adds. "You can get such dense fibrosis that it's really difficult to get that lens out. You can't dial it or slide it because of the lens design; it's trapped on both sides."

Planning the Exchange

These preoperative strategies will help to ensure a good outcome:

• ***Don't assume a lens in the bag can't be explanted because it's been in place for more than six months.*** "I hear this all the time, but it's simply not true," says Dr. Rosenthal. "I've exchanged lenses that have been in the bag for a decade. Yes, the more time has passed since the surgery, the more difficult it is to remove the lens; there will be more adhesions, and it will require a little more skill to disengage and dissect the lens free of the capsular bag. But there's nothing sacrosanct about six months."

• ***Always get an endothelial cell count as part of the preoperative workup.*** "The surgeon has to know the condition of the endothelium in order to make a decision about how to proceed with the surgery," Dr. Rosenthal explains. "The surgical technique may need to be modified, and the condition of the endothelium should certainly influence your decision about whether to exchange a lens or reposition it. For example, if the patient has a very low endothelial cell count, repositioning an existing lens might give the endothelium a better chance of surviving."

• ***When planning to scleral-fixate a lens, be meticulous about your measurements.*** "Be sure to place the lens the right distance back from the limbus so that it's not too close to the iris," says Dr. Daluvoy. "If it's too close to the iris it may rub against it, causing UGH syndrome. Also, make sure your placement of the IOL is symmetrical so you don't have lens tilt."

• ***If the patient has glaucoma, you may be able to address that during the exchange surgery.*** "In some cases, I may do a goniotomy in conjunction with a lens exchange," notes Dr. Grayson. "I've treated patients who've had secondary lenses, were already aphakic, or had a subluxed lens due to zonular compromise, when securing the existing lens wasn't an option. If a patient like that has glaucoma, I'll do a goniotomy when I put in the secondary AC lens."

• ***If a patient has dysphotopsias with a monofocal in the bag, consider placing the new lens in the sulcus.*** "Putting the new lens in the bag might result in the same problem," Dr. Miller points out. "Putting the replacement lens in the sulcus should help avoid the problem. Just be sure to adjust the lens power to compensate for the change in the effective lens position."

During the Surgery

Surgeons offer these tips to make the exchange surgery go more smoothly:

• ***Do what you're comfortable with.*** "If you have the skills and you're comfortable with the tools, then learning and using the newer techniques is reasonable," says Dr. Daluvoy. "But if you only do one or

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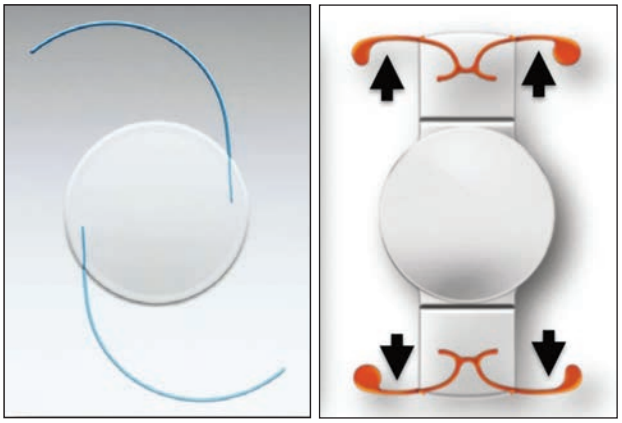
two exchanges a year, then do what's safe and what you're used to—place an AC-IOL or scleral-fixate the lens."

• ***Consider sliding the new lens in before removing the old.*** Dr. Grayson says he frees up the old lens, lifts it into the sulcus and puts the new lens in the bag before removing the previous lens. "This way, the capsule is protected when you have to make a cut in the previous lens to explant it," he explains.

"I've used that technique in the past when the posterior capsule was intact," notes Dr. Daluvoy. "It depends on how stable everything looks. If there's already a YAG capsulotomy, I'd take the first lens out and make sure my support is good before having two lenses in there."

• ***When removing a lens, don't be stingy about the size of the wound.*** "Today, surgeons often try to be valiant about minimizing the size of the wound," notes Dr. Rosenthal. "In my experience, any downside of making a larger incision, such as induction of astigmatism or the need for a suture, is mitigated by the greater safety of having an adequate wound size to remove the lens. I typically use a 2.75-mm keratome, and then open the sides of the wound a little bit, making it about 3.2 mm. I can easily explant a lens through that."

• ***Consider using an existing wound to remove the old lens.*** "When removing a lens I just refresh the existing wound, just like you'd refresh a LASIK flap," Dr. Grayson explains. "You can refresh a wound two or three months out and avoid cutting a new one. However, you don't want to put a keratome into a previous wound, because inevitably you'll create different levels and disrupt Descemet's, which can get stuck in the new wound site if it has multiple levels."



Lens and haptic design make a huge difference in how easy a lens is to explant after fibrosis has occured. A loop-haptic lens (left) can usually be dialed out of the bag without a problem. The design of a Crystalens (right) makes it very difficult to explant once fibrosis occurs around the four haptics.

• ***If the lens has been in the bag a long time, adjust your technique.*** "When you need to explant a lens that's been in the bag for a long time, two techniques will help," Dr. Rosenthal notes. "The first is to gently lift the edge of the capsule using a hypodermic needle or other fine instrument. One instrument that does this well is the LASIK flap lifter. The second technique is to use a combination of blunt dissection and viscodissection. You can get the capsular bag reopened in most cases using that approach."

• ***Don't be forceful when removing a lens.*** "You need to avoid pulling vigorously on the lens, because the globe may collapse," says Dr. Rosenthal. "If that happens you may injure the corneal endothelium, not to mention cause retinal issues. You should just glide the lens out."

Vitrectomy Tips

Although performing an anterior vitrectomy may not be a part of every lens exchange, it pays to be prepared to do it. Surgeons offer this advice:

• ***Make sure anterior vitrectomy is in your skill set.*** "I teach every resident that all anterior segment surgeons should have the ability to do an anterior vitrectomy through the pars plana," says Dr. Rosenthal. "We teach a course on pars plana vitrectomy for the anterior segment surgeon at the ASCRS and Academy meetings, and residents these days typically learn this. It's very important to be able to access the vitreous through the pars plana in conjunction with these techniques."

• ***Know when to call in a vitreoretinal colleague.*** "If you're only doing a limited vitrectomy because of a capsulotomy, it's probably not necessary to have a vitreoretinal surgeon present," says Dr. Rosenthal. "However, if the lens is completely dislocated and sitting on the optic nerve or the macula, and you have to bring it up in order to reposition it, someone trained in vitreoretinal surgery should be doing that."

• ***When exchanging a lens in the presence of a capsulotomy, try viscoelevating the lens.*** "To do this, put some viscoelastic behind the lens, elevating it into the anterior chamber, injecting viscoelastic as you go," explains Dr. Rosenthal. "The viscoelastic kind of plugs the capsulotomy, helping to prevent vitreous prolapse. I like to use Healon 5 for this because it's a very retentive, viscous viscosurgical device, and it does a good job of plugging the capsulotomy. Once you've lifted the lens up you can implant the new lens underneath it, with the Healon 5 still in place. That helps to keep the bag maximally dilated, which is useful even if you decide to place the lens in the sulcus or use another method of fixation."

• ***In the presence of a capsulotomy, only do a very limited vitrectomy.*** "This is a good idea for two reasons," Dr. Rosenthal explains. "First, the purpose of doing a limited vitrectomy is to keep the anterior vitreous from prolapsing through the posterior capsule opening. You only need to remove a small amount of the anterior vitreous to accomplish this. The second thing is, you don't want to do an extensive

vitrectomy because you're often going back into an eye with zonular or other support issues. You don't want to compromise the vitreous humor completely, because it's still helping to stabilize the capsular bag."

• ***When doing a limited vitrectomy, stain the anterior vitreous using triamcinolone.*** "If you're less experienced doing vitrectomy, putting a little triamcinolone in there will help you determine whether you've done enough," explains Dr. Rosenthal. "Then, you just do enough vitrectomy so that you don't see any triamcinolone, except behind the capsule. That tells you that you've done an adequate amount."

• ***When doing a vitrectomy because of a capsulotomy, use trocars.*** "Rather than doing a one-time sclerotomy, I like to place pars plana trocars so I can go back in again if I need to do a little bit more vitrectomy," explains Dr. Rosenthal. "This also gives me the option of using the vitrector to elevate the lens out of the bag. You can go in from behind and push it up."

• ***If things don't go well during the surgery, stop and come back later.*** "If a case is going south and you have to do a vitrectomy, you have retained nuclei, and the case was done under topical anesthesia and the patient's getting restless, sometimes you have to just walk away from the table with no lens in the eye," says Dr. Grayson. "The worst thing you can do is try to stuff in an AC lens or quickly put a lens in the sulcus. You can end up with iris prolapse, or an iris that's shredded. That's when those patients end up with long-term CME and corneal problems. Clean up as much as you can and then come back three or four weeks later when things cool down and the cornea's clear and do your procedure."

Patient Management

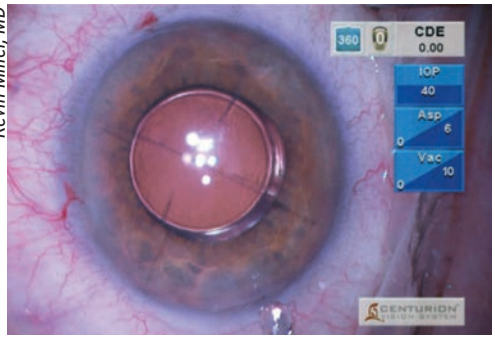
In addition to managing patient expectations before surgery, you need to be prepared for situations in which the patient still isn't happy, or cases where you choose to refer the patient to another surgeon.

Dr. Grayson points out that in some cases you may have to to give premium patients their money back. "Sometimes when you replace a multifocal with a monofocal the patient expects to get a refund," he notes. "So, once you start taking premium lenses out, you have to be prepared to do something financially for the patient.

"If I have a patient who doesn't adapt to a multifocal, and I'm taking the lens out and putting in a monofocal, I give them their money back for the multifocal lens," he says. "The need to switch out the lens isn't their fault or mine; the patient just turned out to be unable to adapt."

Dr. Grayson also advises against referring a lens-exchange patient unless you have a good relationship with the surgeon you're referring to. "If you've never done an exchange, or you only do one every few years, you might want to refer the patient," he says. "However, you have to have a good relationship with the doctor you're referring to. You can't just tell the patient, 'Go there and he'll take care of you.' It has to be a coordinated effort.

"Nobody wants to deal with an unhappy patient unless they have a good relationship with the referring doctor," he explains. "If a patient just wanders in for a second opinion, and explains that the first doctor has told the patient he can't do anything, I wouldn't want to get involved. Among other things, if the patient needs a multifocal explanted and replaced with a monofocal, he or she may expect to get their money back. In that situation, I have to tell the patient to take that up with the original doctor. That has to be between the patient and the surgeon who put the lens in."



Kevin Miller, MD

This patient's previous radial keratotomy caused a hyperopic lens power error. The surgeon opted to exchange the lens rather than attempt a corneal laser correction over the RK incisions.

Being Prepared

"My philosophy," says Dr. Grayson, "is that if you want to be in the multifocal or post-refractive-surgery arena, you need to be able to do any modality of postop correction, including lens exchange. You can't always say, 'Oh, I'm going to do a PRK or LASIK touchup,' especially in the post-refractive-surgery crowd. I look at a refractive touchup as a last resort, reserved for situations in which I'm not able to exchange the lens.

"I trained back in the 90s, when we were taught that if you put a lens in, it's not coming out," he says. "I think that philosophy is totally wrong. If you're getting into the arena of refractive cataract surgery, and people are going to pay $3,000 or $4,000 for femtosecond multifocal visual improvement, you have to be able to fix any postop problems. You can't just say, 'Oh well, too bad. Wear glasses.' "

"I think it's important to embrace the lens-exchange skill set," he concludes. "People who feel they can teach themselves should do so. Watch videos online. Try parts of it during a regular cataract surgery; pop the lens out of the bag to see how it comes out. If you don't want to develop those skills, that's OK. However, in that case you'll need to develop a good relationship with another doctor that you can refer those patients to."

Angle-Closure Suspects And LPIs: Yes or No?

Recent studies offer insight regarding whether or not to perform laser peripheral iridotomy on these patients.

TIN AUNG, MBBS, MMED(OPHTH), FRCS(ED), FRCOPHTH
SINGAPORE

People with primary angle-closure glaucoma make up a significant portion of glaucoma patients worldwide; it's estimated that PACG impacts more than 20 million people. It's especially prevalent in Asia, where narrower angles are more common than in some other parts of the world.

According to the International Society of Geographical and Epidemiologic Ophthalmology, glaucoma-related disease associated with narrow or closed angles can be classified as occurring in three stages:

- primary angle-closure suspect (PACS), defined as narrow angles but no other signs of angle dysfunction;
- primary angle-closure (PAC), where elevated pressure and/or signs such as peripheral anterior synechiae are present; and
- primary angle-closure glaucoma, where glaucomatous damage to the optic nerve is evident.

By definition, angle-closure suspects don't have glaucoma, but they do have narrow angles, which means there's a risk of the angle closing further, potentially leading to glaucoma.

This condition—being an angle-closure suspect—is relatively common, at least in Chinese people; as many as 5 to 8 percent of people over the age of 40 are primary angle-closure suspects. According to the Vellore Eye Survey, about 30 percent of angle-closure suspects progress to having primary angle closure within five years.[1] Of those who progress to PAC, 10 to 30 percent then go on to develop PACG over a five-year period. This means that only a small percentage of primary angle-closure suspects end up progressing all the way to angle-closure glaucoma.

The LPI Dilemma

One of the issues that arises when managing a patient with narrow angles—someone who qualifies as an angle-closure suspect—is whether to perform a laser peripheral iridotomy. An LPI can prevent the angle from closing further and helps to mitigate the consequences of angle closure if it occurs. Most important, it reduces the risk of a future acute angle-closure attack, in which the angle abruptly closes and intraocular pressure rises dramatically, leading to pain, and possibly to blindness if left untreated.

This leaves doctors who are managing angle-closure suspects faced with a dilemma: Should we perform a prophylactic LPI? Like many questions in medicine, deciding whether or not to create an LPI is a question of balancing risk and potential benefit. Doing so might mitigate the risk of suffering and possible blindness if an angle-closure attack were to happen in the future, and the laser itself is generally safe. (Studies, including those described below, found that it had very limited side effects.)

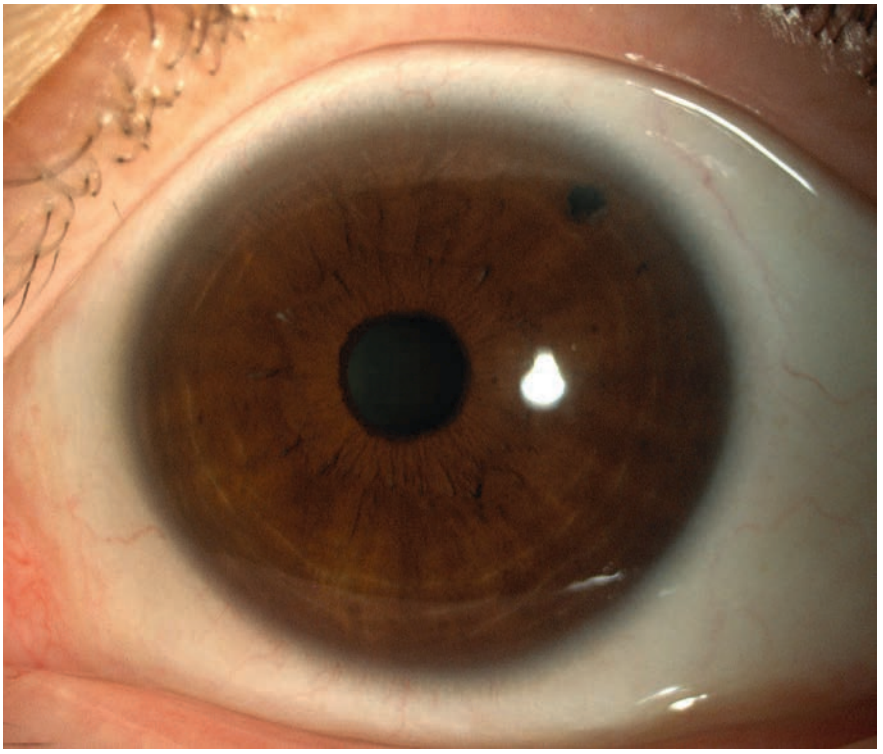
The main issue that can arise following an LPI is that some patients—about 10 percent—experience a visual disturbance; they see a line, or something moving around in their field of vision. The reason for this is that you've created a second hole in the iris (besides the pupil), and light passing through that opening can create a visual disturbance. Most patients will get used to this over time, even if they're initially bothered by it, but a small percentage of these patients find this extremely irritating. (It's worth noting that if a patient is truly unable to live with this, it's possible to tattoo the cornea over the LPI, darkening it, so the LPI doesn't cause the visual disturbance. So far I've never had to do that, but it's an option.)

Unfortunately, the LPI decision also has medico-legal ramifications. No one wants to be sued for not having done the procedure if an angle-closure attack happens later.

Part of the reason this has been a challenging decision to make is that until recently, there's been very little concrete data about how often someone with narrow angles actually progresses to the point at which an angle-closure attack is a real concern. Now, that's changed, thanks to two clinical trials addressing this question, one conducted in China, one in Singapore. (I participated in both trials.)

This article has no commercial sponsorship.

Dr. Singh is a professor of ophthalmology and chief of the Glaucoma Division at Stanford University School of Medicine. **Dr. Netland** is Vernah Scott Moyston Professor and Chair at the University of Virginia in Charlottesville.



A laser peripheral iridotomy lowers the risk of future angle-closure-related damage, but the risk turns out to be small—and some LPI patients are bothered by visual side effects.

The Chinese (ZAP) Trial

The Chinese trial is called the Zhongshan Angle-closure Prevention trial, or ZAP trial—an appropriate acronym given that it involves a laser—because it was done in the Zhongshan Eye Hospital in Guangzhou. (It was done in collaboration with Moorfields Eye Hospital/University College London, and the Wilmer Eye Institute at Johns Hopkins University.)

One interesting aspect of the ZAP trial is that it randomized treatment and control within each participant, by eye. All subjects had narrow angles in both eyes, so one eye was randomly assigned to receive an LPI while the other eye was the control. The endpoint for the study was primary angle closure, the stage just before glaucoma at which the pressure starts going up, and/or PAS develop, or an acute angle closure attack happens. The aim was to see how often the eye that received an LPI reached that endpoint, compared to the eye that was simply observed. The trial followed patients for six years.

The ZAP trial found, first of all, a very low overall progression rate. That was surprising, because it had been thought that 10 to 30 percent of angle-closure suspects would progress if left untreated. But in the ZAP trial, only about 4 percent of the eyes left untreated progressed during the five-year follow-up period; that translates to less than 1 percent per year. This was far less than expected. However, the study did find that doing the laser reduced the risk by approximately half, to 2.2 percent.

The ZAP trial was conducted to guide population-wide health policy for China. If the study had showed a huge effect, it would have made sense to advocate for population-wide screening for angle closure, as well as population-wide prophylactic LPI. But after seeing the data, that's no longer being considered. Instead, ophthalmologists are being advised that choosing to simply observe an angle-closure suspect is a reasonable option, even in Chinese people, where the risk of angle-closure glaucoma is much higher than in Europeans.

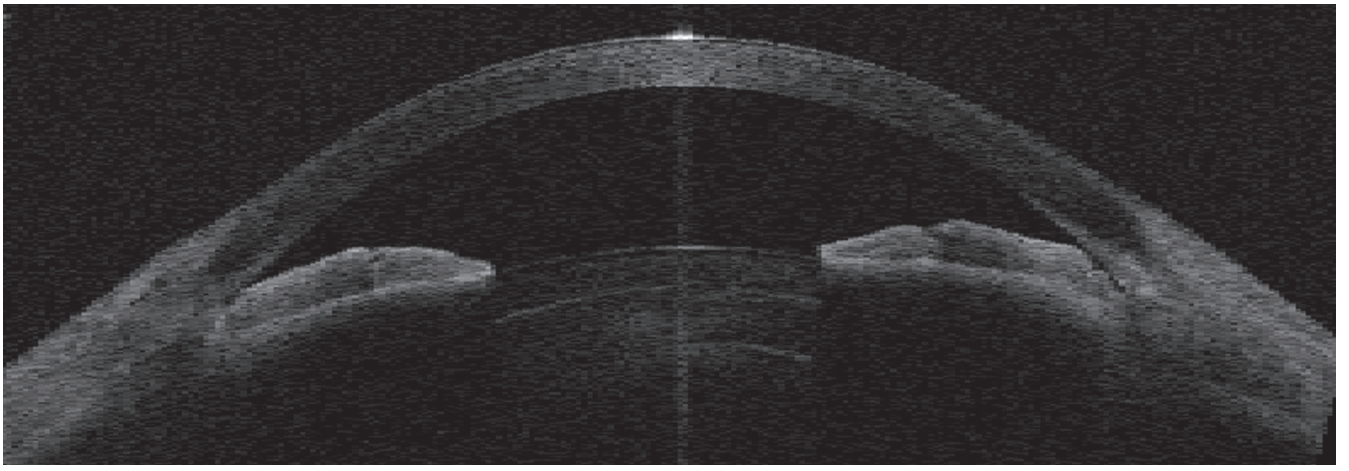
The Singapore ANA-LIS Trial

Our group conducted a similar trial in Singapore. (Actually, our study started before the ZAP trial, but it took much longer for us to recruit the patients we needed. China is better organized for this sort of project, so recruitment went much faster there; as a result, the ZAP trial was completed before we completed ours.)

The findings from our study were similar to those of the Chinese study. The most striking difference was that we found higher progression rates from angle-closure suspect to primary angle closure: Almost 10 percent of our PACS subjects progressed within five years. However, the benefit of performing an LPI was the same: Doing an LPI reduced the risk by half.

Why did the studies find different rates of progression? Several factors may explain this:

- First, Singapore is a multi-ethnic country; as a result, we had some patients in our study who weren't Chinese. Thus, the ethnicities of the trial participants were somewhat different.
- Second, we used a different method to recruit patients. Our recruitment was hospital-based; people who came to the eye hospital to be examined or treated for eye problems who had angle closure or narrow angles were referred for the trial. In contrast, recruitment for the Chinese study was done through community-based screening. The researchers went to certain areas of Guangzhou, the capital city of Guangdong Province, and invited everyone over the age of 50 to come for an eye examination. From that exam they picked out the people with narrow angles and referred them for further evaluation. Those



An angle-closure attack can occur if a patient has narrow angles, leading to a sudden, painful and dangerous rise in intraocular pressure.

who were confirmed to have narrow angles were invited to take part in the trial.

This may have affected the results for at least two reasons: First, people coming to our hospital were likely to have existing eye problems, such as visual acuity issues or mild cataract. Co-existing conditions suggest a vulnerability to future eye problems, including angle closure. Second, most people who come to a free screening, like those in the ZAP trial, are unlikely to have existing eye problems—and the fact that they took advantage of a free screening also suggests that they're more health-conscious. (In many situations, if you do a health screening, the people who are not well stay home.)

• A third difference between the study populations was that the patients in China had slightly wider angles at baseline than the population recruited for the Singapore trial, based on the clinical exam. (The reason for this baseline difference isn't clear.) It makes sense that slightly wider angles at baseline would produce a slightly lower rate of progression to primary angle closure.

Despite the differences between the two trials and their results, the conclusion one might draw from the data is similar: Overall, the risk of progression from narrow angles to primary angle closure is quite low.

Of course, most of the participants in these studies were of Asian descent, so we can't directly apply these results to Europeans or Africans; many studies have shown that the prevalence of angle closure is different among Europeans and Africans than among Chinese people. Nevertheless, the findings from these trials should provide helpful information to guide management for all clinicians.

Advising the Patient

Because we now have some concrete data as a reference point, it's possible to tell your patient the likelihood that he or she will develop angle closure over time, allowing the patient to make a more informed decision. I tell my patients that the risk of developing angle closure is 5 to 10 percent over five years, or 1 to 2 percent per year. I also explain that the laser cuts the risk by half.

In some cases, your patient may ask your opinion about whether or not to proceed with an LPI. This is a challenging position to be in. If a patient asks me that, I probe further to find out if the patient understands the concept of risk. If the patient isn't keen to have the laser procedure, and clearly understands that the risk is low but not zero, then I'd say skipping the procedure is fine. But if the patient doesn't seem to understand the concept of risk—or doesn't want to take any risk at all—then I'd recommend proceeding with the laser. (If there's no clear reason to go one way or the other, I'd err on the side of doing the laser.)

The kind of relationship you have with the patient also makes a difference. If you have a good relationship—if he or she has been your patient for a long time—it's a lot easier to make the call, based on what you know about the patient. On the other hand, if you're dealing with a brand new patient off the street, it's a lot trickier. In that situation, it's a lot more difficult to judge how well the patient understands the concept of risk.

Of course, one may still wonder if there's a reason to recommend that certain specific patients have the procedure done. Ideally, that recommendation would be based on knowing who is most at risk of progressing. For example, it would be great to be able to say, "If your angle is this narrow, you should have the LPI procedure," or that a patient with an intraocular pressure above a certain value should get the treatment.

Unfortunately, even with the completion of these two trials, that data is limited. Because of the study design, the ZAP trial didn't find many risk factors. Our Singapore trial did find some risk factors—and that

(Continued on p. 68)

Monthly

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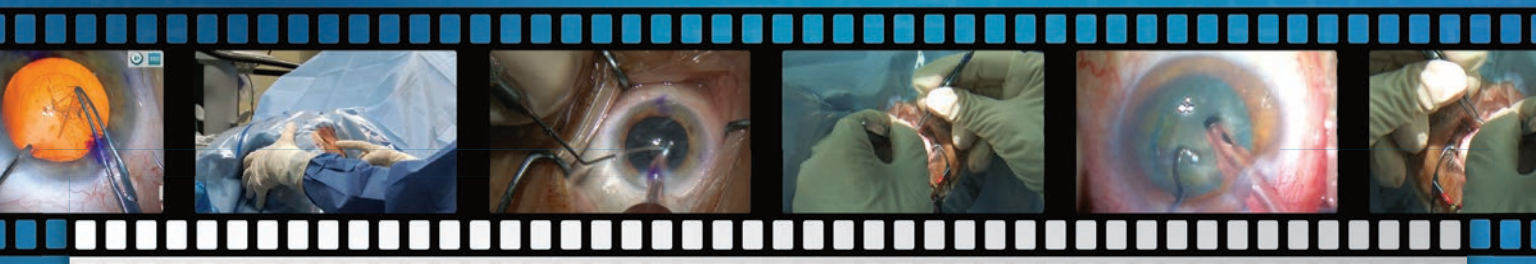
CME SERIES | SURGICAL VIDEOS



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Episode 70:
"A Highly Myopic Patient Requires Deep Sedation"

Surgical Video by:
Richard J. Mackool, MD

Video Overview:

A highly myopic patient requires deep sedation in order to overcome an extremely forceful Bell's phenomenon. Methods to deal with this problem while maximizing the safety of the procedure in such patients are presented.

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Richard J. Mackool, MD

We are excited to continue into our sixth year of Mackool Online CME. With the generous support of several ophthalmic companies, I am honored to have our viewers join me in the operating room as I demonstrate the technology and techniques that I have found to be most valuable, and that I hope are helpful to many of my colleagues. We continue to edit the videos only to either change camera perspective or to reduce down time – allowing you to observe every step of the procedure.

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After completion of this educational activity, participants should be able to:

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Rethinking Retinal Tamponades

Two surgeons discuss their work developing a new alternative that won't make patients miserable.

CHRISTOPHER KENT
SENIOR EDITOR

It's no secret that patients dislike the protocol they have to undergo following retinal detachment surgery, with its requirement for very uncomfortable positioning—not to mention the postop visual side effects and travel restrictions. This reality has inspired a number of researchers to try to develop alternatives that might eliminate these downsides.

Among those working to solve this problem are Tomasz (Tommy) Stryjewski, MD, and Tony Stefater, MD, PhD, two young retinal surgeons in Boston. Here, they explain how this problem caught their attention, and where their work has led so far.

Getting on the Trail

"After retinal surgery, if there are any breaks or holes in the retina, you have to fill the eye with something that's going to keep the hole sealed while the laser sets," Dr. Stryjewski explains. "For more than 40 years ophthalmologists have been using special gases and hydrophobic oil to create a seal. Unfortunately, if you have any kind of gas or oil inside your eye, your vision is quite poor—unlike after cataract surgery, when patients can see quite well from day one. That's a very big problem, especially if it's your only eye. In addition, you have to position your body in ways that can be very uncomfortable, and you have limitations such as not being able to travel via airplane because of the air pressure changes flying entails.

"We became interested in this problem when we were both residents at Mass Eye and Ear," he explains. "We marveled that patients didn't complain about their eye after retinal detachment surgery; instead, they complained about their neck and back and how uncomfortable they were with the positioning they underwent. We wondered if we could come up with a tamponade material that could provide a seal against the retina and then degrade, without all of the side effects and limitations. Patients could have a much better experience after retinal surgery."

Dr. Stryjewski says they began working on the problem five or six years ago. "We envisioned ourselves eventually becoming academic physicians working on NIH grants," he says. "We were passionate about doing research and contributing to the fund of knowledge. But because we were in Boston working at this big life-science biotech hub, we got interested in the idea of starting a company to develop this. As a result, we decided to found Pykus Therapeutics, with the goal of trying to develop this type of technology for patients."

Dr. Stryjewski explains that their initial funding came from winning a business competition put on by Harvard. "Eventually, we were able to raise enough capital to hire a team of chemists, product and development

This new retinal tamponade gel will remain clear inside the eye until it breaks down and leaves through the eye's normal outflow system after about a month.

This article has no commercial sponsorship.

Dr. Colvard is a surgeon at the Colvard-Kandavel Eye Center in Los Angeles and a clinical professor of ophthalmology at the Keck School of Medicine of the University of Southern California. **Dr. Charles** is the founder of the Charles Retina Institute in Germantown, Tennessee.

PHYSICAL CHARACTERISTICS OF PYK-1105

Parameter	Result
Time to injection (duration of minimal viscosity after mixing at 25° C)	10 minutes
Time to viscous gel formation after injection at 37° C	4 minutes
Time until degradation	11 - 14 days
Refractive index	1.3385
Transparency	>90% across the visible spectrum

specialists, and regulatory experts. Then, we established a laboratory in the Boston area, where we've conducted our early research using an animal model."

Dr. Stefater acknowledges that other researchers are striving to reach the same goal. "We're not the first people to think of this," he notes. "There's a lot of published literature about work done in animals and other preclinical models using hydrogels and other substances to treat retinal detachments. But for a variety of reasons, none of them have advanced to the clinic. It turns out to be a challenging problem." They note that seemingly promising alternatives tried by others that have not made it to the clinic so far have included heavy silicone oils, magnetic oils, combination gas-oils, retinal sealants, intraocular capsules and hydrogels.

Addressing the Challenge

"In the past few years we've had first-hand experience with all of the issues that surround developing a novel tamponade agent for the retina," Dr. Stefater explains. "There are three problems that are especially thorny: First, many molecules and compounds are inflammatory in the eye. Second, the product should ideally degrade inside the eye so it doesn't have to be removed. That means that the substance has to clear through the eye's normal clearance system without causing elevated pressure.

"The third major problem relates to getting the product into the eye," he continues. "Retinal surgery has gotten safer and safer because it's now done through very tiny incisions, but that's a challenge if you want to inject a hydrogel into the eye. If you push gelatin through a syringe, for example, it's not going to be solid when it comes out of the needle. So how do you get a substance that's rigid enough to support the retina into the eye through a tiny incision? Actually, several groups, including ours, have begun to make real progress solving that last problem. We've been developing polymers that are liquid outside the eye but form a hydrogel inside the eye."

Dr. Stryjewski says they identified a class of molecules that performs the way they needed it to. "However, there were still plenty of challenges," he notes. "For example, how do you store a material with such unusual properties? Will it remain stable? The materials we looked at worked well, but in some cases they couldn't be stored on the shelf. Or, there would be issues of solubility; you might need to warm it up in a glass beaker and stir it to get it to dissolve before injection into the eye. That's not practical for a practicing clinician. Our goal has been to create a product with clinical use requirements that would be familiar to surgeons, not exotic. So a lot of the challenge has been marrying the ideal chemical properties with a product that's manageable in the clinic.

"That's where very experienced formulation chemists are really valuable," he says. "They've helped us achieve the goal of creating a product that's shelf-stable and can be easily handled in the OR in a way that's familiar to surgeons. This product (PYK-1105) comes in two parts that are mixed; it forms a thick, viscous liquid that rapidly turns into a soft gel when it reaches body temperature.

"We consider ourselves to be retina surgeons first and foremost," he concludes. "We've come to appreciate the tremendous amount of work it takes to create a product that's clinically feasible. There's a tremendous gulf between an interesting science project and something that's clinically practical."

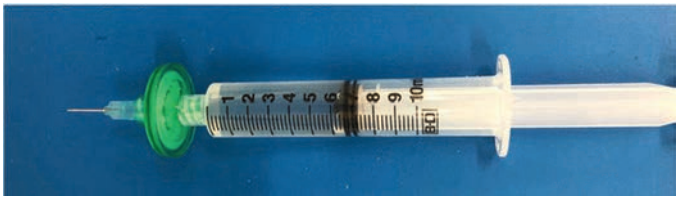
Dr. Stryjewski explains how the product would be used in the clinic. "Tamponades function by keeping the hole in the retina dry, blocking water from accessing the subretinal space while the laser scar sets," he says. "With our product, the retina would be repaired in the usual manner. A fluid-air exchange would be performed; the tear would be lasered. Once the retina is flat under air and you've applied your laserplexy, the gel would be added to the eye in much the same way surgeons currently inject an oil tamponade, and the gel would set on top of the break. Once the gel has been applied, the case is over.

"The gel would remain in the eye for about a month," he continues. "In contrast to oil and gas, the patient will be able to see through this substance. After about a month, the gel will break down and leave the eye. In the meantime, the gel would keep the repair dry and the laser treatment would be able to set." Dr. Stefater adds that they anticipate that the product will be covered by insurance, making it available to everyone.

The Future Looks Bright

Dr. Stefater points out that one reason this problem has remained unaddressed for so long is that using

gas for retinal tamponade works well—at least from the surgeon's perspective. "The burden isn't really on the surgeon, however," he notes. "It's on the patient who has to position face-down for a week. When you talk to patients, they'll often tell you it was the worst week of their lives. It's hard to imagine how unpleasant it is if you haven't gone through it.



The new substance is liquid outside the eye, but forms a hydrogel inside the eye that can protect the retina while it heals.

"The next phase of retinal surgery evolution will hopefully eliminate that patient burden," he continues. "Patients will be able to see after surgery; they'll be able to fly; and they won't have to position face-down. It would definitely make it a much better experience. But of course, there are many challenges to making this a reality; that's why it's taken us several years to get to this point. And it will be a little while longer before we have a product that gives patients a perfect postop experience."

Their preclinical studies demonstrated that the current formulation is well-tolerated in a rabbit and mini-pig vitrectomy model. "After presenting a summary of our pre-clinical work at the 2019 Vail vitrectomy meeting and the 2020 Retina Society meeting and publishing in the Journal of Vitreoretinal Diseases, we've been able to launch our first human study this year," Dr. Stryjewski notes. "We're recruiting 10 retinal detachment patients with low visual potential; the study is ongoing. As you can imagine, we've spent much of this year navigating the challenges involved in conducting a study during a pandemic. It's too early to offer any details about our early findings, but there have been many encouraging signs that we're on the right track. We hope to complete enrollment in the pilot clinical study this year."

"Everyone working on this problem wants to help patients recover more easily from retinal detachment surgery," Dr. Stryjewski concludes. "My hope is that, whether it's our product or someone else's, a generation from now patients undergoing retinal surgery will have a much more comfortable postoperative experience."

DISCLOSURES

Dr. Stryjewski is in private practice at Tallman Eye Associates (Lawrence, Mass.); **Dr. Stefater** is in private practice at Ophthalmic Consultants of Boston. Drs. Stryjewski and Stefater are cofounders and equity co-owners of Pykus Therapeutics, which is developing this technology for clinical use.

Angle-Closure Suspects and LPIs

(Continued from p. 64)

data will be published soon in *Ophthalmology*—but the most important piece of information would be knowing which patients are fast progressors, since many people with narrow angles don't progress for years. Unfortunately, the number of participants in our trial wasn't sufficient for us to detect the fast progressors with any statistical certainty.

Despite this lack of data, there are some patients with narrow angles whose circumstances would make an LPI worth considering. I'd suggest that the following patients be considered for an LPI:

- ***Those who have symptoms such as pain or headaches.*** These individuals might be good candidates for an LPI because those symptoms suggest that they may already be having intermittent angle closure.
- ***Patients with diabetes.*** The Singapore study showed that diabetes is a risk factor for progressing to angle closure. This might be true in part because these patients are dilated frequently during exams, but it could also be because people with diabetes tend to have some autonomic dysfunction, which could affect the pupil.
- ***People who are being dilated on a regular basis to monitor other conditions.*** Those conditions would include macular degeneration and diabetes. Dilating the pupil can provoke an acute angle-closure attack, so regular dilation puts these individuals at greater risk.
- ***Patients who have poor access to follow-up.*** If a patient may not be able to easily get help should an angle-closure attack occur, it makes sense to lower the risk as much as possible.
- ***Patients whose families have a history of angle closure glaucoma.*** This could indicate a higher-than-average risk.

It's worth noting that a patient who is having a cataract removed will be less likely to be at risk, because taking out the cataract will also remove the mechanism of pupillary block. Thus, I recommend cataract surgery for many patients with narrow angles and cataract.

As always, we want to do what's best for our patients; this is simply one of those situations in which it's difficult to be sure which option really is the best. But given the data from the two trials discussed above, making that determination is now a little bit easier.

1. Foster PJ, Buhrmann R, Quigley HA, Johnson GJ. The definition and classification of glaucoma in prevalence surveys. Br J Ophthalmol 2002;86:238-42.

ABOUT THE AUTHOR

Prof. Aung is the Kwan Im Thong Hood Cho Temple Professor of Ophthalmology at Duke-NUS Medical School in Singapore, executive director of the Singapore Eye Research Institute and vice chair of research for the Singapore National Eye Center. He has no relevant financial disclosures.

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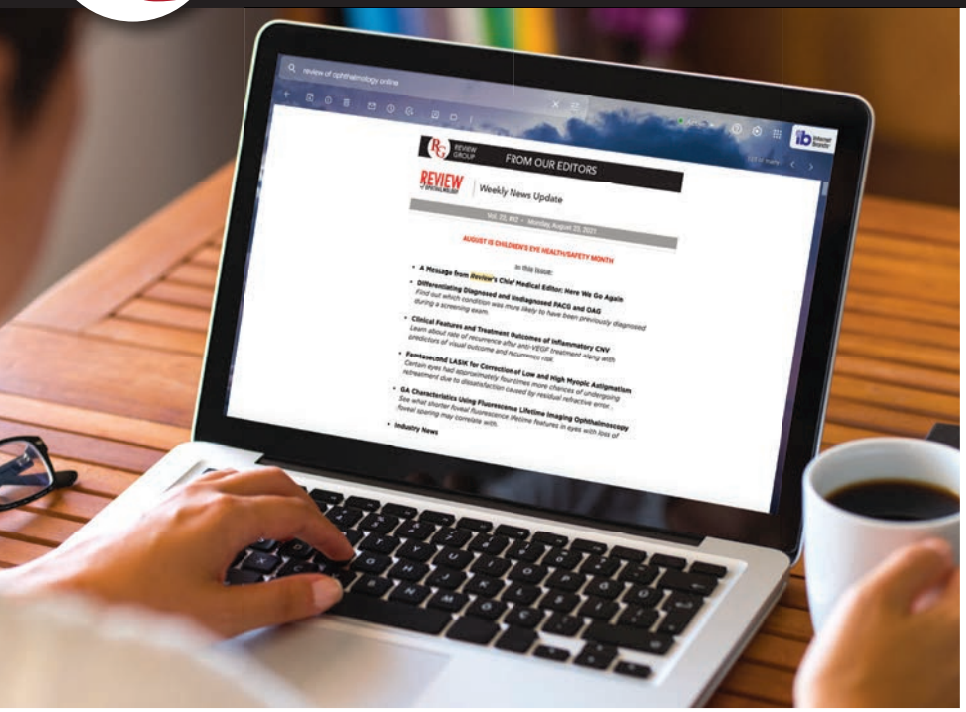

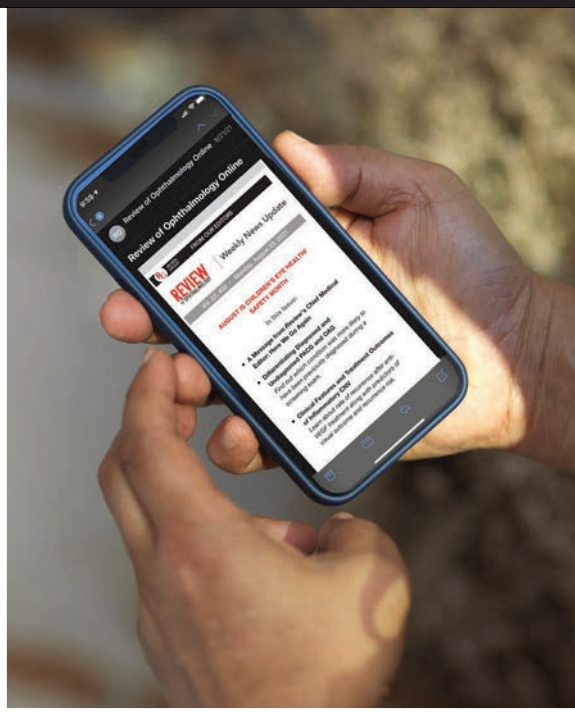

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REVIEW OF OPHTHALMOLOGY Weekly News Update

Vol. 22, #32 • Monday, August 23, 2021

AUGUST IS CHILDREN'S EYE HEALTH/SAFETY MONTH

In this Issue:

- **A Message from *Review*'s Chief Medical Editor: Here We Go Again**
- **Differentiating Diagnosed and Undiagnosed PACG and OAG**
  Find out which condition was more likely to have been previously diagnosed during a screening exam.
- **Clinical Features and Treatment Outcomes of Inflammatory CNV**
  Learn about rate of recurrence after anti-VEGF treatment along with predictors of visual outcome and recurrence risk.
- **Femtosecond LASIK for Correction of Low and High Myopic Astigmatism**
  Certain eyes had approximately four times more chances of undergoing retreatment due to dissatisfaction caused by residual refractive error.
- **GA Characteristics Using Fluorescence Lifetime Imaging Ophthalmoscopy**
  See what shorter foveal fluorescence lifetime features in eyes with loss of foveal sparing may correlate with.
- **Industry News**

A message from *Review*'s Chief Medical Editor, Mark H. Blecher, MD: Here We Go Again

I am, like most of you, totally over COVID. But as the cliché saying goes, "COVID isn't over us," which was mildly funny until it wasn't. We had a small happy window of normalcy this spring when marginally successful vaccinations caused the infection rate to plummet. The sun started to shine again ... and then it was gone. The smug satisfaction the vaccinated among us enjoyed was

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A 57-year-old woman with interface haze after DMEK

PATRICK B. RAPUANO, MD, ZEBA A. SYED, MD
PHILADELPHIA

Presentation

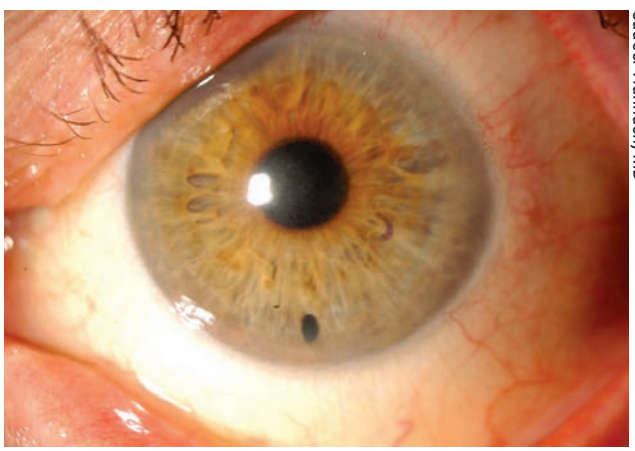
A 57-year-old otherwise healthy woman presented for a second opinion of recently diagnosed Fuchs' endothelial corneal dystrophy. She noted blurry vision that declined over the course of the day, worse in the left eye compared to the right eye. She was using sodium chloride 5% drops three times daily in both eyes and a hairdryer in the morning (the drying action of which can improve vision for a time) with minimal improvement in vision.

Medical History

The only medical history of note was the patient had a history of hypertension.

Exam

The patient had a best-corrected visual acuity of 20/25 in the right eye and 20/60 in the left. Anterior segment exam was notable for 2+ guttae in the right eye and 3+ confluent guttae and mild edema in the left eye, as well as 2+ nuclear sclerosis cataracts in both eyes. Dilated fundoscopic exam was noted to be within normal limits. Pachymetry showed a central corneal thickness of 523 um in the right eye and 611 um in the left eye. Specular microscopy showed an endothelial cell count of 2,212 cells/mm^2 in the right eye and 2,469 cells/mm^2 in the left eye. The remainder of the ocular examination was within normal limits.



Sadeer Hannush, MD

A postop DMEK eye. (the image is from a different patient than the one described in this month's case).

What is your diagnosis? What further workup would you pursue? The diagnosis appears on p.72.

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Work-up, Diagnosis and Treatment

For her FECD and visually significant cataract in the left eye, the patient elected to undergo combined Descemet's membrane endothelial keratoplasty and cataract extraction with intraocular lens implantation. The early postoperative course was routine, and the patient was managed with topical prednisolone acetate 1%, moxifloxacin 0.5%, and ketorolac 0.5% as per standard protocol. At postoperative month one, the patient had an uncorrected distance visual acuity of 20/40 with a well-positioned graft and a clear cornea, and prednisolone acetate 1% was continued four times daily.

The patient returned at postoperative week seven with new symptoms of photophobia and tearing, describing a migrainous left-sided headache. Examination at that time was notable for a worsened UDVA of 20/125. Anterior segment examination was notable for new DMEK graft interface haze, with clinical photos and anterior segment optical coherence tomography (AS-OCT) presented in Figure 1.

Given that the interface opacity did not feature any characteristics of fungal interface keratitis *(see Discussion)*, the patient was managed with difluprednate 0.05% every two hours and cyclopentolate 1% twice daily. She experienced improvement in photophobia, although she did report persistent tearing.

Topical corticosteroids were tapered over several months with improvement in graft interface haze. At postoperative month 11 the patient was noted to have persistent trace interface haze and UDVA 20/200, although BCVA was 20/25 with a refraction of +1.00 +1.50 x155. Figure 2 shows clinical photographs and AS-OCT from this visit, notable for persistent, though much improved, interface opacification. After discussion with the patient, the decision was made to continue monitoring the interface haze given its gradual improvement, and she was counseled that repeat DMEK could be considered in several months pending clinical progression.

Discussion

The patient in this case presented with dense and visually significant corneal guttae in the left eye despite using hypertonic saline drops during the day and a hairdryer in the morning. She elected to undergo a DMEK triple for FECD as well as for her visually significant cataract in the left eye. The early postoperative course was routine and the patient was recovering well until postoperative week seven when she presented with graft interface haze.

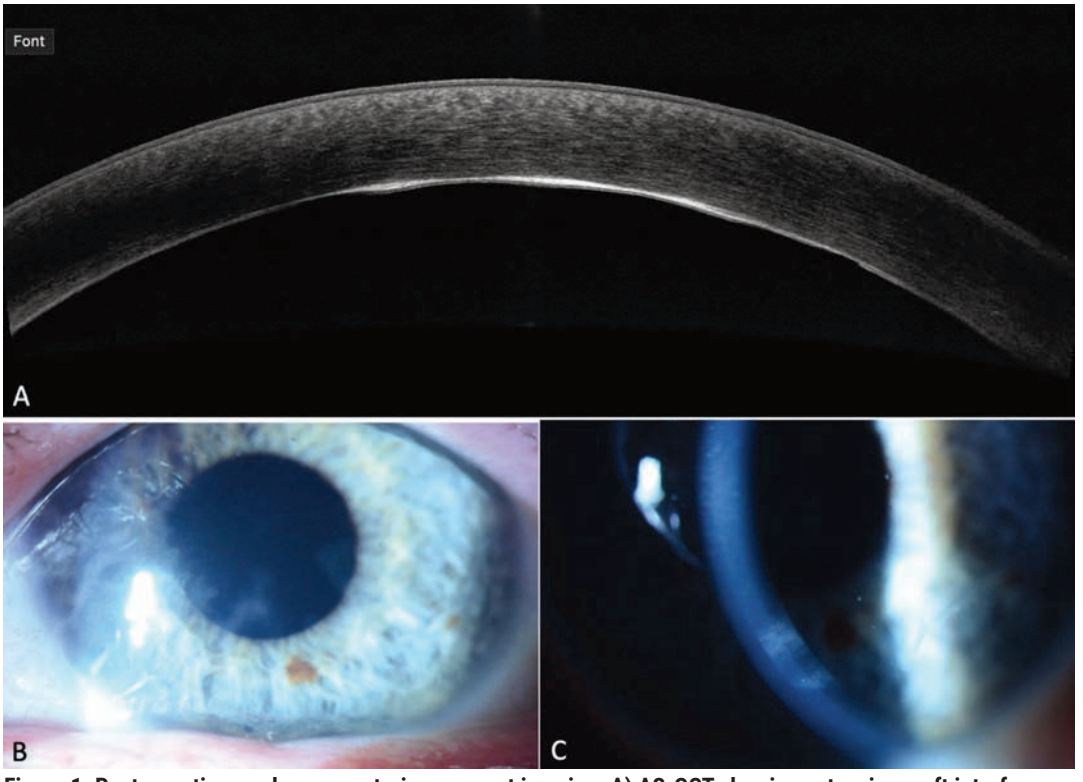

Figure 1. Postoperative week seven anterior segment imaging. A) AS-OCT showing extensive graft interface haze. B) External photograph showing appearance of patchy inferior haze. C) Slit beam photograph showing a magnified view of the interface haze.

DMEK is a safe and effective treatment for corneal endothelial failure, with a mean rate of immune rejection of 1.9 percent.[1] Fungal interface keratitis after DMEK is a rare but devastating complication, occurring in approximately 0.15% of cases,[2] and there is a trend toward an increase in the rate of fungal interface keratitis.[3] Many surgeons routinely perform donor corneal rim fungal cultures at the time of transplant.[4] Although there is no consensus on appropriate management of patients with positive culture results in the absence of clinically evident fungal infection, surgeons who perform donor rim fungal cultures tend to follow patients

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with positive cultures more closely.[4,5] The decision to prophylactically treat a patient with a positive donor fungal culture is not taken lightly, as topical therapy has not shown efficacy in preventing infection and alternatives include systemic azole antifungals or repeat transplant with intracameral antifungal therapy.[5]

This patient's clinical presentation was initially concerning for either fungal interface keratitis or non-infectious interface inflammation. The decision to treat the patient aggressively with antifungal therapy or to treat the interface haze as a non-infectious inflammatory process with topical corticosteroids was based solely on clinical evaluation and interpretation of AS-OCT. The interface haze seen in this case corresponded to a diffuse hyperreflective process along the graft interface as seen in Figures 1 and 2. In contrast, fungal interface keratitis presents with characteristic focal infiltrates and an otherwise non-inflamed interface on AS-OCT,[6] and this patient's AS-OCT was therefore not consistent with a fungal interface keratitis. The interface in this case was more consistent with previously described elongated textural interface opacities.[7] While difficult to differentiate fungal infection from other interface inflammation based on slit lamp examination alone, AS-OCT was critical in suggesting that this inflammation wasn't fungal in etiology and could therefore be treated with frequent topical corticosteroids, albeit with close follow up. The improvement seen in the graft interface haze during treatment with topical corticosteroids supports the diagnosis of an inflammatory, rather than fungal infectious, etiology. Interestingly, the hyperopic astigmatism the patient manifested may be due to posterior corneal changes induced by the haze over time.

AS-OCT is a relatively new imaging modality that is an excellent tool for evaluating endothelial graft morphology and function after routine endothelial keratoplasty.[8] This report highlights another potential use of AS-OCT to manage postoperative complications after endothelial keratoplasty, including diagnosing (or ruling out) fungal interface keratitis. As we begin to perform AS-OCT more routinely on eyes after endothelial keratoplasty, we hope to further characterize the spectrum of graft interface changes and use this knowledge to improve patient outcomes.◀

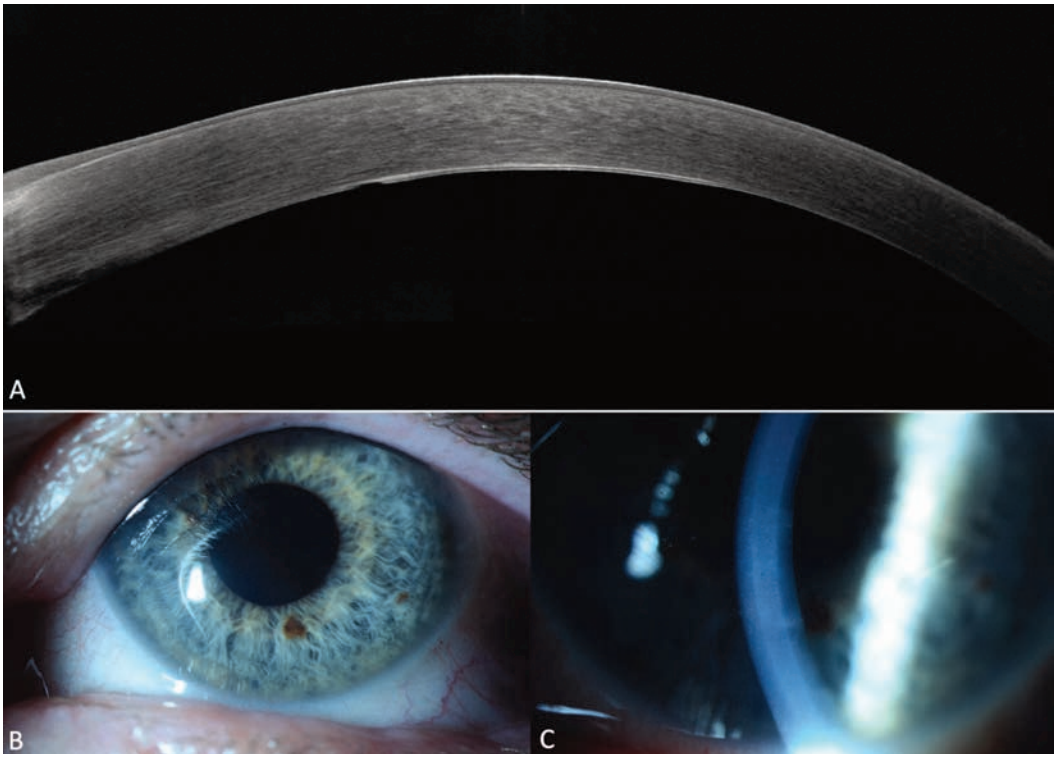

Figure 2. Postoperative month 11 anterior segment imaging. A) AS-OCT showing persistent interface haze, though much diminished from the initial presentation (Figure 1). B) External photograph showing marked improvement in inferior haze. C) Slit beam photograph shows mild persistent interface haze, which was also much improved from the initial presentation (Figure 1).

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The Many Benefits of a Pre-op Patient Prep Kit

Pro tips on how to help patients prepare their eyes for surgery

Neel Desai, MD
Eye Institute of West Florida

Marjan Farid, MD
University of California Irvine

Cynthia Matossian, MD
Matossian Eye

Responding to demand from eye care professionals, Bruder Healthcare recently introduced a pre-surgical prep kit containing the three core hygiene products patients need in a single, self-contained kit.

What benefits matter most to you?

Dr. Matossian: Ocular surgery results are dependent on pre-operative care. This is why it's important for patients to do their part to stabilize the ocular surface and keep lids healthy and clean.

Dr. Farid: Post-op comfort is an important goal in my practice. Patients feel dryer after surgery, but using these products before surgery, and then a week or so after surgery, really helps us get in front of that.

Dr. Desai: By making this pre-op prep process routine, the patient is going to have a better experience overall because we are taking steps to reduce post-op dry eye, discomfort and infection while optimizing our pre-op measurements.

How do you anticipate patients will respond when you ask them to use the kit?

Dr. Matossian: Collecting multiple hygiene products online or at a pharmacy can be overwhelming and impractical for many patients preparing to undergo cataract or other corneal procedures. This kit removes that burden.

Dr. Farid: I agree; this is a significant practical benefit. This kit makes pre-op prep simple and straightforward. Now you can just say, "grab a kit on your way out."

Dr. Desai: This prep kit is a win-win-win for the patients, the practice, and the doctor.

Which patient groups can benefit most from the kit?

Dr. Matossian: Some patients need more interventions than others, but, this kit addresses a common need. Preventing endophthalmitis and optimizing the tear film is important in every patient.

Dr. Desai: Some degree of dry eye is present in most cataract patients and preoperatively addressing ocular surface disease, particularly lid margin disease, is important in terms of preventing infections and in terms of getting more accurate biometry and a smoother post-operative course of recovery.

Dr. Farid: The prep kit is great choice for every pre-op cataract patient, regardless of the type of IOL they're getting, because we always want to optimize the ocular surface and proactively guard against infection.

Included in the Kit

- **Bruder Hygienic Eyelid Cleansing Wipes**. These textured pre-moistened wipes contain a mild surfactant designed to remove build up, oil, dirt, pollen and desquamated skin that may cause eye irritation and infection.
- **Bruder Hygienic Eyelid Solution** (0.02% Pure Hypochlorous acid) Naturally-occurring hypochlorous acid (HOCl) has shown high efficacy against a wide range of microorganisms. Applying one to two sprays of the solution daily to closed eyes helps fight infection, reduce inflammation and bacteria, and enhance natural ability to heal.
- The **Bruder Sx Pre-Surgical Moist Heat Eye Compress**. This enhanced compress is designed specifically for the unique needs of the pre-surgical patient using EyeOnic™ fabric woven with antimicrobial silver threads. Like the original Bruder Moist Heat Eye Compress, the Sx mask is filled with self-hydrating, silver-infused, patented antibacterial MediBeads® to unclog meibomian glands and stabilize the tear film to improve pre-surgical measurements. Patients microwave the mask for 20 seconds then apply for 8-10 minutes.
- **Bruder Sx Case**. All of the essential items that pre-op patients need are neatly housed in an attractive, yet practical case that's large enough for doctors to customize by adding complimentary products, prescriptions or patient education paperwork.

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IMPORTANT SAFETY INFORMATION

Corneal collagen cross-linking should not be performed on pregnant women.

Ulcerative keratitis can occur. Patients should be monitored for resolution of epithelial defects.

The most common ocular adverse reaction was corneal opacity (haze). Other ocular side effects include punctate keratitis, corneal striae, dry eye, corneal epithelium defect, eye pain, light sensitivity, reduced visual acuity, and blurred vision.

These are not all of the side effects of the corneal collagen cross-linking treatment. For more information, go to www.livingwithkeratoconus.com to obtain the FDA-approved product labeling.

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*Photrexa® Viscous and Photrexa® are manufactured for Avedro. The KXL® system is manufactured by Avedro.

REFERENCE: 1. Photrexa [package insert] Waltham, MA: Glaukos, Inc. 2016.

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