Wills Eye Resident Series: An older woman presents with vision loss, *p.60*

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Clinical advice you can trust

Hope Emerges for Geographic Atrophy

With one FDA-approved GA therapy available—and another likely not far behind—retina specialists are hopeful. **P. 34**

Also inside

ALL THOSE IN FAVOR OF PRESERVATIVE FREEDOM, SAY EYE

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VOLUME XXX • NO. 8

AUGUST 2023

Study Finds Low-dose Atropine Ineffective vs. Myopia

While myopia management is gaining prominence worldwide, it's nevertheless still new enough to leave many important questions unanswered at present. The top interventions—multifocal contact lenses, orthokeratology and atropine eye drops—have each demonstrated efficacy, but protocols to guide clinical application are often lacking.

Researchers have sought clarity on how to balance efficacy with side-effect profile when selecting the appropriate concentration of atropine at least since 2006, when the ATOM1 study was published. While the pharmacological intervention has been studied primarily in Asia, generally with favorable results, a new U.S.-based clinical trial published in *JAMA Ophthalmology* failed to replicate the slowing of myopia progression seen in studies of East Asian kids.

An OD-MD group of researchers from the Pediatric Eye Disease Investigator Group tested atropine 0.01% against placebo for slowing myopia in U.S. children. Kids aged 5 to 12 years old across 12 different community- and institution-based practices were included. Refractive error ranged from low to moderate bilateral myopia (-1 D to -6 D). The primary outcome of the study was both-eye mean change in spherical equivalent refractive error (SER), from baseline to 24 months. Other outcomes were spherical equivalent change from baseline out to 30 months (the last six months not receiving treatment) and axial length change at both time points.

A total of 187 children were included in the study (mean age 10 years), with 67 percent receiving atropine and 33 percent receiving the placebo. Follow-up at 24 months was completed by 95 percent of the atropine group and 94 percent of the placebo group. At 30 months, the atropine group displayed a 94-percent follow-up rate and placebo group a 92-percent rate.

The adjusted mean change in SER at the 24-month primary outcome visit was -0.82 D in the atropine group and -0.8 D in the placebo group. At 30 months—that is, six months after cessation of treatment—adjusted difference in mean SER change from baseline was -0.04 D. Adjusted mean changes in axial length from baseline to 24 months was 0.44 mm for the atropine group and 0.45 mm for placebo recipients, and mean axial elongation from baseline to 30 months was +0.009 mm.

Based on the similar numbers between groups, the study authors concluded in their paper that "these results do not support the nightly use of low-dose atropine 0.01% eye drops to slow myopia progression in U.S. children."[1]

In terms of how this may affect clinicians in their practice, study co-author Michael X. Repka, MD, of Johns Hopkins, says, "They'll reevaluate the concentration they're using. There was already some push to use a stronger concentration because of the Hong Kong study, so this may move the group. Even if they were having success with 0.01% they might use 0.05% now. I don't think it'll dissuade development. I think there's still a lot of interest."

As Dr. Repka says, this study's results are different from five clinical trials conducted in East and South Asian populations with similar age and refractive error eligibility criteria. In 2012, the ATOM2 trial saw differences in SER myopia progression but not axial elongation over two years; however, there was no placebo control group, which reduced certainty of evidence. More recently, the 2019 LAMP study saw reduction in myopia progression and axial length elongation over one year, but higher atropine concentrations were found more effective than lower ones. Another study saw myopia progression reduction after two years and another after one year, while yet another saw reduction in mean SER progression after one year; all studies used 0.01% atropine.

This contrasts with one two-year clinical trial conducted in Western Australia, which didn't find significant myopia progression difference when compared with placebo. That study also had similar age and refractive error eligibility criteria to the present research appearing in *JAMA*

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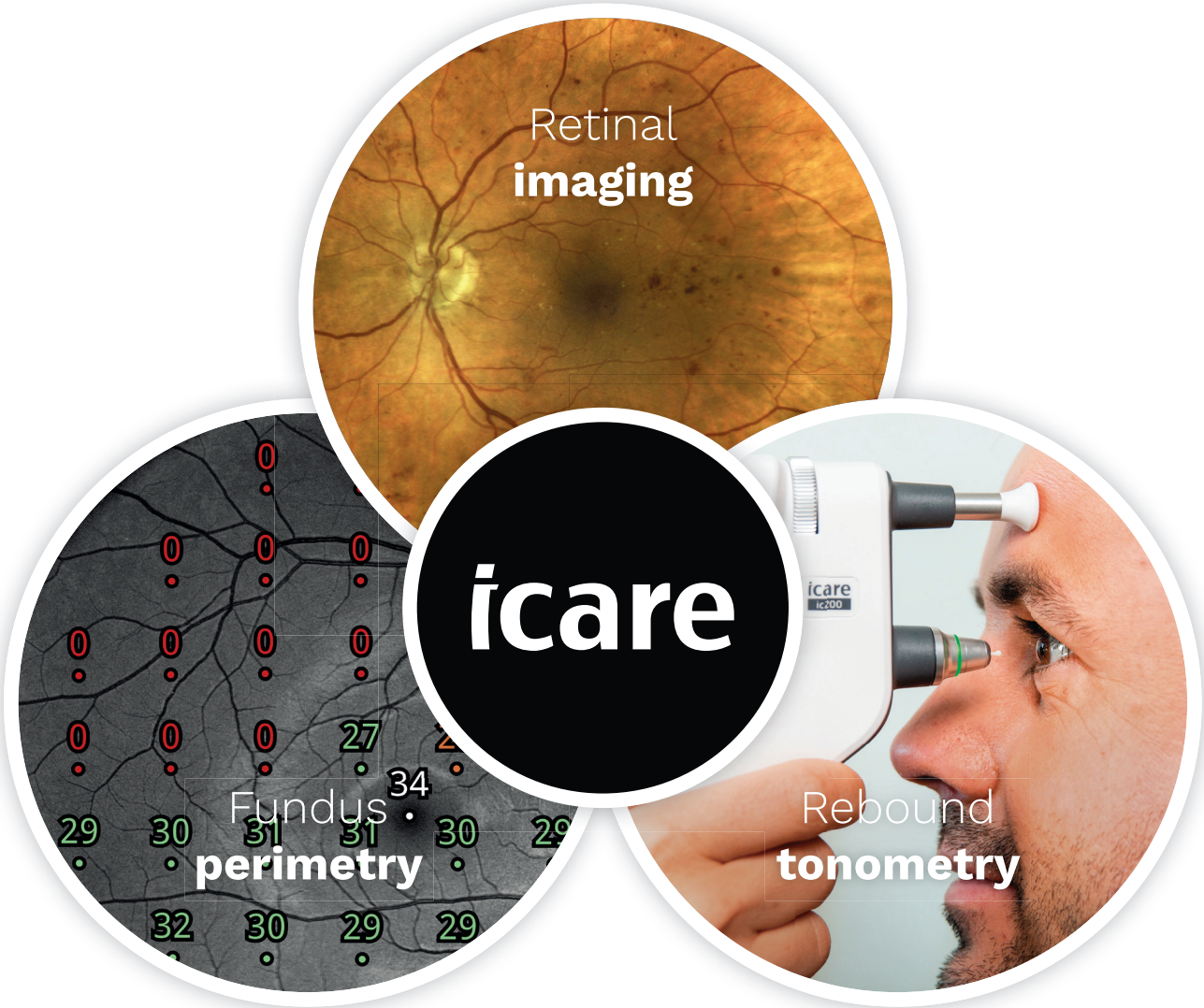

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Atropine Study

Ophthalmology.

Elucidated by the authors and expanded upon by an invited commentary also published by *JAMA Ophthalmology*,[2] one potential reason for this observed difference is that low-concentration atropine may work better for Asian children than other racial or ethnic populations, particularly those of Caucasian origin. Since atropine binds to melanin, the commentary authors noted that the darker irises typical of Asian subjects may have resultant slower release and longer active drug time, which may yield higher effectivity in Asian children.

Dr. Repka also notes that Asian subjects show a faster progression of myopia, which may have an effect. "I think a more likely factor is they progress more, so there's more room for slowing down the effect," he says. "There's more room for slowing the growth of myopia in the ages placed in the study."

Another possibility noted by the commentary is that studies longer than one year frequently don't report additional accrual of treatment effect, so longer trials are less likely to report significant effects, like the present study, when compared with the mostly one-year trials of Asian children.

Finally, the commentators explain age may play a role, since myopia progression slows with age, and studies conducted on Caucasian children have included subjects up to 16 years old, while the Asian studies maxed out at age 12 in three out of four conducted.

"Age does play a role," Dr. Repka avers. "You want to do the treatment in the children that will get the most benefit, so you want it during the time they have the greatest progression." No one's yet determined that age, yet, however. "That's the tough part," Dr. Repka continues, "we don't have a lot of longitudinal history data on that."

In light of these possibilities, the study authors believe that "future studies of pharmacologic myopia control in U.S. children should consider increased atropine concentrations, new pharmaceuticals, objective measures of treatment adherence, alternative eye-drop delivery systems and schedules as well as evaluating the impact of environmental and genetic factors and optical interventions on myopia control treatment."[1]

The authors of the commentary feel similarly and point out that "stronger concentrations of atropine should be considered for first-line treatment of myopia progression, especially when considering eye growth outcomes in white children."[2]

Along those lines, Dr. Repka says their next study should look at a diffrent concentration. "We're trying to gauge interest to see if our group will spend the resources to do that study," he says, "but I think it needs to be done. We'd try a 0.05% dose, which hasn't been studied in the West. There's a reasonable signal of beneficial effect of that dose in the publications."

1. Repka MX, Weise KK, Chandler DL, et al. Low-dose 0.01 atropine eye drops vs. placebo for myopic control: a randomized clinical trial. JAMA Ophthalmol. July 13, 2023. [Epub ahead of print].
2. Walline JJ, Berntsen DA. Atropine, 0.01%, or myopia control. JAMA Ophthalmol. July 13, 2023. [Epub ahead of print].

Risk of Detachment after Cataract Surgery

With the rate of cataract surgery increasing comes an increase in postop complications, such as rhegmatogenous retinal detachment (RRD). In a new study, Swedish researchers analyzed preoperative visual acuity to see if they could discern the risk of RRD after cataract surgery.[1] They concluded that there must be strong indications of need for IOL implantation in those with a high risk of retinal detachment, and the patient must be given adequate information on the risk-benefit trade-offs. Many could get by adequately with spectacle correction, for instance, they argued.

Preoperative visual acuity in nearly 60,000 patients undergoing cataract surgery between during 2015 and 2017 was analyzed (n=58,624), with data retrieved from the Swedish National Cataract Register. This was then cross-referenced with patients undergoing surgery for retinal detachment at the Skåne University Hospital in Lund from 2015 to 2020. The main outcome was the risk-benefit ratio of measuring preoperative visual acuity before cataract surgery and the risk of RRD.

Groups were divided into the following: those aged 60 and younger, those aged 60 and younger with axial length over 25 mm and males aged 60 and younger with axial length over 25 mm.

In a previous study, the same group identified pseudophakic patients with a high risk of long-term complications such as RRD, especially men under the age of 60 with axial length exceeding 25 mm who had almost 10-percent risk within five years. These patients should be thoroughly informed of the risks associated with cataract surgery, and the indications for cataract surgery should be strong.

In the group of patients under 60 years with an axial length over 25 mm with a 6.4-percent risk of RRD in less than five years, more than 15 percent saw 0.8 or better. "The risk-benefit ratio is subjective to each patient, but in our opinion, these

patients could have avoided cataract surgery and obtained the same improvement in vision with better spectacles," the authors noted in the present study.

Between the group being small and the considerable variation in the visual acuity within the group, the authors noted it's important to inform patients with relative good visual acuity that new spectacles may be an alternative to cataract surgery.

Also, in the same group more than 55 percent saw better than 0.5 logMAR, which used to be the indications in several regions for surgery, based on a 2010 study from Spain that found cataract surgery was usually deemed inappropriate in patients whose visual function wasn't impaired or only slightly impaired. In this new study, the patients with RRD had similar visual acuity in the operated eye as the whole study group, but there was a large difference in the fellow eye, where the RRD patients had better visual function.

"This indicates that cataract surgery isn't necessary for many who have a risk for RRD as their binocular vision is still adequate," the authors noted in their paper.

Many of the patients probably underwent cataract surgery on the eye with poorer vision, and then later on the better eye, especially in the case of myopic patients to avoid anisometropia. "Postoperative refraction must be considered when choosing the intraocular lens for the first eye to avoid putting them at risk for RRD with cataract surgery on the fellow eye," the authors noted.

Although there are few complications during surgery and shortly after, based on these findings, the authors concluded that a greater awareness of the long-term risk of RRD is required in high-risk patients before cataract surgery.

"We illustrate in this study that many times the visual acuity for these patients is surprisingly good preoperative of cataract surgery where perhaps the best option for the patient is to wait with the surgery," the authors concluded. "We hope that in the future there will be an individual risk assessment for each patient to consider before doing the surgery." ◀

1. Thylefors J, Jakobsson G, Zetterberg M, Sheikh R. Visual acuity prior to cataract surgery and risk of retinal detachment-A population-based study. Clin Ophthalmol. 2023;2023:17:1975-80.

INDUSTRY NEWS

Demodex Treatment Approved by FDA
In July, Tarsus announced that the FDA approved Xdemvy (lotilaner ophthalmic solution) 0.25% for the treatment of *Demodex* blepharitis, making it the first approved treatment that targets the mites. The company says the therapy will be available by the end of August 2023.

Harrow Acquires Drugs from Santen
Harrow announced the signing of agreements with affiliates of Santen Pharmaceuticals under which Harrow will acquire certain U.S. and Canadian commercial rights for several branded products from Santen. The products include Flarex, Zerviate and Verkazia.

Visiox Acquires Omlonti License
Visiox Pharma has entered into an agreement with Santen to license Omlonti (omidenepag isopropyl ophthalmic solution) 0.002%, a glaucoma drug recently approved by the FDA. They plan to launch the drug early next year.

Regeneron Receives Complete Response Letter
Regeneron recently announced that the FDA has issued a Complete Response Letter (meaning that it can't approve the application in its present form) for the company's approval application for aflibercept 8 mg for the treatment of patients with wet age-related macular degeneration, diabetic macular edema and diabetic retinopathy, solely due to an ongoing review of inspection findings at a third-party filler. *For a deeper look at the topic, see our feature on new retinal treatments on p. 29.*

Video Journal of Cataract, Refractive, & Glaucoma Surgery **Available**
The latest installment of the video journal offers a sample of 27 video highlights of the ESCRS meeting in Milan. View the new video journal at https://vjcrgs.com/.

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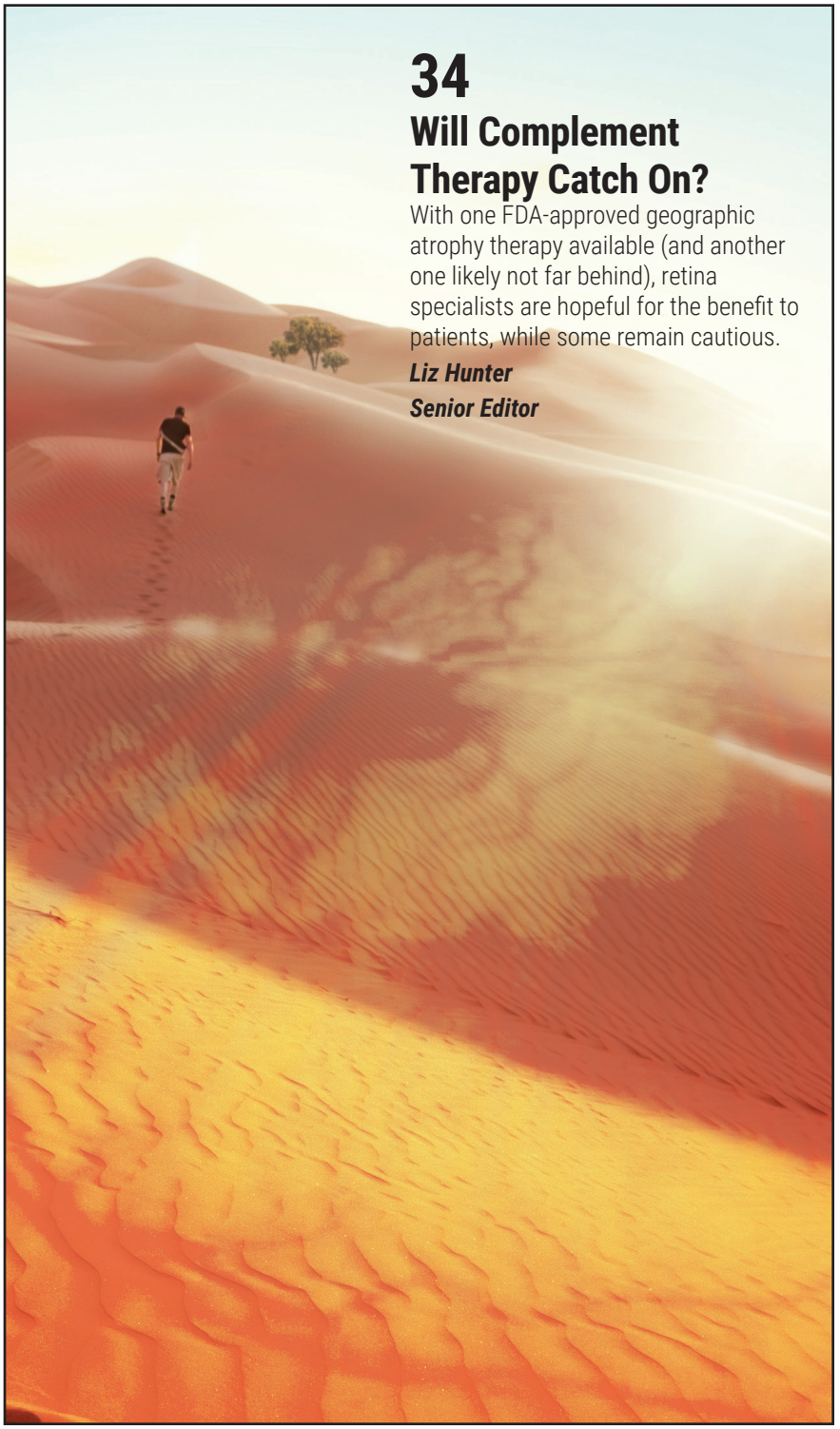
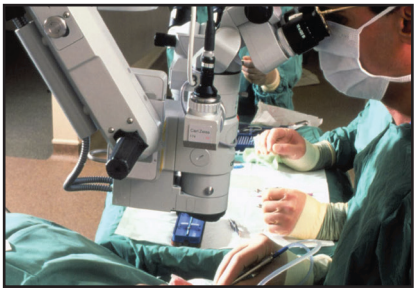


DEPARTMENTS

August 2023



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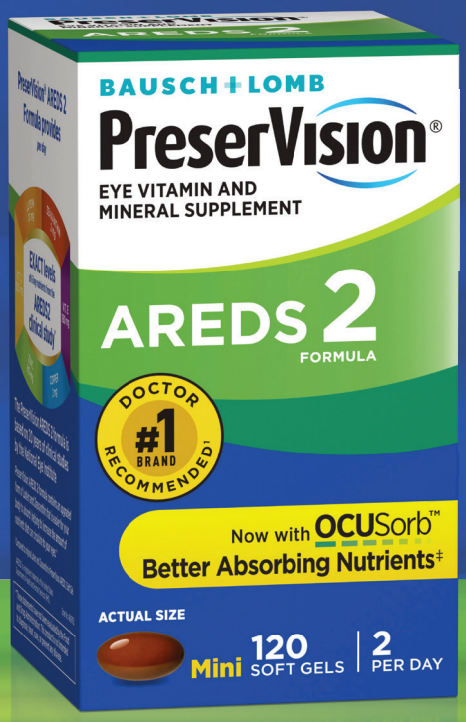

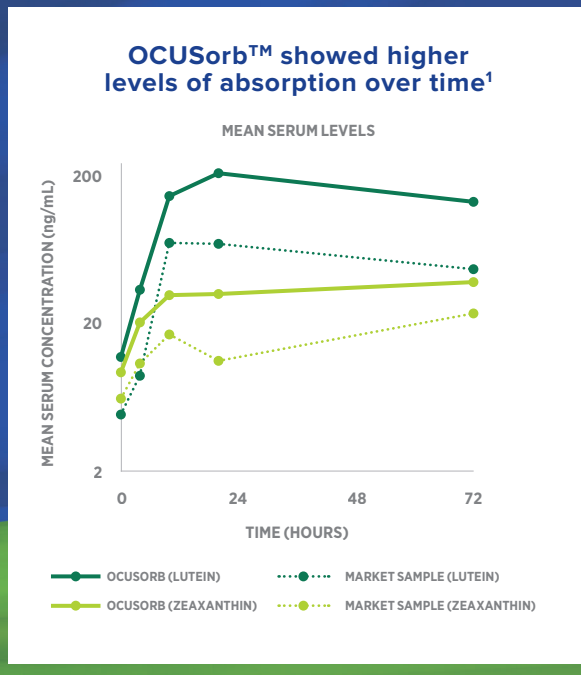

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1. Compared to the market sample. Kotagiri SR, Morde A, Rai D, et al. Ophthalmol Ther. 2022;11(4):1463-1477

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REVIEW OF OPHTHALMOLOGY (ISSN 1081-0226; USPS No. 0012-345) is published monthly, 12 times per year by Jobson Medical Information, LLC/WebMD 283 - 299 Market St. 2 Gateway Center - 4th Floor Newark NJ 07102. Periodicals postage paid at New York, NY and additional mailing offices. Postmaster: Send address changes to Review of Ophthalmology, PO Box 71, Congers, NY 10929-0071. Subscription Prices: US One Year $63.00, US Two Year $112.00, Canada One Year $99.00, Canada Two Year $181.00, Int'l One Year $158.00, Int'l Two Year $274.00. For subscription information call (877) 529-1746 (USA only); outside USA, call (845-267-3065. Or email us at revophthalmology@cambeywest.com. Canada Post: Publications Mail Agreement #40612608. Canada Returns to be sent to Bleuchip International, P.O. Box 25542, London, ON N6C 6B2.

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Global Perspectives on Steroids:

Study Designs and Diabetic Macular Edema Management Around the World

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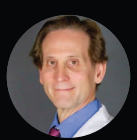

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Predictive Factors for Advanced AMD

Investigators aimed to determine if AMD family history and genetic variants identify eyes at higher risk for progression to advanced AMD (AAMD), after controlling for baseline demographics, behavioral factors and macular status.

The prospective, longitudinal cohort study including eyes with non-advanced AMD at baseline in The Age-Related Eye Disease Study were classified using the AREDS severity scale. Non-genetic and genetic predictors for progression to AAMD, geographic atrophy and neovascular disease were evaluated. Cox proportional hazards models using the eye as the unit of analysis were used to calculate hazard ratios, accounting for correlated data. Discrimination between progressing and non-progressing eyes was assessed using C-statistics and Net Reclassification Improvement (NRI).

Here are some of the findings:

- Among 4,910 eyes, 863 progressed to advanced AMD over 12 years.
- Baseline AMD severity scale and status of the fellow eye were important predictors; genes provided additional discrimination.
- Family history of AMD also independently predicted progression after accounting for genetic and other covariates: one family member vs. none (HR=1.21; CI: 1.02 to 1.43; p=0.03); at least two family members vs. none (HR=1.55; CI: 1.26 to 1.90; p<0.001).
- A composite risk score calculated using beta estimates of non-genetic and significant genetic factors predicted progression to AAMD (HR=5.57, 90th vs. 10th percentile; AUC=0.92), providing superior fit vs. other models with only ocular (NRI=0.34, p<0.001; AUC=0.87) or non-genetic variables (ΔAUC=0.05 ±0.005, p<0.001).
- The study investigators noted that an online risk calculator was available.

Investigators determined that genetic variants and family history provided additional discrimination for advanced age-related macular degeneration prediction, after accounting for ocular and other covariates.

Am J Ophthalmol. 2023 Jul 10:S0002-9394(23)00250-7.
Seddon JM, De D Rosner B.

Risk of Drug-induced Ocular Hypertension After DSEK

Researchers assessed the long-term risk of steroid-induced ocular hypertension and the need for glaucoma treatment with long-term use of topical prednisolone acetate 1% in patients without preexisting glaucoma who underwent Descemet's stripping endothelial keratoplasty.

The researchers retrospectively reviewed the charts of 211 DSEK patients without previous glaucoma, who underwent the surgery and then used topical prednisolone acetate long-term to prevent graft rejection. Dosing was four times daily for four months and tapered to once daily. The main outcomes were ocular hypertension (defined as intraocular pressure ≥24 mmHg or increase of ≥10 mmHg over baseline) and initiation of glaucoma treatment.

The median patient age was 70 years (range: 34 to 94 years). Here are some of the findings:

- The indications for DSEK were Fuchs' endothelial dystrophy (88 percent), pseudophakic corneal edema (7 percent), failed DSEK (3 percent) and failed penetrating keratoplasty (2 percent).
- The median follow-up period was seven years (range: 1 to 17 years).
- The cumulative risks of steroid-induced ocular hypertension were:
  – at one year, 29 percent;
  – at five years, 41 percent; and
  – at 10 years, 49 percent.
- The cumulative risks of requiring glaucoma treatment were:
  – at one year, 11 percent;
  – at five years, 17 percent; and
  – at 10 years, 25 percent.
- Among 35 eyes treated for glaucoma, 28 (80 percent) were managed medically and seven (20 percent) had filtration surgery.

The authors concluded that long-term use of topical corticosteroids such as prednisolone acetate 1% added substantial risk of developing steroid-induced ocular hypertension in postop DSEK patients. As a result, they suggested that frequent monitoring of intraocular pressure would be required.

The researchers added that with corneal transplantation, the risk of steroid-induced ocular hypertension can be mitigated by using techniques with a low inherent risk of rejection, such as Descemet's membrane endothelial keratoplasty, whenever possible, to enable earlier reduction of the corticosteroid's potency. ◀

Cornea 2023; June 7. [Epub ahead of print].
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NO patients reported experiencing pain[2]

*In the clinical trial, no patient undergoing routine cataract surgery receiving IHEEZO required supplemental treatment to maintain anesthesia; this was not the case for patients receiving tetracaine. Supplemental treatment was defined as general anesthesia, intraoperative systemic analgesia, or local anesthesia. Though supplemental administration was not required by any patient in the clinical trial, IHEEZO may be reapplied as needed to maintain anesthesia.[1,2]

†Sufficient anesthesia with IHEEZO lasted an average of 21.5 minutes in the clinical trial, while mean total surgical time was 13.9 minutes.[2]

APPROVED USE

IHEEZO is indicated for ocular surface anesthesia.

IMPORTANT SAFETY INFORMATION

IHEEZO is contraindicated in patients with a history of hypersensitivity to any component of this preparation.

IHEEZO should not be injected or intraocularly administered.

Patients should not touch the eye for at least 10 to 20 minutes after using anesthetic as accidental injuries can occur due to insensitivity of the eye.

Prolonged use of a topical ocular anesthetic may produce permanent corneal opacification and ulceration with accompanying visual loss.

Do not touch the dropper tip to any surface as this may contaminate the gel.

IHEEZO is indicated for administration under the direct supervision of a healthcare provider. IHEEZO is not intended for patient self-administration.

The most common adverse reactions in studies following IHEEZO administration (incidence greater than or equal to 5%) were mydriasis, conjunctival hyperemia, and eye irritation.

You are encouraged to report suspected adverse reactions to the FDA. Visit **www.fda.gov/medwatch**, or call **1-800-FDA-1088**.

Please see Brief Summary of Full Prescribing Information for IHEEZO on adjacent page.

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References: 1. Iheezo. Prescribing information. Harrow IP, LLC; 2022. **2.** Data on File. Harrow IP, LLC; 2023.

IHEEZO™

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

IHEEZO™ (chloroprocaine hydrochloride ophthalmic gel) 3% is a preservative-free ester anesthetic indicated for ocular surface anesthesia.

4 CONTRAINDICATIONS

IHEEZO is contraindicated in patients with a history of hypersensitivity to any component of this preparation.

5 WARNINGS AND PRECAUTIONS

5.1 Not for Injection or Intraocular Administration

IHEEZO should not be injected or intraocularly administered.

5.2 Corneal Injury Due to Insensitivity

Patients should not touch the eye for at least 10 to 20 minutes after using anesthetic as accidental injuries can occur due to insensitivity of the eye.

5.3 Corneal Opacification

Prolonged use of a topical ocular anesthetic may produce permanent corneal opacification and ulceration with accompanying visual loss.

5.4 Risk of Contamination

Do not touch the dropper tip to any surface as this may contaminate the gel.

5.5 For Administration by Healthcare Provider

IHEEZO is indicated for administration under the direct supervision of a healthcare provider. IHEEZO is not intended for patient self-administration.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

The data described below reflect 201 patients undergoing various surgical ocular procedures in two placebo-controlled trials (Study 1 and Study 2). Patients in Study 1 were randomized to receive a single instillation of 3 drops of IHEEZO or placebo. Patients in Study 2 were randomized to receive a single or multiple instillations of 1, 3, or 3+3 drops of IHEEZO or placebo.

The most common adverse reactions in these studies (incidence greater than or equal to 5%) following IHEEZO administration were mydriasis, conjunctival hyperemia, and eye irritation.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of IHEEZO use in pregnant women to inform a drug-associated risk. There are no animal reproduction studies for chloroprocaine.

8.2 Lactation

Risk Summary

There are no data on the presence of chloroprocaine 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 IHEEZO and any potential adverse effects on the breastfed infant from IHEEZO.

8.4 Pediatric Use

The safety and effectiveness of IHEEZO have not been established in pediatric patients.

8.5 Geriatric Use

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Chloroprocaine, like other local anesthetics, blocks the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, slowing the propagation of the nerve impulse, and reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.

12.3 Pharmacokinetics

The systemic exposure to chloroprocaine following topical ocular administration of IHEEZO has not been studied.

Elimination

Metabolism

Chloroprocaine is metabolized by plasma pseudocholinesterases and nonspecific esterases in ocular tissues. Chloroprocaine is rapidly metabolized in plasma by hydrolysis of the ester linkage by pseudocholinesterase. The hydrolysis of chloroprocaine results in the production of ß-diethylaminoethanol and 2-chloro-4-aminobenzoic acid, which inhibits the action of the sulfonamides.

Excretion

Chloroprocaine plasma half-life in vitro is approximately 25 seconds in adults and approximately 43 seconds in neonates. The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by urinary perfusion and factors affecting urinary pH.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals to evaluate carcinogenic potential of chloroprocaine have not been conducted.

Mutagenesis

2-chloroprocaine and the main metabolite, ACBA, were negative in the in vitro bacterial reverse mutation test (Ames assay) and the in vitro chromosome aberrations assay.

Impairment of Fertility

Studies in animals to evaluate the impairment of fertility have not been conducted with chloroprocaine.

14 CLINICAL STUDIES

14.1 Study 1 and Study 2

Study 1 (NCT04779606) and Study 2 (NCT04753710) were randomized, double-blinded, placebo-controlled studies conducted to evaluate the efficacy, safety, and local tolerability of IHEEZO in 145 healthy volunteers.

In Study 1, 85 healthy males and females were randomized in a 4:1 ratio to receive a single ocular instillation of IHEEZO (n=68) or placebo (n=17). The double-blinded treatment included an IHEEZO or a placebo dose of 3 drops instilled at 1-minute (±15 seconds) intervals in the right eye of each volunteer. The median age was 39 years (range 19 to 55 years); 59% female and 41% male.

In Study 2, 60 healthy males and females were randomized (40:20) to receive single or multiple ocular instillations of an IHEEZO dose of 3 drops in the right eye. The median age was 25 years (range 18 to 59 years); 54% female and 46% male.

The efficacy in Study 1 and Study 2 was determined by proportion of patients achieving full conjunctival anesthesia evaluated by conjunctival pinching 5 minutes after administration.

Efficacy results of Study 1

The proportion of subjects with successful anesthesia was 90% in the IHEEZO group and 12% in the placebo group (P<0.01). The median time for the IHEEZO group achieving anesthesia was 0.67 minutes. The median duration of anesthesia was 14.3 minutes.

Efficacy results of Study 2

The proportion of subjects with successful anesthesia was 95% in the IHEEZO group and 20% in the placebo group (P<0.01). The median time for the IHEEZO group achieving anesthesia was 0.67 minutes. The median duration of anesthesia was 19.3 minutes.

14.2 Study 3

Study 3 (NCT04685538) was a randomized, prospective, multicenter, active-controlled, observer-masked study conducted to evaluate the efficacy and safety of IHEEZO (n=166) versus tetracaine ophthalmic solution 0.5% (n=172) in patients undergoing cataract surgery.

The primary endpoint was defined as the proportion of patients in each treatment group gaining successful anesthesia without any supplementation. On average, patients needed 1 to 1.5 minutes to obtain sufficient anesthesia to successfully perform the surgical procedure, which lasted on average 22 minutes.

No patient treated with IHEEZO required supplemental treatment to complete the intended surgical procedure.

17 PATIENT COUNSELING INFORMATION

Eye Care Precaution

Do not touch the dropper tip to any surface as this may contaminate the gel. Advise patients that their eyes will be insensitive for up to 20 minutes due to the effect of the anesthetic, and that care should be taken to avoid accidental injuries.

For Full Prescribing Information, please visit www.iheezo.com/prescribinginformation.

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Highlights from the TFOS Lifestyle Reports

A selection of key takeaways from the largest global dry-eye panel to date.

AN INTERVIEW WITH CHRISTOPHER STARR, MD
BY CHRISTINE YUE LEONARD, SENIOR ASSOCIATE EDITOR
NEW YORK CITY & PHILADELPHIA

Dry eye has a profound effect on quality of life. While we have a full armamentarium of treatments to offer patients, we can't always account for the impact of certain day-to-day lifestyle choices or situations when managing this chronic and often debilitating disease. Patients often want to know what else they can do to get through each day, in addition to the dry-eye treatments provided by their eye-care provider.

For years, ophthalmologists have offered up suggestions for lifestyle modification such as adding humidifiers to bedrooms, trying to blink more often or incorporating more fish into one's diet. But what does the literature tell us? The Tear Film & Ocular Surface Society (TFOS) Workshop, "A Lifestyle Epidemic: Ocular Surface Disease" was initiated to answer this question. This Workshop was the first global panel of experts (a total of 158 members from 38 countries around the world) to undertake a comprehensive evidence-based review of the literature on how our various lifestyle and societal factors impact the ocular surface.

Eight reports covering contact lens wear, cosmetics, digital screen usage, elective medications and procedures, climate, lifestyle, nutrition and societal challenges were published. Three additional subcommittees focused on evidence quality, industry liaising and public awareness. Evidence was assessed using the Academy's three-level Preferred Practice Pattern guidelines for evidence grading. In parallel with the narrative reviews, members of each topic area subcommittee worked with the evidence quality subcommittee to answer a unique key question using systematic review methodology.

In many instances, there wasn't enough high-quality evidence to draw definitive conclusions about a given factor's effect on the ocular surface. Hopefully these reports will inspire others to fill in the gaps with new research.

While all eye-care practitioners are encouraged to read the full report, below you will find some of the key findings from each subcommittee report.

Contact Lenses

Many of the day-to-day choices that contact lens wearers make can have marked consequences on ocular surface health. Findings showed that sleeping in contacts is the single largest risk factor for contact lens-related adverse events, including microbial keratitis, corneal ulcers and corneal infections.

Other risk factors included nonadherence to contact lens maintenance protocols and replacement schedules, both of which will negatively affect safety and performance. It's important to remind patients to clean and replace cases periodically and to avoid exposing contact lenses to tap water. Topping off solution increases the risk of microbial keratitis by 2.25 times and poor storage case hygiene practices were associated with a 3.7-times increased risk. Good lens hygiene is especially important in challenging environments, such as high levels of dust, air pollution and chemical exposure.

Additionally, the report indicated that purchasing poor-quality contact lenses, showering and swimming while wearing contact lenses, failing to see an eye-care provider regularly, wearing lenses when unwell or resuming wear too soon after ophthalmic surgery also increased the risk of ocular surface complications and dry eye.

Daily disposable contact lenses have a number of established benefits compared with weekly or monthly lenses, and the report confirmed this, citing lower rates of inflammatory-related complications and better visual acuity outcomes following microbial keratitis.

Interestingly, the findings showed that contact lens-associated risks weren't directly impacted by the COVID-19 pandemic. External factors such as mask-associated dry eye, increased screen time and exposure to hand sanitizer can certainly affect lens performance, but there wasn't a lot of high-quality

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data demonstrating direct impact. Despite this, because contact lens wear may reduce tear-film quality and exacerbate dry eye, it's recommended that contact lens wearers stop using lenses if they become infected with COVID-19. 'Long COVID' has been linked to corneal epithelial nerve loss and an increase in corneal immune cell density.

The contact lens report's systematic review sought to examine associations between lifestyle factors and soft contact lens drop-out rates. The researchers looked at 34 studies (15 randomized controlled trials and 19 cohort studies). The group identified discomfort as the most frequently reported reason for drop-out (35 percent), followed by lens handling (33 percent), vision quality with multifocals and loss of interest. Ocular discomfort was most often linked to feelings of dryness. Though the influence of lifestyle factors remains poorly understood and more research is needed, the report ultimately concluded that contact lens wear enhances quality of life when used appropriately.

Cosmetics

Humans have been using cosmetics for thousands of years, and though it's less common to find mercury in cosmetics nowadays, there still remain plenty of ocular surface toxins to be aware of. This report examined common cosmetic ingredients and their effects on the ocular surface.

The thin skin around the eyes and eyelids permits easy absorption of chemicals. Most cosmetics aren't intended to go on the ocular surface, but it's not uncommon for these products to migrate into the eye or eyelids. This is a common cause of or source of exacerbation for dry-eye disease symptoms since these products often contain ingredients that are toxic to the ocular surface and eyelids (many of which are classified as allergens, irritants, carcinogens, immunosuppressants, toxins, endocrine disruptors, mutagens or tumor promotors).

In addition to common culprits such as mascara, eyeliner, eyelash glue and foundations that may migrate into the eye and block meibomian glands or obstruct lacrimal pathways, skincare items such as retinoid creams may cause meibomian gland changes and salicylic acid cleansers may lead to ocular surface toxicity if they come into contact with the eye. Many products marketed as "natural" also contain eye irritants such as castor oil, gold, tea tree oil and talc that may cause contact dermatitis.

Cosmetics aren't widely regulated in the United States. The FDA estimates that around 12,500 chemicals are used in cosmetics but fewer than 20 percent of these have been reviewed for safety by experts in the Cosmetic Ingredient Review.

Some of the key toxic ingredients to be aware of include parabens, phenoxyethanol, chlorphenesin, formaldehyde and benzalkonium chloride:

• ***Parabens.*** Parabens are very common in the United States, found in more than 22,000 products. They're toxic to human corneal, conjunctival and meibomian gland epithelial cells *in vitro*. They're also allergens and endocrine disruptors and possess estrogen latency and antiandrogen activity.

• ***Phenoxyethanol.*** Even in concentrations one-tenth of those allowed for consumer consumption, this drug decreases meibomian gland epithelial cell survival. This compound has also been demonstrated to induce hepatotoxicity, renal toxicity and hemolysis in many species.

• ***Chlorphenesin.*** Found in more than 1,300 cosmetics, this drug in 300-fold-lower concentrations than allowed has also been shown to reduce meibomian gland epithelial cell survival.

• ***Benzalkonium chloride.*** BAK amounts in cosmetics can be 20,000 times lower than approved levels and still be toxic to the ocular surface. In fact, concentrations hundreds-fold lower than the human limit for commercial products were found to kill all human corneal, conjunctival and meibomian gland epithelial cells *in vitro* within 18 hours. *In vivo* models demonstrated effects including tear-film instability, goblet cell loss, conjunctival squamous metaplasia and apoptosis, corneal neurotoxicity and corneal epithelial barrier disruption. We see signs of epithelial damage on the ocular surface with BAK-containing eyedrops, and we certainly see these signs in BAK-containing cosmetics as well.

• ***Formaldehyde.*** Similarly, formaldehyde concentrations 2,000 times lower than accepted levels in cosmetics are toxic to the ocular surface and also have carcinogenic properties. The International Agency for Research on Cancer has classified formaldehyde as a human carcinogen, yet it remains a common ingredient in many cosmetics.

In addition to toxic ingredient awareness, be sure to remind patients to pay attention to their cosmetics' expiration dates. Certain products may go rancid after a period of time, and repeated use of a cosmetic product over time introduces microbes and other contaminants into the container. The report found that 35 percent of mascaras had a microbial presence after three months of use, and another study reported that 79 percent of used mascaras tested positive for *Staphylococcus aureus* and 13 percent for *Pseudomonas aeruginosa*. Product contamination is related to the amount of use, the age of the product and the number of users. Sharing makeup products (e.g., among friends or tester products in stores) can also transfer viruses and *Demodex* mites. Dirty makeup

application tools may also play host to bacteria and microbes.

Cosmetic procedures including Botox, fillers, platelet-rich plasma injections, tattooing, eyelid piercing, eyelash curling, eyelash extensions, microneedling and skin resurfacing also pose potential risks to the ocular surface through damage, inflammation or migration of bacteria.

This report's systematic review examined randomized controlled trial evidence for ocular surface signs and symptoms with the use of eyelash growth products. Patient reported symptoms and clinical parameters such as fluorescein staining, tear breakup time and osmolarity were assessed, as were secondary outcomes such as eyelash length, thickness and incidence of ocular adverse events. Unfortunately, none of the 14 eligible trials in the review reported on either of the two prespecified primary review outcomes associated with symptoms and signs based on validated systems, so consequently, given the lack of available literature, it wasn't possible to answer the key questions. Based on the low-certainty findings we do have, it seems likely that eyelash growth products such as bimatoprost may lead to ocular adverse events seen with other prostaglandin analogues, such as irritation, stinging, itching or meibomian gland dysfunction. More high-quality studies in the future will help us learn more to educate eye-care providers and patients.

Digital Environment

One of the goals of this impact report was to develop a unified definition for digital eye strain. Prior to this, there was no agreed-upon criteria to assess the impact of digital devices on the ocular surface or to differentiate true eye strain caused by viewing digital screens from dry eye exacerbated by screen time. The current validated questionnaires, such as the Computer Vision Syndrome Questionnaire, don't differentiate between overlapping symptoms with and without digital screen use.

It's important to be able to properly diagnose digital eye strain since there are other conditions such as uncorrected refractive error or binocular vision problems like strabismus that may masquerade as digital eye strain. We want to be able to identify the true underlying cause—perhaps a patient has esotropia or cranial nerve palsy—and treat it in a timely and appropriate way.

> **The TFOS definition for digital eye strain is "the development or exacerbation of recurrent ocular symptoms and/or signs related specifically to digital device screen viewing."**

The TFOS definition for digital eye strain is "the development or exacerbation of recurrent ocular symptoms and/or signs related specifically to digital device screen viewing." It can occur as early as 20 minutes into device use and usually occurs after one, four and five hours of screen usage. According to the report, "a diagnosis should be able to differentiate a change in symptoms and/or signs that occur in a digital but not in an equivalent non-digital environment, conducted for the same duration, that exceeds the noise of repeated measures."

Patients must report development or exacerbation of ocular symptoms specifically related to screen use. Typical symptoms of digital eye strain may include burning, headache, eye redness, photophobia, tearing, repeated frequent blinking, itching, blurred vision, near double vision and foreign body sensation.

Addressing digital eye strain can be undertaken from multiple fronts. The report's systematic review looked at several possible treatments and identified oral omega-3 supplementation as a likely effective treatment, due to its anti-inflammatory properties. Antioxidants and blue-light blocking glasses, on the other hand, showed no effects on reducing digital eye strain. Somewhat effective treatments included artificial tears and using apps to set reminders to blink and take breaks from screen usage or follow the 20/20/20 rule.

Patients can also try to alter their device settings, such as reading in Dark Mode, which can reduce the accommodative load and improve visual acuity performance; adjusting screen brightness to mimic ambient light; using e-ink or e-paper devices; increasing display size/resolution to improve text readability; and ensuring good head and neck posture.

Elective Medications and Procedures

Medication-induced dry eye is already on many clinicians' radars, with preserved artificial tears and glaucoma drops ranking high among possible causes or contributors. We know that preservatives in eyedrops, especially BAK, can have a toxic effect on the ocular surface, breaking down the tear film, damaging corneal epithelial cells, corneal nerves and meibomian glands. Alternatives include preservative-free drops or those with milder preservatives such as Polyquad, Purite, SofZia and sodium perborate.

Other medications affecting ocular surface health and contributing to dry eye include:

- antihistamines
- mast cell stabilizers

- NSAIDs
- isotretinoin
- topical alpha adrenergic receptor agonists
- corticosteroid
- hydroxychloroquine
- ivermectin
- hormone replacement therapy
- antidepressants
- cannabis
- anti-androgens
- tamsulosin (Flomax).

Additionally, titanium dioxide and zinc oxide nanoparticles, found in mineral sunscreens, are cytotoxic to corneal cells. Eye whitening products are also not recommended, with 32.4 percent of users diagnosed with dry eye after undergoing the procedure (with only 2.8 percent initially presenting with dry eye).

One of the most severe complications of a medication is toxic epidermal necrolysis/Stevens Johnson Syndrome. Use of antimicrobials such as trimethoprim, sulfamethoxazole, sulfonamide antibiotics, aminopenicillins, quinolones and cephalosporins were risk factors for developing this condition and other severe ocular surface alterations. For any drug-induced reaction, it's important to identify the cause and stop use or switch to a less toxic alternative.

Punctal plugs and low-level light therapy both demonstrated positive effects in dry eye, with low-level light therapy improving meibomian gland dysfunction. Interestingly, manuka honey eye drops were found to improve ocular surface staining and meibomian gland expressibility. Adverse effects included redness, itching, inflammation and allergic reactions.

As for elective procedures, those that lift the brow or alter the eyelid may increase corneal dryness by altering eyelid position, eyelid closure or damaging the cornea or lacrimal structures. Upper blepharoplasty alone may alleviate dry-eye symptoms. Ptosis surgery wasn't found to worsen dry-eye symptoms. Corneal refractive surgery is also a well-known contributor to dry eye.

The systemic review of this report focused on SMILE, reporting a high satisfaction index, improvements in quality of life and minimal interference with the ocular surface. Based on the findings, SMILE is a reasonable alternative to other corneal refractive procedures and is considered a good option for treating refractive error. Overall, SMILE refractive surgery seems to cause more vision disturbances than LASIK in the first month post-surgery, but less dry eye symptoms in long-term follow up. More high-quality prospective studies are needed to further distinguish these vision correcting techniques.

Environmental Conditions

This report identified several environmental variables that contribute to dry eye, some of which are modifiable and others not. Here are the key conditions affecting the ocular surface:

• ***Temperature.*** Temperature affects ocular surface homeostasis directly and indirectly and can precipitate ocular surface disease symptoms. Extremely high or low temperature in the indoor and outdoor environment have been associated with dry eye. One study reported that in an indoor environment at 22.2 to 25.6 degrees Celsius (72 to 78 degrees Fahrenheit), a 1-degree Celsius temperature decrease improved dry-eye symptoms in 19 percent of participants. Temperature variations may also be implicated in allergic conjunctivitis.

• ***Humidity.*** Population-based studies revealed a negative association between humidity and risk of dry-eye disease. High indoor humidity (30 to 40 percent) was associated with lower ocular surface symptoms. Humidifiers set to 40 percent, especially in the bedroom, can help alleviate dry eye. Low humidity environments such as deserts, airplane cabins and certain geographic regions can aggravate symptoms. Allergies and adenovirus conjunctivitis were negatively correlated with low humidity.

• ***Wind speed.*** The current literature provides very little evidence for wind speed and ocular surface diseases, with studies limited to case reports or retrospective reviews. Based on these, we know corneal frostbite and desiccation keratitis were found to occur with prolonged exposure to high wind speeds and sub-zero temperatures in ultra-marathon runners. Corneal freezing has been described in military freefall parachutists exposed to freezing temperatures and high winds. Higher occurrences of corneal ulcers have been found in onion harvesters in southern Taiwan, a monsoon area with prevailing gusty winds.

• ***Altitude.*** At higher altitudes, conditions are cold, dry, hypobaric and hypoxic, with strong ultraviolet radiation and more hours of sunshine. The most common ocular surface disease related to altitude is pterygium. There is also increased risk for photokeratitis.

Dewpoint, the temperature to which air must be cooled to reach maximum water saturation, is positively correlated with tear breakup time. A higher dewpoint (e.g., when there's fog and precipitation) may be a protective factor for dry eye.

• ***Allergens.*** High concentrations of indoor and outdoor allergens such as mold spores, grasses, weeds, tree pollen, dust mites and pet dander exacerbate dry eye and conjunctivitis, as do longer and earlier allergy seasons.

• ***Air pollution.*** Evidence shows that some airborne pollutants may be harmful to the ocular surface. These include a mixture of toxic chemicals and compounds includ-

ing carbon monoxide, nitrogen dioxide, sulfur dioxide, ozone and particulate matter less than 10 µm. Ocular surface disease symptoms may be worse among individuals living near sources of particulate matter such as volcanoes and wildfires, fuel combustion, factories, transportation, agriculture and air conditioning systems or units. Primary Sjogren's syndrome was associated with occupational chemical solvent exposures (chlorinated and aromatic solvents).

One of the less often acknowledged dimensions of air pollution is sick-house or sick-building syndrome. Patients with this condition have worsening ocular surface symptoms when in a particular house or building due to mold, allergens, dust and toxins such as paint thinners and construction materials.

The environmental systematic review examined the associations between outdoor environment pollution and dry-eye disease symptoms and signs in humans in 19 studies from 10 different countries. These studies confirm increased dry-eye disease with air pollution (from NO_2) and soil pollution (from chromium), but no increase in dry-eye disease with air pollution from CO or particulate matter <10 µm.

Nutrition

Poor diet is the second highest risk factor for dry-eye disease, leading to chronic inflammation, impaired immunity and gut microbiome dysbiosis. This report considered ocular surface effects of micro- and macronutrients, water, eating habits and systemic disease. Positive effects on the ocular surface were found with some of the following:

• ***Omega-3s.*** A higher ratio of omega-6s to omega-3s was found to be proinflammatory while a lower ratio was anti-inflammatory. Increasing omega-6 intake conferred an approximately 2.5-times higher risk of developing dry-eye symptoms while every gram of omega-3 consumed was associated with a 30-percent reduction in dry-eye risk. The ideal ratio of omega-3 to omega-6 reported was 4:1.

The Mediterranean diet, which is high in omega-3s, was shown to decrease the signs and symptoms of dry eye vs. baseline in patients with Sjögren's syndrome in one randomized study.

> **In many instances, there wasn't enough high-quality evidence to draw definitive conclusions about a given factor's effect on the ocular surface. Hopefully these reports will inspire others to fill in the gaps with new research.**

• ***Certain micronutrients.*** Strong evidence was also found for vitamin A, vitamin B12, vitamin C and vitamin D. Vitamin A was found to decrease stress symptoms compared to no treatment. Limited evidence was reported for selenium and lactoferrin.

• ***Some dietary supplements.*** A randomized controlled trial found that curcumin or turmeric decreased dry-eye symptoms and increased Schirmer scores and tear breakup time. Additionally, a combination of curcumin, lutein, zeaxanthin and vitamin D3 taken for eight weeks decreased dry-eye symptoms.

Eating honey conferred no change in dry-eye symptoms but did increase tear breakup time and Schirmer's score, according to a double-masked eight-week randomized controlled trial.

Interestingly, the large-scale literature review turned up a misconception about hydration. A population-based study on water intake with approximately 31,000 individuals concluded that water intake wasn't protective for eye dryness.

Worsening dry eye was linked to cytokines, eating disorders such as anorexia (but not bulimia), food intolerances and food allergies. The effect of intentional food restriction on the ocular surface remains unclear and better-quality studies are needed on dietary effects.

Several systemic disorders that are affected by nutrition and diet such as inflammatory bowel disorder and celiac disease also demonstrated associations with ocular surface health, possibly through inflammation and disruption of the body's ability to process and distribute certain nutrients. A systematic review investigated the effects of intentional food restriction on ocular surface health; of the 25 included studies, most investigated Ramadan fasting (56 percent), followed by bariatric surgery (16 percent), anorexia nervosa (16 percent), but none were judged to be of high quality, with no randomized-controlled trials.

Lifestyle Challenges

The lifestyle subcommittee examined ocular surface effects related to mental health challenges, physical factors such as chronic pain, and recreational drug use.

Almost 30 percent of individuals with dry eye have depression. Meta-analyses show that dry-eye disease symptom scores are significantly associated with depression severity scores. Multiple studies have reported no relationships between dry-eye disease symptoms and signs with depression but given the high risk of these two conditions coexisting, and the fact that SSRI antidepressant medications have been reported to cause ocular surface changes, it's worth learning if your patient is suffering from or being treated for depression.

Similarly, anxiety disorders also demonstrated a positive association with dry-eye disease, with studies finding a higher proportion of dry-eye patients with anxiety-related diagnoses, including post-traumatic stress disorder. Stress may flare dry-eye symptoms.

Unsurprisingly, sleep quality and dry eye were associated. Patients who exhibited poor sleep quality, less time spent asleep or had more sleep disturbances had a higher prevalence of dry eye. In terms of possible mechanisms, the literature tells us that sleep deprivation leads to epithelial disruption, lipid abnormalities, morphologic changes to the microvilli and decreased tear production. Resting for 14 days after sleep deprivation reversed these observed changes in one study.

Patients with obstructive sleep apnea who use continuous positive airway pressure (CPAP) machines may experience dry eye from air leakage around the mask. The same has been found among face mask wearers. In a study of mask-associated dry eye, 27 percent reported worsening symptoms while wearing a mask. Mask wear greater or equal to six hours per day, five days per week resulted in an increase of dry-eye symptoms compared to pre-pandemic scores.

Chronic pain is a risk factor for dry eye. A systematic review reported that dry-eye disease in adults with primary pain disorders was more likely compared with a control population. Migraine, fibromyalgia, irritable bowel syndrome and back pain are just a few of the pain conditions with links to dry eye.

Limited and contradictory data was available for tobacco and cannabis use, with one meta-analysis finding no significant association between tobacco use and dry eye and three general population studies finding significant associations. Cannabis data showed potential long-term decreased corneal endothelial density, but dry-eye studies were limited. Alcohol consumption and dry eye was thought to be part of a larger issue involving poor nutrition and vitamin A deficiency.

Caffeine may have a beneficial effect on dry eye. Two prospective placebo-controlled cross-over studies demonstrated increased tear meniscus height and higher Schirmer's test scores with caffeine use.

Overall, the evidence supports comorbidity between chronic conditions and dry-eye disease but mostly pertaining to symptoms rather than signs. The effect of recreational drugs on the eye is dependent on the actions of the drugs and their methods of delivery.

Societal Challenges

As with many other medical conditions, societal factors such as education, access to care and health-care utilization play a role in ocular surface disease presentation, management, prioritization and outcomes. Many elements of this report were previously covered in other TFOS Lifestyle Workshop Reports, including systemic diseases, age, sex, race, smoking status, COVID-19 effects and regional climate. This report went on to investigate socio-economic and cultural effects on ocular surface disease, as well as the impact of employment, poverty, sanitation, violence and trauma and access to health-care services.

Many societal challenges are associated with acute and chronic ocular surface disease but the presence of confounders requires further research with appropriately powered studies. This report noted that the effects of sex may be confounded by social and gender constructs, affecting access to health care, employment, poverty and education. Additionally, different reported rates of ocular surface among Indigenous versus non-Indigenous populations may be affected by access to health care, poverty, trauma and marginalization.

Alluded to briefly with sick-building syndrome, working and living conditions can put individuals at increased risk for dry eye and other ocular surface diseases. Poverty and poor sanitation also contribute to increased risk, as well as violence, war, immigration, food insecurity, water quality and climate variations. ◀

Further Reading

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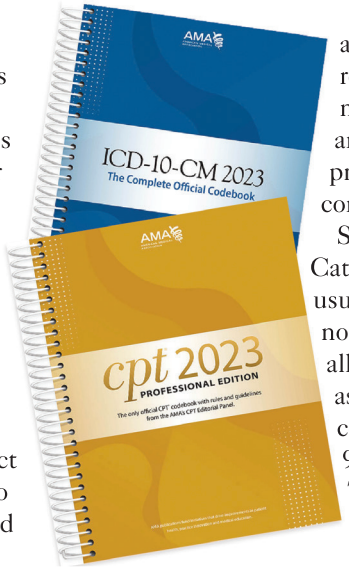
MEDICARE Q&A

A Review of the 21st Century Cures Act

We answer the burning questions that have arisen since the Act's going into effect in 2019.

Ophthalmologists and optometrists have an obligation to file claims to Medicare and other third-party payers for covered services; they can't bill patients for items or services that would have been covered under the patient's medical benefit. The 21st Century Cures Act of 2016, which went to effect in 2019, changed the Medicare's LCD process and how coverage decisions are made. It elicited several questions from providers, which we'll cover here.



Q Why does providing non-covered services appeal to ophthalmic and optometric practices?

A Reimbursement rates are declining as the work associated with the claims process is increasing due to factors such as preauthorization issues, onerous claims filing instructions, and staff time dedicated to follow-up and appeals of denied claims. For services deemed as non-covered, patients pay the provider's full fee, hopefully at the time of service. No contractual adjustment applies. Cosmetic and refractive surgery, premium intraocular lenses and new investigational procedures are usually considered non-covered.

Services identified with Category III codes have usually been considered non-covered. Additionally, providers often assume miscellaneous codes (codes ending in 99) are non-covered. There are no assigned relative value units and no assigned reimbursement rates in the Medicare Physician Fee Schedule. Practices are in the habit of treating these as 'cash pay' services in lieu of submitting claims for payment from Medicare or other third-party payers. Within ophthalmology, a series of services to diagnose and treat dry eyes are identified with Category III codes and are impacted by this change, causing confusion in some offices.

Q How does the 21st Century Cures Act impact payment for non-covered services and how should billers respond?

A The lack of RVUs in the fee schedule doesn't mean the services are always non-covered. Under this law, Medicare Administrative Contractors can no longer issue a blanket non-coverage policy for all Category III codes. Instead, they must issue an individual policy for each individual decision on each claim.

For billers, don't assume the patient is financially responsible. Those involved in the billing process must check with Medicare and other third-party payers for coverage guidelines. Review payer publications. Follow the predetermination of benefits process, when available. If no guidance is provided by the insurer and coverage is uncertain, submitting a claim is the only way to confirm coverage. For Part B Medicare beneficiaries, there's no preauthorization process and there are very few LCDs so filing a claim is not optional for participating or non-participating providers.

Claims submitted to insurance are often of value to the patient even if the primary payer denies payment. The secondary insurance may reimburse some amount, or the denied claim may be used, in some instances for patients to seek reimbursement from a health savings plan.

Q What documentation is needed?

A Predetermination requests usually require the CPT and ICD-10 codes to identify the service in question, as well as the indication for the service. Document the patient's understanding of their responsibility using Medicare's Advanced Beneficiary Notice of Noncoverage (ABN), as a tool for collecting payment from a Medicare beneficiary.

Medicare Law (§1879) contains a provision that waives the financial liability if the beneficiary isn't likely

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to know or didn't have a reason to know that the services wouldn't be covered.[1] If the beneficiary doesn't receive proper notice, they are relieved from liability. The provider is then responsible, not the patient. Consequently, an ABN informs the patient in writing of their financial responsibility. It requires them to decide whether to have the services or not and whether a claim may be filed or not. A copy of the current ABN form can be located online.

The traditional ABN form may be used with Part B Medicare only. It is noteworthy that about half of all Medicare beneficiaries are covered by Part C Medicare - Medicare Advantage. CMS explicitly instructed the Medicare Advantage Organizations (MAOs) not to use ABN forms. They are obligated to make pre-service determinations of benefits at the request of the patient or the provider. Unfortunately, there is no single process for all MAOs. Check with each plan for instructions.

Likewise, commercial insurers may not use the ABN form, but most accept the idea of patient financial responsibility for noncovered services. For those plans, a financial waiver is still useful. Providers often have more latitude with notification. A Notice of Exclusion from Healthplan Benefits form may be used.

When an ABN or suitable waiver is used, the claim is usually reported with modifier -GA to inform the payer that a signed waiver is on file.

In conclusion, keep these few points in mind: Services described with Category III codes or miscellaneous codes might be covered—don't assume they're not. Codes listed in the payer's fee schedule with a zero allowed amount are not automatically non-covered. An ABN or financial waiver doesn't mean a claim for reimbursement isn't required. Tread carefully. ◀

1. SSA §1879 MCPM Chapter 30 §50.9B.

Lessons on Clear Lens Extraction

IOL technologies are creating more appeal for refractive lens exchange. Here's guidance on patient selection.

LIZ HUNTER
SENIOR EDITOR

The line between cataract and refractive surgery has become more blurred in recent years as patient demands for impeccable vision have increased and technologies have advanced, particularly in the realm of IOLs. The dawning of the modern-day IOL put tools previously reserved for cataract surgeons into the hands of refractive surgeons for elective procedures. For patients who don't meet the criteria for corneal refractive surgery, refractive lens exchange has become an appealing alternative to achieve spectacle independence.

However, refractive lens exchange is nuanced. Patients can't be matched with just any IOL, it's a careful process of reviewing the benefits and potential trade-offs for each option.

"Just as important as clinical and surgical acumen, is knowing when a patient isn't a good candidate for a certain procedure," says Arjan Hura, MD, a cataract, refractive and anterior segment surgeon in practice at the Maloney Shamie Vision Institute in Los Angeles. "Thus, I feel that decision-making about whether to offer refractive lens exchange to a patient, like offering laser vision correction, has to be based on solid ethics, clinical acumen and surgical competency. Much of this is informed by the experience level of the surgeon. Refractive surgeons with the knowledge and skill set for RLE understand the ins and outs, pros and cons, and nuances with patient selection and counseling. The ultimate goal is safely achieving vision correction and helping patients see better and actualize their life. Not everyone is a candidate for RLE."

Despite the niche criteria for RLE candidates, that hasn't stopped patients from inquiring about the procedure. "Refractive surgery awareness in the United States is interesting," says Dr. Hura. "LASIK has such a high level of brand awareness that patients often think of all forms of eye surgery as LASIK. Thus, awareness of other forms of vision correction like RLE may not be as well known. I practice in Los Angeles and operate in Beverly Hills so the awareness of RLE and other specific forms of vision correction is likely higher than average. I often see patients referred to me specifically for refractive lens exchange, or patients who have done their own research or who have friends who have had RLE and are interested in having surgery themselves."

It's a trend being noticed in the Midwest as well. "I'm noticing refractive surgery becoming more lens-based," says William F. Wiley, MD, medical director at the Cleveland Eye Clinic. "We've seen younger myopes moving more towards implantable contact lenses, and hyperopes leaning towards lens exchange even at a younger age."

Presbyopia does play a role in a patient's candidacy for RLE. "As patients get older, once they get to the presbyopic age, we have to decide: Are they going to be a better candidate for corneal refractive or a lens exchange?" says Dr. Wiley. "There are a few different things that go into that, but when they're myopic and pre-presbyopic, we're going to perform either ICL or LASIK/SMILE (corneal refractive). If they're presbyopic, then we're going to be considering either LASIK or refractive lens exchange."

The Nuances of Patient Selection

There are several demographics who are suitable for RLE, Dr. Hura says. "I typically think of RLE as an option on the spectrum of refractive surgery for a patient who's in their 40s to 60s without signs or symptoms of visually significant cataracts. It's also a great option for patients who may not be good candidates for laser vision correction, or presbyopes who don't want monovision. There's also a subset of younger patients with extreme refractive error who aren't candidates for laser vision correction or phakic IOLs, or patients with corneal disease who may be good candidates. Patients with very high hyperopia or high levels of astigmatism—these patients tend to be thrilled with the results of RLE," he says.

Dr. Wiley uses the rule of three to

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

define his home-run multifocal IOL candidate. "A multifocal IOL can, in theory, correct three different vision problems," he says. "It can correct a cataract if the patient is of that age, it can correct distance vision, and it can also correct presbyopia or near vision. If you're correcting all three, it's almost automatically a home run and patients are going to be happy. If you have a cataract patient who's hyperopic and is already in bifocals, they're a no-brainer because it's going to correct the cataract, distance and near, and those are three things they're already missing in their vision so that's a home run."

But it's a bit different when a cataract isn't involved. "On the other extreme, the worst patient might be somebody who just turned 40 and is a plano presbyope, and they're just having a little bit of loss of near vision," says Dr. Wiley. "In my mind, you're probably only correcting one issue with the multifocal IOL and those are probably the hardest patients because you're really not correcting their distance issue. They're already enjoying great distance vision and they don't have a cataract yet. They're just experiencing that loss of near vision and the multifocal lens, although it can treat that patient, I think it's going to be a harder one to make happen with plano presbyopes.

"More often though, you'll have patients that are somewhere in between," Dr. Wiley continues, "such as a 60-year-old who doesn't have cataracts but is hyperopic or even a higher myope, and so they really can't see at distance, they really don't have functional near vision. You'd be correcting two of the three things, and in general if you're correcting at least two of the three, you're going to have a relatively happy patient. However, you have to go through some of the expectations that the quality of vision with the artificial lens will be different than what it would be with a natural, clear lens. There are some give and takes.

WebMD

RLE allows patients to take advantage of advancements in IOL technology.

Thankfully, most people over the age of 40 have already started experiencing some dysfunctional lens syndrome symptoms and, although they might not have a full cataract, they have some glare at night or certainly some loss of function, and I think that the new artificial lenses do well for those patients. But again, the more that you're correcting with their visual problems, I think the higher the chance of patient satisfaction."

There is one group of patients that should be approached with particular caution, though. "Most of the controversy with refractive lens exchange is related to performing it in high myopes due to the risk of retinal detachment after surgery," says Dr. Hura. "This is based on data from the 1980s and 1990s and has been followed up every decade with subsequent studies. Although technology and surgery have advanced, the risk of retinal detachment after RLE is related to immutable clinical factors such as pre-existing retinal pathology like lattice degeneration or retinal holes/tears, lack of a posterior vitreous detachment and axial length."

An extended seven-year follow-up of noncomparative case series evaluated the incidence of complications after clear lens exchange in 52 eyes of 30 patients with myopia greater than -12 D.[1] During the seven years, retinal detachment occurred in four of 49 eyes. One patient had bilateral retinal detachments. The overall incidence of posterior vitreous detachment was 16.3 percent.

Another 15-year retrospective study of 437 eyes that underwent refractive lensectomies by a single surgeon revealed a 0.69 percent overall rate of retinal complications, 0.23 percent of which were retinal detachments.[2]

"In particular if a high myope hasn't had a posterior vitreous detachment, that risk for retinal detachment goes up because the act of doing the surgery can cause a PVD," adds Dr. Wiley. "During an examination we'll check to see whether they've had a PVD or not. If they've had a PVD, we're a little more confident with lens exchanges, but if they haven't had a PVD, we warn them that it could happen and clear lens exchange could exacerbate that at a younger age. We make sure to discuss signs and symptoms of retinal tear detachment."

Dr. Hura suggests consulting with a retina specialist, or refraining from refractive surgery altogether potentially. "High myopia is typically best treated with a phakic IOL like the EVO ICL," he says. "If a patient isn't a good candidate for laser vision correction or EVO ICL, and if RLE is being considered instead for a high myope, I feel that coordination with a retina specialist and thorough informed consent is important. Ultimately, a patient may simply not be a candidate for any form of refractive surgery."

In addition to evaluating their ocular anatomy, Dr. Hura says every surgical plan must be tailored to the individual and their personality and expectations. "It's rare that an operating room day goes by where I'm not using lenses from all different manufacturers," he says. "I view this to some extent as the art of refractive surgery. Getting a patient a great outcome involves more than just safely doing the surgery. Getting to a great outcome involves understanding the patient's personalities, hobbies and how they use their vision on a day-to-day basis. These are all things I'm assessing: patient personality—are they type A or type

B personality? Are they incredibly demanding? Do they have realistic expectations?"

The Right IOL for Each Patient

Modern IOLs give a greater range of vision to patients, but usually come with some caveats. It's a matter of how much of an impact they'll make on each patient.

Even easygoing patients need to know about the side-effect profile of multifocal lenses, continues Dr. Hura. "If I have a relatively easygoing patient and they say, 'Doc, I just want to be out of glasses,' I'll usually lean toward the multifocal lenses because we know that they give really good distance, intermediate and near vision. But there's no free lunch with optics, so the side-effect profile is reduction in contrast sensitivity and increased dysphotopsias at night, which is inherent to the diffractive optics that are used in these types of lenses. I personally tend to overemphasize the side effects of diffractive optics. If after a discussion, the patient says that doesn't really bother them and they seem pretty laid back, then I know they're going to do great with a multifocal lens. But if they're apprehensive about the idea of slightly reduced contrast, halos and glare, then I'll probably shy away from that lens.

"A patient who's a good candidate for a multifocal is someone who has a pristine optical system—they don't have a lot of dry eye, they don't have Fuchs' endothelial dystrophy, ERMs, macular degeneration, glaucoma, etc.," says Dr. Hura.

If they have mild pre-existing ocular disease or they're averse to the discussed side effects of multifocal lenses, Dr. Hura will discuss an extended-depth-of-focus lens with or without mini-monovision. "I'll emphasize to patients that there will still be certain situations where they'll need their reading glasses, such as reading a restaurant menu in dim lighting," he says.

Dr. Wiley says he uses a variety of lenses, including the trifocal PanOptix (Alcon) and the Tecnis Synergy (Johnson & Johnson). "We've been leaning toward PanOptix, but I think they're both great lenses," he says. "They have distance, intermediate and near, which is great, but some patients do experience glare and halo so I caution patients that have certain lifestyles—a police officer, truck driver, airline pilot—who might not appreciate the quality of nighttime vision. We're very aware that there is a trade-off there and some patients are fine with that trade-off and other patients would rather have better clear vision at night without glare and are willing to wear glasses for near."

Monofocal-plus lenses are a good option for those patients who are concerned about the nighttime symptoms, continues Dr. Wiley. "There are newer lenses marketed as monofocal-plus that give a little bit more intermediate than a traditional monofocal," he says. "We do have those discussions—if you're going to take the lens out, should you give the patient the full range with a trifocal, but we also have patients who are fine with a monofocal-plus style lens with really high-quality distance, maybe a little bit of intermediate, but they'll wear reading glasses and they don't have the nighttime symptoms that a multifocal would have."

The Light Adjustable Lens (RxSight) may be a good option for patients who previously had RK, LASIK, PRK or SMILE, some surgeons say. "If they're post-refractive surgery patients and especially if they've enjoyed monovision before, then I tend to opt more for a Light Adjustable Lens," says Dr. Hura. "This allows the patient to 'test drive' their vision after surgery and we can postoperatively refine the refractive error."

Dr. Wiley agrees. "The LAL does a great job for monovision because it allows you to hit those near and distance targets really nicely," he says. "Monovision has a little bit higher demand on hitting the visual target so the LAL is going to work great. It allows you to fine tune that intermediate vision or near vision, and the patient can also test drive it before we've completely locked it in. This gives them confidence that we're going to give them the functional near in one eye and distance in the other and they can live with that trade-off before we lock it in."

Dr. Hura adds, "It's important to note that in eyes that have had refractive surgery it can often be difficult to achieve the desired refractive outcome after surgery because of the changes that refractive surgery causes in the eye anatomy. Thus, the LAL is a great option in these eyes because, even if the initial refractive target isn't achieved, the light treatments can get the patient to the finish line."

Another lens that could put RLE within reach for more patients is the Apthera IC-8 (B + L) and refractive surgeons are excited by the potential.

"The IC-8 lens can certainly be used for refractive lens exchange," Dr. Hura says. "The small aperture optics of the IC-8 confer extended depth of focus. Typically patients will be aimed plano with a monofocal lens in the dominant eye and then an IC-8 in the non-dominant eye set for about -0.75 D sphere, and that can give quite a broad range of vision as long as the patient understands that they experience a sense of dimming in that eye. The IC-8 can also be used for post-RK eyes, irregular astigmatism or atypical corneas—but this is all off-label."

Dr. Wiley says he's still determining the best use for the Apthera. "For someone who's younger with irregular astigmatism, we found that the small-aperture optic can help neutralize their irregular astigmatism and give some better quality of vision," he says. "If a patient had previous corneal cross-linking for

(Continued on p. 62)

Another July

Musings on life, medicine and the practice of ophthalmology.

MARK H. BLECHER
CHIEF MEDICAL EDITOR

I've written about this before, but each year it never ceases to amaze me how truly momentous this time of year is. The last time I addressed this topic, two years ago, I focused on how we teach cataract surgery, how it's changed and how it may or should change. This time I'd like to focus on the transition itself, from outgoing third-year resident to wide-eyed newbie.

I know it's now August as you read this, but for those of us involved with resident education, July is almost a cliché. "Don't get sick in July," and "Definitely don't have surgery in July–or August." New residents step up in seniority, and start to take over more of the surgery from their outgoing upperclass folks. The theory goes that, during this learning period, patient care is more suspect, and the lives of those who teach and supervise residents is more stressful. I have volunteer attendings who simply refuse to supervise resident surgery during the summer—as if that would speed their learning or improve patient care.

An old mentor of mine often said, "You only have so many Julys in you as a surgical teacher." I never felt that way, however. Yes, the surgery does take a fair bit longer, yes you have to talk more, be more alert, be prepared to take over more. So, I guess it is more work and more taxing. Although I'd submit that it's very much a function of the style and personality of the attending in question. We're all different and I have no doubt that these differences affect how each of us handles the stress of teaching surgery, especially to new surgeons. It never really bothered me though. This is fortuitous, as in my new role I have a very flexible schedule and am able to cover resident surgical slots when my colleagues are 'away.' Lots of them. And it's been great—not only great to teach, but great to get to know my new third years better earlier in the year. Sitting inches apart from each other for hours will do that. Having done this for almost 40 years, you'd think I'd be bored, or at least jaded. And I'll admit some of my teaching tag lines are a bit long in the tooth. But lucky for me every year I get a new audience who hasn't heard them before. The only issue is that some of my cultural references are so dated, they have no idea what I'm talking about. For instance, one of my concepts is that in cataract surgery we should strive for reproducibility of excellent surgical maneuvers and be able to deliver this on each case. Or, as I used to say, "Perfect rice every time." They look at me funny. I sigh.

Getty

What really doesn't get old each July is their reaction when they successfully complete a surgery and the eye looks great. The excitement, the enthusiasm and an appreciation for the wonder of modern cataract surgery is beyond gratifying. It softens my curmudgeonly exterior and reminds me why I continue to work, and most importantly continue to teach. I guess it sounds kind of shallow, but seeing this response keeps me from hanging up my phaco tips and riding off into the sunset. As much as I beat up on the Millennials, and soon Gen Z's as they come through the residency, I'm very glad to see that even this detached generation can be engaged by the same wonder and awe that inspired me as a resident and still does to this day. Hope is not lost. Even though it's July. ◀

This article has no commercial sponsorship.

Dr. Blecher is an attending surgeon at Wills Eye Hospital.

EXPANDING RETINA'S ARMAMENTARIUM

Here's how specialists are using the latest treatments for wet AMD, DME and RVO.

CHRISTINE YUE LEONARD
SENIOR ASSOCIATE EDITOR

Within the space of just a few years, several new retinal treatments have been approved for wet age-related macular degeneration, diabetic macular edema and retinal vein occlusion, promising increased durability and better drying. These toolbox additions are encouraging for treating resistant and newly diagnosed patients.

As with any newly available treatment, uptake is often gradual, and doctors may wonder whether it's worth it to stock another drug. Here, retina specialists share how these new drugs are performing in the clinic, and which investigational treatments show promise.

Bi-specific Durability

Faricimab-svoa's (Vabysmo, Genentech) uptake has been increasing since its FDA approval in 2022 as retina specialists become more familiar with the new drug and its durability. Faricimab blocks both VEGF-A and Ang-2 to reduce further inflammation and vascular leakage by stabilizing blood vessels.

"The clinical trials for both wet AMD and DME imply that faricimab works at least as well visually and appears to dry a little bit better and faster than older drugs," says Carl Regillo, MD, chief of the retina service at Wills Eye Hospital in Philadelphia. "For some patients, this can translate into better outcomes. Faricimab looks to be more durable and longer lasting, and we're seeing this as we switch patients on older or first-generation anti-VEGFs to faricimab."

Experts say this drug can be used as a first-line treatment and in patients who are resistant or difficult to treat. "I'd like to use it more often as a first-line option, but the reality is that there are usually payer issues that mandate the use of older drugs first, typically bevacizumab-first policies," Dr. Regillo says. "Then, they mandate using ranibizumab or aflibercept before I can get to faricimab. So, usually there are a lot of logistics in dealing with payer reimbursement that holds up utilization of the newer drugs in general."

David S. Boyer, MD, of Retina-Vitreous Associates Medical Group in Los Angeles, says he's had "a mixed experience" with faricimab. "I was able to dry some patients better and extend others a bit longer. Then I have some patients in which it didn't seem to make much of a difference, and I went back to the previous treatment paradigm I was using, which was usually Eylea at that point."

"We started switching some of our patients who'd been on aflibercept for many years to faricimab, as well as some of our resistant patients," says Jay Chhablani, MD, a professor of ophthalmology at the University of Pittsburgh School of Medicine. "I also offer faricimab to my naïve cases. I've seen many patients with good response (*Figure*). Some of the patients who were resistant to other drugs are able to be maintained on monthly faricimab. Others have been switched to

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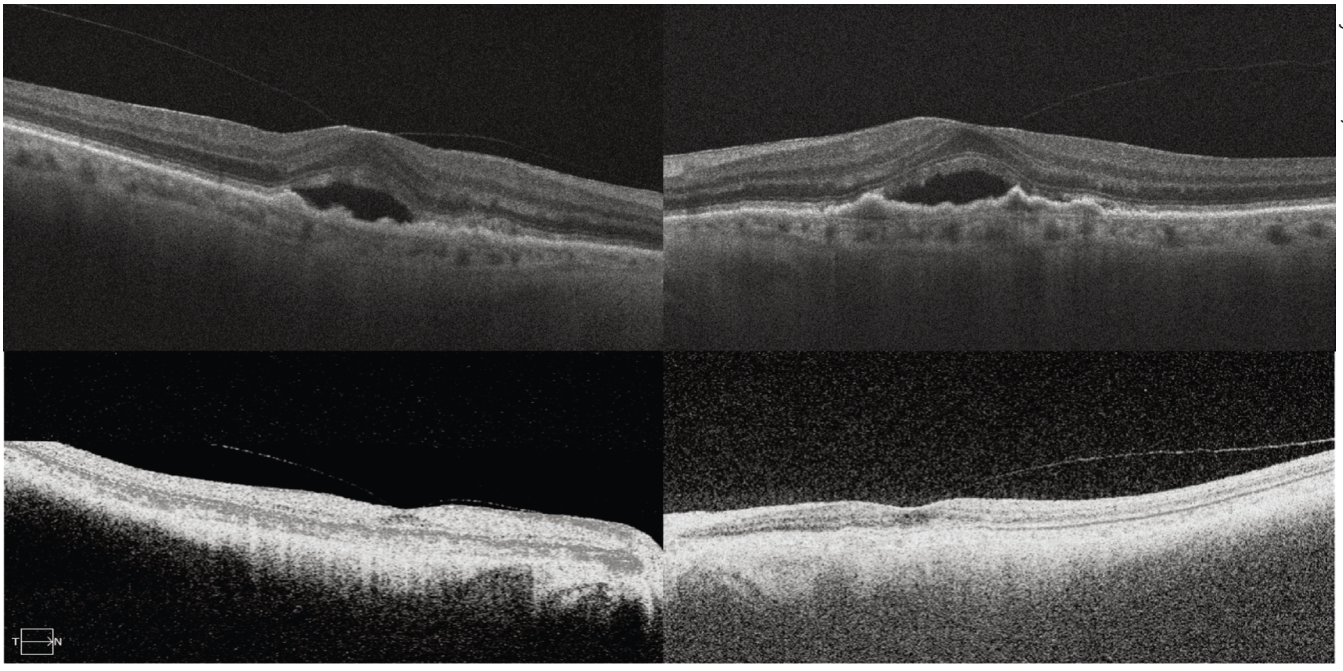
Dr. Boyer is a consultant for Regeneron, Genentech/Roche, Oculis SA, Opthea, Novartis, Bausch + Lomb and EyePoint. **Dr. Regillo** is a consultant for Regeneron, Genentech/Roche, Kodiak, Novartis, EyePoint and Ocular Therapeutix. **Dr. Chhablani** has no financial relationships with products mentioned in this article.



Jay Chhablani, MD

Figure. OCT scans of both eyes of a patient with wet AMD who was on six-to-eight-week intravitreal injections for three years with persistent fluid (top row) and then underwent intravitreal faricimab. OCT scans (bottom row) show significant response after single intravitreal faricimab with resolution of long-standing subretinal fluid.

every three or four months."

Dr. Chhablani uses a combination of telemedicine and office visits to follow newly switched faricimab patients. "If I see that after one or two injections the response is good, I may incorporate some telemedicine visits," he says. "Since they've switched to a new drug, I don't know what the exact treatment-free interval could be, so in these patients, I tell them, 'Your response is really good, so I'm skipping your injection today, but I'd like to get an OCT and telemedicine in four weeks.' This gives me the confidence of not doing the shot but at the same time keeping a close watch for any early recurrence. Once we show that the patient does well at, say, 12 weeks, I'll push their next visit to four weeks with a telemedicine visit and pushing the maximum treatment free interval.

"These are the patients who were used to getting monthly injections," he continues. "I don't want to lose their confidence by having them feel as if they're not being followed as often or taken care of as closely as before. Adding telemedicine is a nice combination where I can ensure they're symptomatically stable but do less frequent injections. If there are any changes in vision or symptoms at their testing-only visit, then our technicians know to obtain fundus autofluorescence and fundus photographs and inform the provider immediately."

The clinical trials and real-world experience so far have shown that faricimab's safety profile is comparable to that of ranibizumab or aflibercept. "No unique adverse events were associated with faricimab, and its safety profile is similar to what we've been using," Dr. Regillo says. "It's very well tolerated." Extension studies AVONELLE-X (NCT04777201, n=1,036) and RHONE-X (NCT04432831, n=1,479) for wet AMD and DME, respectively, are ongoing to assess long-term safety and tolerability.

Biosimilars

Ranibizumab biosimilars have had a slow uptake with the availability of newer, more durable drugs like faricimab, and the tried-and-true original anti-VEGFs, but experts say biosimilar use will likely expand as payers incorporate it into step therapy. Ranibizumab-nuna (Byooviz, Biogen) and ranibizumab-eqrn (Cimerli, Coherus Biosciences) have both been available in the United States since 2022, though only ranibizumab-eqrn is considered interchangeable with Lucentis.

"Biosimilars don't offer any clinical advantage over the reference products," Dr. Regillo says. "The only reason to use them would be for some cost savings, and that's usually savings by the payer. Some payers may mandate the use of a biosimilar, or if a patient has to pay out of pocket, they might prefer something that costs less. That's pretty unusual for a patient to have to bear the full cost of these drugs, but it can occasionally happen."

Dr. Chhablani agrees that biosimilar uptake will likely come less from the provider's side and

more from the payer's. "I believe the payers are going to push us to bill for biosimilars, since the cost is going to be cheaper compared with the original molecules," he says. "How much time will it take to get to this point, where we're not using the original molecule but using biosimilars? I think biosimilars have some place but considering there's so many new drugs available and coming soon, I think they'll have a tough time."

Dr. Boyer points out that fewer patients are on Lucentis nowadays, with Eylea and Vabysmo available. "There are only so many things you can carry in your refrigerator," says Dr. Boyer. "If you carry Lucentis, Vabysmo, Eylea and Avastin, there's limited space available for biosimilars. Now, this may change when aflibercept biosimilars come out, as retinal specialists are very familiar with aflibercept and use it frequently."

Aflibercept biosimilars in Phase III include SOK583A1 (Sandoz), CT-P42 (Celltrion Healthcare), ALT-L9 (Alteogen).

Another ranibizumab biosimilar may appear in the armamentarium in the coming years. The supplemental Biologics License Application for XSB-001 (Xlucane, Xbrane Biopharma) was accepted by the FDA on June 21, 2023. Its Biosimilar User Fee Amendment goal date is April 21, 2024.

"I think there will eventually be acceptance of biosimilars," Dr. Chhablani says. "Oncology is totally based on biosimilars, and they've been using biosimilars for years. I think it's probably time that we also accept this as a way to treat our patients."

Suprachoroidal Injection

In 2021, the FDA approved the first suprachoroidal triamcinolone acetonide injectable suspension (Xipere, Clearside Biomedical/ Bausch + Lomb) for macular edema associated with uveitis. Dr. Chhablani says, "Xipere has been performing well in many of our patients. We have yet to see the long-term results, but the short-term results are promising. I've seen patients go up to four or five months so far."

"The Xipere injection has a short learning curve, and it's not a difficult injection to give though it's a little more cumbersome than others to draw up and inject if you're not used to doing those," says Dr. Boyer. "Fortunately, I was involved in studies that used that technique. It's fairly comfortable for patients."

The company offers training with its suprachoroidal space microinjector. The training includes a kit with a practice syringe and a synthetic eye.

Brolucizumab in Reserve

Brolucizumab-dbll (Beovu, Novartis) is a humanized monoclonal single-chain variable fragment that inhibits VEGF-A to decrease neovascularization. It received FDA approval for wet AMD in 2019 and for DME in 2022.

"Brolucizumab doesn't get as much use because its safety profile isn't as good as all the other agents we've been using or those recently approved," explains Dr. Regillo. "It has high rates of intraocular inflammation and some unique adverse events such as a retinal vasculitis and vasculitis-related retinal occlusions. That's not something we've seen with other anti-VEGFs or faricimab to date. These added safety concerns have considerably held back brolucizumab's uptake and utilization since its FDA approval."

Some retinal specialists say they don't use brolucizumab at all, others only in rare circumstances. Dr. Boyer says that brolucizumab was the strongest drug he'd ever used, but it's the last one he would consider using due to the safety profile. "It dried phenomenally well and worked in patients whom I couldn't dry at all before," he says. "But, because of its vison-threatening side effects, it's reserved for patients who are very difficult to treat. I'm down to one patient on brolucizumab who's previously failed every other anti-VEGF treatment. So unfortunately, it's a great drug but its side effect profile limits its use to rare cases. I'd call this a fourth-line drug, especially in view of faricimab's improvement in overall drying."

As with any anti-VEGF drug, patients on brolucizumab should be followed carefully for any signs of inflammation, especially after the first few treatments, Dr. Regillo says. "If there's any inflammation, the drug shouldn't be used. It could very well be that if a patient has any inflammation, they're more inclined to get more inflammation, which could have a severe effect if the drug is reintroduced."

High-dose Aflibercept

Aflibercept 8 mg is a novel intravitreal formulation in a 70 µL injection (114.3 mg/mL) that delivers a four-times higher molar dose compared with aflibercept 2 mg. This increased dose is hypothesized to provide longer effective vitreal concentration and more sustained effect VEGF signaling.

Retina specialists will have to wait a bit longer for the much-anticipated aflibercept 8 mg. In late June, due to dissatisfactory inspection findings at a third-party filler, the 8-mg dose's approval was postponed. Fortunately, no issues were found with aflibercept 8 mg's clinical efficacy, safety, trial design, labeling or manufacturing, and the FDA requested no additional data.

"High-dose aflibercept has demonstrated longer durability and some better drying in its Phase III studies for wet AMD and DME," Dr. Regillo says. "It seems it would offer similar benefits to what faricimab has provided thus

far. Its FDA approval is expected for both indications in the very near future. Once that happens, it will be another good option for our patients."

In late June, Regeneron also released top-line, two-year data from the pivotal PHOTON trial for DME. Patients in the trial were randomized to either 12-week (n=328) or 16-week (n=163) dosing intervals after three initial monthly doses, with dosing flexibility if certain criteria were met, or aflibercept 2 mg dosed every eight weeks (n=167). The company reports that 89 percent of patients maintained ≥12-week dosing throughout the two-year period; 83 percent maintained ≥16-week dosing; and 43 percent met criteria for ≥20-week dosing by week 96.

Compared with the on-label regimen, aflibercept 8 mg dosed every 12 or 16 weeks reduced the mean number of injections at two years (13.8 injections vs. 9.5 and 7.8 injections, respectively). Mean BVCA improvement was comparable among the on-label and the 12- and 16-week high-dose regimens (8.4-, 8.8- and 7.5-letter gains, respectively).

Safety data consistent with that of aflibercept 2 mg were reported. The most common ocular adverse events were cataract, vitreous floaters and conjunctival hemorrhage. No cases of retinal vasculitis, occlusive retinitis or endophthalmitis occurred. The intraocular inflammation rate was 1.2 percent for both 2-mg and 8-mg groups.

In the one-year data from the PULSAR trial for wet AMD, 79 percent of 316 patients maintained 12-week dosing and 77 percent of 312 patients maintained 16-week dosing. BCVA was non-inferior to aflibercept 2 mg. At one year, patients receiving on-label aflibercept received an average of 6.9 injections, compared with 6.1 and 5.2 injections for 12- and 16-week dosing, respectively.

Additionally, 69 percent of 8-mg patients were without central subfield fluid at one year, compared with 59 percent of 2-mg patients. A fluid-free central subfield was achieved at a median of eight weeks for on-label patients and four weeks for 8-mg patients. Safety was consistent with the 2-mg dose. Two-year PULSAR data for aflibercept 8 mg for wet AMD is expected in the third quarter of 2023.

Dr. Regillo speculates that when it's first introduced, high-dose aflibercept will experience a gradual adoption over time, like faricimab. "I think that as retina specialists get familiar with the drug and test the waters, if you will, they'll start using it for a combination of both established and new-onset wet AMD and DME," he says.

> **Adding telemedicine is a nice combination, where I can ensure [patients are] symptomatically stable but do less frequent injections.**
>
> ***— Jay Chhablani, MD***

"One question will be whether retina specialists switch from aflibercept 2 mg to high-dose aflibercept or faricimab," notes Dr. Chhablani. "Some may want to switch resistant patients to a different molecule rather than inject the same molecule. There may also be patients who don't respond to faricimab whom we might consider offering high-dose aflibercept."

"Cost makes a big difference," says Dr. Boyer. "I don't know what the company will do with the 2-mg dose, especially in light of the fact that aflibercept 2-mg biosimilars will be coming out soon. I'd say that depending on the cost of the biosimilar and the cost of 8-mg dose, there may be some insurance plans that would keep patients on the 2-mg dose rather than go up to the 8-mg dose. That will just have to play out in the marketplace."

Retinal specialists are hopeful about the 8 mg's increased durability but note that the real-world interval may be slightly shorter. "Whenever you do a clinical trial, your goal is to ensure you're not leaving vision on the table compared to the comparators available at the time," Dr. Boyer says. "There's always rescue criteria for some degree of fluid or degree of loss, or a combination has to be met before retreatment. In retinal specialists' hands, we usually don't tolerate any fluid. So, I think we won't be able to extend it as far as the ads say, just as I'm not getting faricimab as far out as the advertisements say because I don't tolerate any fluid in the treatment of wet AMD or diabetic retinopathy. I do think aflibercept 8 mg will somewhat extend the treatment interval, but to what degree, we don't know yet."

What's in Phase III?

Here is an overview of some potential new treatments coming down the pipeline:

• ***OCS-01 (Oculis).*** The first noninvasive treatment for DME may be coming in the next few years with Oculis' investigational dexamethasone eyedrops. In the Phase III DIAbetic Macular edema patients ON a Drop (DIAMOND) study, patients were randomized 2:1 to OCS-01 (n=100) or vehicle (n=48) six times daily for a six-week loading phase and three times daily for a six-week maintenance phase. Topline results from stage one of the study showed a statistically significant increase in visual acuity at week six compared

with vehicle (7.2 vs 3.1 letters, p=0.007), which lasted out to week 12 (7.6 vs 3.7 letters, p=0.016). More patients achieved a ≥15-letter gain (27.4 percent vs 7.5 percent at week 12, p=0.009) and improvements in retinal thickness (-61.6 µm vs -16 µm at week 12, p=0.004) compared with vehicle. No unexpected adverse events were observed. Stage two of DIAMOND, expected to begin in the second half of 2023, will include two global trials, each enrolling approximately 350 to 450 patients.

"The Phase II studies showed good results vs. Lucentis," Dr. Chhablani says. "There will be some criticism about a Lucentis comparator, since more patients are started on Eylea for DME now, but if it works out then this delivery method could be a very good step forward for many diseases. One important thing to consider is how retina specialists would accept this option, as a combination with intravitreal therapy as maintenance or as primary therapy."

• ***OPT-302 (Opthea).*** OPT-302 is a first-in-class, highly specific VEGF-C/-D "trap" molecule in development for wet AMD, to be used in conjunction with ranibizumab. It's received fast-track designation from the FDA.

Dr. Boyer points out, "it's two injections given at the same time, which is a bit less convenient than one injection," but he adds that this new molecule could help address the problem of tachyphylaxis experienced by some patients, where a drug works well for a while and then suddenly its effects wear off.

"Tachyphylaxis may be secondary to upregulation of VEGF-C in humans," he explains.

In the Phase IIb trial (n=366), OPT-302 + ranibizumab demonstrated statistically significant gains in BCVA from baseline to week 24 compared with ranibizumab monotherapy (16.1 vs 10.3 letters, p=0.0002). Currently, Opthea is running two Phase III registration trials of intravitreal OPT-302 2 mg, used in combination with 0.5 mg ranibizumab or 2 mg aflibercept at different intervals, ShORe (NCT04757610, n=990) and COAST (NCT04757636, n=990), respectively.

• ***HLX04-O (Shanghai Henlius Biotech/Essex).*** Shanghai Henlius Biotech and Essex have developed an ophthalmic version of their bevacizumab biosimilar (HLX04 [Hanbeitai]), HXL04-O for wet AMD. HLX04-O 1.25 mg/0.05 ml every four weeks was well tolerated in the Phase I/II trial (NCT04993352). In February, the first U.S. patient was dosed in the global Phase III trial (NCT04740671), which compares the efficacy and safety of HLX04-O with ranibizumab. Patients are randomized 1:1 to receive either HLX04-O 1.25 mg or ranibizumab 0.5 mg every four weeks for 48 weeks. The primary outcome measure is mean change from baseline in BCVA at 36 weeks.

• ***ONS-5010/Lytenava (Outlook Therapeutics).*** ONS-5010 (bevacizumab-vikg) is an investigational formulation of bevacizumab in development for treating wet AMD and other retinal diseases. In October 2022, the FDA accepted filing for a Biologics License Application for wet AMD. The Prescription User Fee Act goal date is August 29, 2023.

The Phase III NORSE II trial (NCT03834753, n=288) assessed the safety and efficacy of ONS-5010 dosed monthly compared with ranibizumab dosed on-label. All primary and secondary endpoints were met: 41.7 percent of patients gained ≥15 letters of vision (p=0.0052); 56.5 percent of patients ≥10 letters of vision (p=0.0016) and 68.5 percent gained ≥5 letters (p=0.0116), respectively. An additional secondary endpoint of mean change in BCVA from baseline to month 11 showed an 11.2-letter gain with ONS-5010 compared with a 5.8-letter gain with ranibizumab (p=0.0043). ONS-5010 was well tolerated, with only one ocular inflammatory adverse event occurring in NORSE II and none in NORSE I (a clinical experience trial, n=61) or NORSE III (an open-label safety study for BLA submission [NCT04516278], n=197).

"This is going to be an exciting option," says Dr. Chhablani, "but much will depend on whether the company is able to bring the cost close to the off-label one. If it's going to be more expensive, then I doubt we would switch, especially when we already have such strong safety data for off-label bevacizumab spanning more than two decades."

• ***KSI-301 (Kodiak Sciences).*** KSI-301 (tarcocimab tedromer) is an anti-VEGF biopolymer conjugate in development for DME, DR, wet AMD and RVO that blocks all VEGF-A isoforms.

The Phase III BEACON study (NCT04592419, n=568) for RVO met its primary endpoint of noninferiority in mean change in BCVA, with KSI-301 dosed every eight weeks versus aflibercept dosed every four weeks in BRVO and all RVO patients. Kodiak says KSI-301 is the first anti-VEGF agent that's demonstrated comparable visual acuity outcomes to monthly aflibercept with half the doses. BEACON reported low rates of intraocular inflammation and no cases of intraocular inflammation with vasculitis or vascular occlusion.

Several other Phase III trials are underway with topline results expected mid 2023, as of this writing: GLEAM (NCT04611152, n=450) and GLIMMER (NCT04603937, n=450) for DME; GLOW (NCT05066230, n=253) for DR; and DAYLIGHT (NCT04964089, n=557) for wet AMD. ◀

WILL COMPLEMENT THERAPY CATCH ON?

With one FDA-approved geographic atrophy therapy available (and another one not far behind), retina specialists are hopeful for the benefit to patients, while some remain cautious.

LIZ HUNTER
SENIOR EDITOR

Earlier this year, pegcetacoplan made history as the first FDA-approved therapy for geographic atrophy. Commercially marketed as Syfovre (Apellis), pegcetacoplan showed a clinically meaningful reduction in geographic atrophy lesion growth, giving hope to a group of patients who previously had no recourse to slow their significant vision loss.

Syfovre's approval is just the first of what may be the coming wave of geographic atrophy treatments. In February, the FDA accepted Iveric Bio's new drug application for avacincaptad pegol (Zimura) for the treatment of GA. It's possible avacincaptad pegol could be approved by the time this article is published. There's much more in the pipeline, too, and retina specialists are excited about the possibilities while remaining cautious. We spoke with several physicians to find out how pegcetacoplan works, its safety profile and what it all could mean for patients.

The Challenges of Geographic Atrophy

The last stage of dry age-related macular degeneration, geographic atrophy results in progressive and eventually permanent vision loss. Contributing factors to GA include genetics, environment and age, and historically, ophthalmologists had little relief to offer patients other than recommendations to maintain a healthy lifestyle, avoid smoking and take dietary supplements such as vitamin C, vitamin E, beta-carotene and zinc.[1]

This has amounted to frustration on behalf of both the patient and physician.

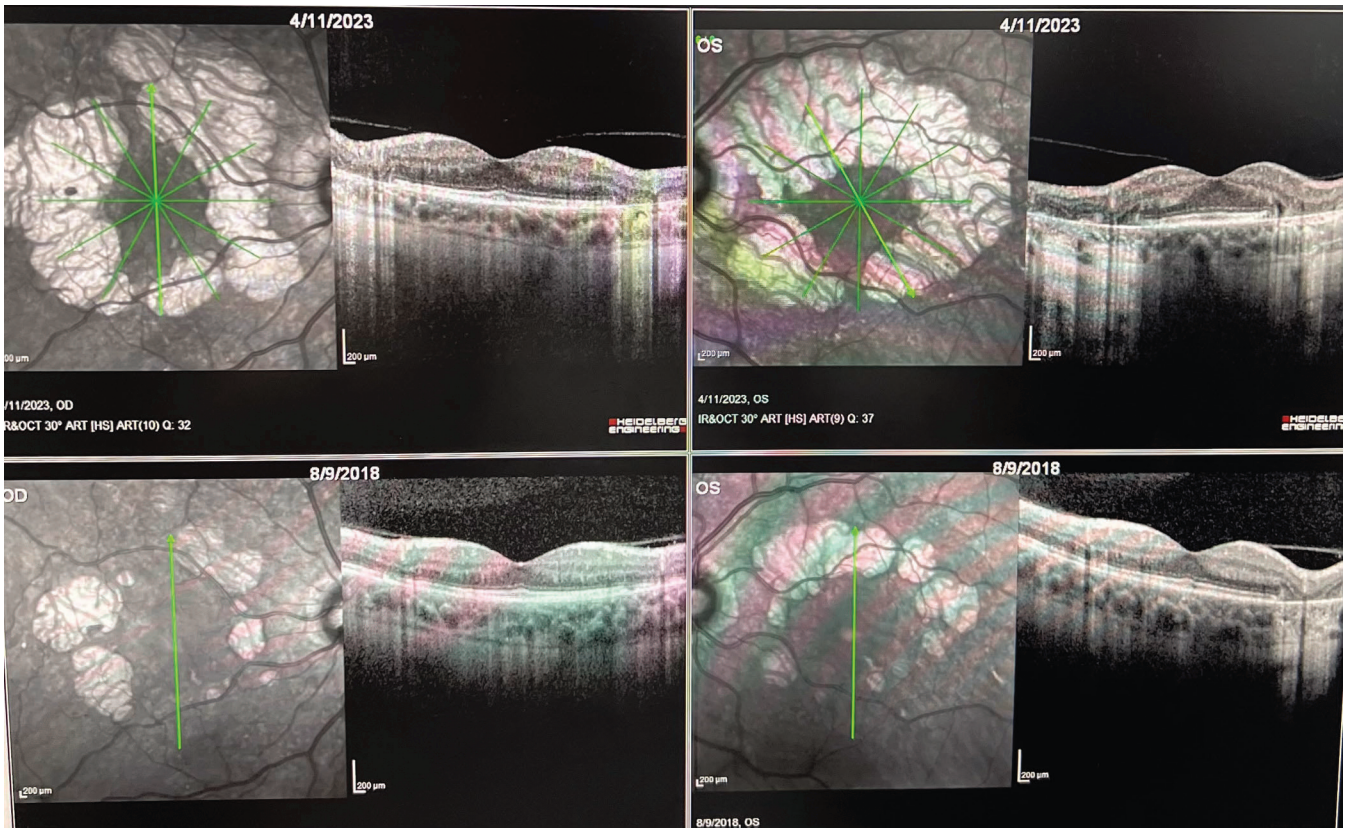
"Historically, geographic atrophy patients are one of the few subsets of patients that we can't help, and this has been a huge source of frustration for us," says Ashkan Abbey, MD, a medical and surgical retina specialist and the director of clinical research for Texas Retina Associates in Dallas. "We've been essentially watching them deteriorate in front of our eyes and all we can offer are low-vision aids, but we haven't really had much to help them or to slow down the process."

The disease can also impact a patient's mental health, says Jaclyn Kovach, MD, FASRS, a professor of clinical ophthalmology at Bascom Palmer Eye Institute, Miller School of Medicine, University of Miami. "Ultimately, most patients with GA need a caregiver to help with their activities of daily living. There are so many secondary effects from GA," she says. "Because of poor vision, patients often withdraw from social interaction and lose their independence as they are unable to drive, and consequently suffer from depression."

"As physicians, we don't like saying there's nothing we can do for them," says Ananda Kalevar, MD, a vitreoretinal specialist and an associate professor and program director at the University of Sherbrooke in Quebec. "They often know friends or family who are receiving injections for wet AMD and end up disappointed when we tell them there's nothing like that for dry AMD."

This article has no commercial sponsorship.

Dr. Abbey is involved with the trials for Syfovre and Zimura and is participating in other GA trials. He is also a speaker and consultant for Apellis and Iveric Bio. **Dr. Kalevar** reports no disclosures. **Dr. Kovach** is a principal investigator for Alexion and Apellis and a consultant for Iveric Bio, Apellis, Regeneron and Genentech.



OCT images demonstrating progression of extrafoveal geographic atrophy over the course of 4 1/2 years in both eyes. The bottom row demonstrates the baseline OCTs for the right and left eyes. Early intervention with a complement inhibitor could significantly reduce the rate of atrophy in this case.

That's all changing with the approval of pegcetacoplan. "Our patients have been waiting for years for a treatment for GA," says Dr. Kovach. "These groundbreaking treatments will give them an opportunity to slow the progression of their disease so they can potentially retain the vision that they have longer. Treatment empowers them to play a role in modulating the future of their disease."

How These Therapies Work

Both pegcetacoplan and ACP target the complement cascade, which is composed of part of the immune system, and comprises three pathways that include plasma and membrane-associated serum proteins, some of which have been linked to the development and progression of dry AMD.[2] The dysregulation of the complement system has been the focus of therapy development, but it hasn't always been successful.

Previously, in 2018, lampalizumab (Genentech) was a therapy targeting complement factor D, and it advanced to Phase III Chroma and Spectri randomized clinical trials. After 48 weeks of treatment, however, lampalizumab failed to reduce GA enlargement vs. sham.[3]

"Research has focused a lot on the complement pathway when it comes to trying to slow down geographic atrophy," says Dr. Abbey. "I think a lot of us were getting frustrated because we kept striking out. We had the issues with lampalizumab where it didn't end up meeting its endpoints for Phase III trials, and there have been multiple other examples of different agents that tried to target the complement pathway and failed in the last 10 years. The numerous failures led some people in the community to start saying, 'Well, maybe we need to stop thinking about complement because it just doesn't seem like it's working out.' "

Dr. Abbey says pegcetacoplan inhibits C3 and C3b in the complement pathway. "By inhibiting C3 and C3b, one of the important downstream effects involves a reduction in the rate of formation of the membrane attack complex (MAC), which is what leads to apoptosis (cell death) of retinal cells for many of our patients when they have geographic atrophy," he says.

In the results of the combined studies, dubbed OAKS and DERBY, patients received intravitreal pegcetacoplan monthly or every other month. After 12 months, GA lesion growth rate was reduced by 17 percent (p<0.0001) and 14 percent (p=0.0012) monthly or EOM, respectively, vs. sham.[4] After 24 months, there was an increased reduction of 26 percent (monthly) (p<0.0001) vs. sham, and 23 percent (EOM)

(p=0.0002) vs. sham in patients with extrafoveal lesions.[4] Dr. Abbey, who participated in the clinical trials, notes that these figures represent pooled data.

"In one of its trials (OAKS), pegcetacoplan showed significance in terms of its effect on the rate of reduction of the lesion size in patients with GA compared to sham, whereas the other trial (DERBY) didn't show significance when compared to the sham," Dr. Abbey says. "However, when the two different Phase III trials' endpoints were pooled together, the data did show significance. That was enough for the FDA to approve it in the end, but that has led to one of the criticisms that it was only one pivotal trial that showed significance in terms of the reduction in the rate of advancement of GA over time."

Dr. Kalevar says this is an exciting time in retina. "This gives us something to offer patients and it's only the first iteration, but it will get better and better and more efficient," he says.

However, with any treatment, the number one goal is safety, he continues. "I will say I'm a little concerned about the side effect profile," says Dr. Kalevar. "In the retina community, we recently had an experience with a therapy that burned us, so we have a bad taste in our mouth. We got really excited about the numbers we saw in terms of improvement for that drug, but we sort of glossed over the signals of safety issues. And then, in postmarketing data, we figured it out."

Dr. Kalevar is referring to brolucizumab (Beovu, Novartis), which was approved for wet AMD in 2019. Within months of that approval, retina specialists were alerted to reports of retinal vasculitis attributed to the drug. It's a lesson learned in the back of every retina specialist's mind.

"One thing we're all concerned about in the retina community regarding Syfovre—after what we went through with brolucizumab—is if there's inflammation that's significant enough that can cause vasculitis or occlusive vasculitis," says Dr. Abbey. "In the clinical trials, we didn't have any evidence of vasculitis or occlusive vasculitis, which was reassuring. But we remain wary because in the trials that get FDA approval, we often don't have sufficient numbers to detect a significant signal for a more rare event that could be visually devastating like that. It's going to be important to see what happens with the real world data as time passes and more injections are performed."

Dr. Abbey continues, saying the American Society of Retina Specialists released a report of a small number of cases of intraocular inflammation and vasculitis associated with Syfovre since its approval. "We are awaiting additional information regarding the specific details of these cases," he says.

Issued in mid-July, the letter from ASRS informed members of its community that its Research and Safety in Therapeutics (ReST) Committee received reports from physicians of intraocular inflammation, including six cases of occlusive retinal vasculitis, all of which were observed between seven and 13 days after Syfovre was administered, according to the letter. The ASRS urged vigilance and close follow up, stating the significance of this real-world data. "Particularly in the setting of a newly approved drug or device, such reports are critical in defining our real-world experience through analysis of the aggregate of collected reports," the ASRS said in the letter. It further reminded members to follow sterile injection protocols as outlined in the Syfovre prescribing information.

Another of the concerns regarding pegcetacoplan is the increased rate of choroidal neovascularization (conversion to wet AMD). According to the combined Phase III results, CNV was reported in 11.9 percent of eyes treated monthly, and 6.7 percent in eyes treated EOM, compared to sham (3.1 percent).[5] "If we're treating someone for geographic atrophy and then they end up getting CNV, if you're in a high-volume practice, that's a lot of patients daily that I'm potentially converting to CNV by using pegcetacoplan," says Dr. Kalevar.

Dr. Kovach says pegcetacoplan therapy could carry a small risk of anterior ischemic optic neuropathy, which was reported in 1.7 percent of patients treated monthly, 0.2 percent EOM and zero percent in sham.[6] "Soon, we'll have long-term clinical trial data and real-world data to better elucidate the prevalence of these risks," she says.

Uptake Within the Field

As Syfovre makes its way into clinics across the country, it's unclear how swift the adoption will be.

"I think there's a spectrum of perspectives," says Dr. Kovach. "Some retina specialists are waiting for long-term clinical trial data and real-world data, especially when it comes to elucidating the risk factors. Other retina specialists are excited to start treating patients."

Dr. Abbey agrees there's a subset of physicians who are simply opposed to using this therapy. "I've spoken with them. Their argument is that they don't believe that the juice is worth the squeeze, so to speak, in these cases," he says. "We have the data showing us roughly a 20 to 30 percent reduction at one year, in terms of the growth of GA lesions by using this injection once a month or once every other month, and to a lot of folks, that just isn't good enough to be putting people through the substantial burden of treatment required to get to that point, along with other potential risks with administering injections that often."

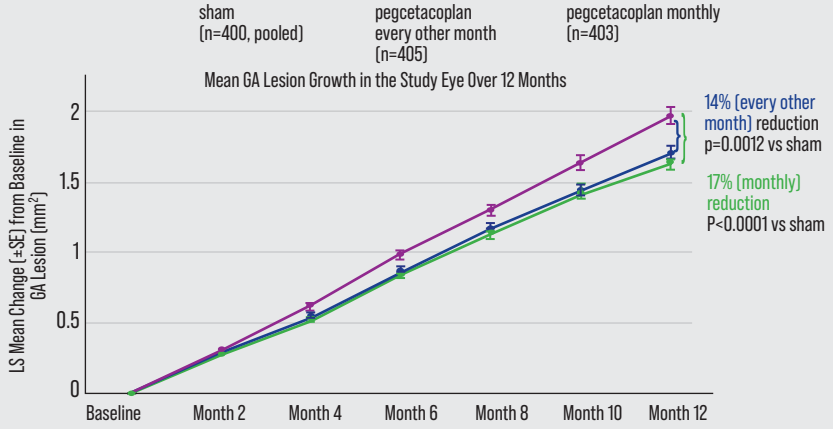
Dr. Kalevar places himself in that camp. "I think uptake is going to be very slow," he says, adding that he's alarmed by the recent safety reports released by ASRS. "Inflammation is one thing but vasculitis is another beast. At this point I wouldn't use these drugs in my practice until more

numbers come out showing better safety. We have to weigh causing potential harm vs. the natural progression of the GA, and I think people would rather the natural progression of the GA go through. If you have a patient who's counting fingers because of geographic atrophy and they don't want to lose it and they're motivated because it's a 20-percent reduction—that's a big number, but we're just talking about growth. It's still growing. If something is close to the fovea and still growing, combined with the CNV rate, it's a little bit hard to justify injecting these patients nonstop."

That's the real challenge for Syfovre to overcome, notes Dr. Abbey. "There will be those retina specialists who dig in and say, 'Well, I'm not actually really helping their vision by doing this either, I'm just trying to slow things down a little bit, and the amount that I'm slowing things down is really not that impressive to me either,' " he says.

"On the other hand, we finally have a treatment for GA, which is great, and it does provide some hope for those patients who are desperate," continues Dr. Abbey. "There are going to be some patients out there—I've treated them myself already—who believe that this is worth the commitment of time and the potential risk. They're willing to deal with that potential treatment burden because they want to keep their vision for as long as possible. The disease has already affected their lives in significant ways. However, I do believe that there will continue to be a bloc of retinal specialists who probably will never be convinced to treat, at least with this iteration of complement inhibition treatment for the disease. Having said that, I know plenty of retina specialists who have already started using it, including myself, and we've been happy with the results so far—as happy as you could be for having Syfovre available for such a short period of time."

Pegcetacoplan reduced lesion growth in a prespecified analysis of DERBY and OAKS combined



SE= standard error. LS means estimated from a mixed-effects model for repeated measures. The mITT population was used for the analysis.

The combined results of the OAKS and DERBY clinical trials showed a reduction of 17 percent (p<0.0001) in patients receiving monthly pegcetacoplan therapy vs. sham, and 14 percent (p=0.0012) every other month vs. sham.

Dr. Kovach recommends a thorough patient analysis and discussion before proceeding with pegcetacoplan injections. "Patients who I would favor treating first would be those who have lost vision in one eye because of AMD and have geographic atrophy encroaching on the fovea in the better eye," she says. "I'd want to treat the better eye to try to slow GA progression as much as possible. The treatment decision requires an analysis of past GA progression on multimodal imaging, including fundus autofluorescence and OCT, and assessing progression biomarkers such as GA focality, location, banding pattern on FAF and reticular pseudodrusen, hyperreflective foci and drusen volume on OCT. Environmental factors, such as smoking, should also be considered. Finally, a detailed discussion with the patient reviewing how their disease is affecting their vision now, past GA progression, their untreated prognosis, risks, benefits and if they're willing and able to come in every four to eight weeks to receive injections, is necessary."

Therapies on the Horizon

Much more is in the pipeline for GA, and avacincaptad pegol (Zimura, Iveric Bio) is expected to garner FDA approval later this summer.

ACP is also a complement inhibitor, but targets C5. "ACP inhibits C5 in the complement cascade, which is more distal in the cascade and more directly related to MAC formation," Dr. Kovach says. "The MAC complex is what directly leads to RPE cell death. ACP works to decrease MAC formation while preserving the functions of C3."

Dr. Abbey says this is part of the appeal of ACP in the retina space. "When you're inhibiting C3, you're inhibiting everything downstream of C3 as well, but some of the parts of the complement pathway after C3 can potentially be a benefit, so you may not necessarily want to be inhibiting everything that's downstream of C3," he says. "For example, we do know that C3, when it's normally activated, is cleaved into C3a and C3b, and C3a specifically can have some anti-inflammatory effects as well. So we may actually want to have more C3a around in a case where inflammation is causing us to have retinal degeneration, like in GA. It's one of those instances where you go ahead and take complete C3 inhibition

because you see that it does reduce the overall inflammation that leads to cell death, but maybe there's also a potential where the C3a portion that's cleaved could actually be helpful in the process of geographic atrophy and reducing the overall inflammation as well.

"If you inhibit at C5," continues Dr. Abbey, "you don't have to worry about that anymore because you'll still have the C3a upstream being produced, and the inhibition of C5 will still lead to a reduction in the overall cell death process and overall inflammation without as much upstream effect on the complement pathway. It's obviously more complicated than that, but that's part of the reasoning why some people would argue that C5 inhibition may be more ideal for this disease."

According to results from the GATHER1 and GATHER2 clinical trials, ACP showed a 27.4-percent (p=0.0072) reduction in the mean rate of GA growth in the 2 mg cohort and 27.8-percent (p=0.0051) in the 4 mg cohort, compared to sham.[6] Among the most common adverse events reported at 12 months in the ACP 2 mg cohort were conjunctival hemorrhage (13 percent), increased IOP (9 percent) and CNV (7 percent).[7]

"Another reason why some would argue that ACP could be better than pegcetacoplan is that ACP had two pivotal Phase III trials that both showed significance, as opposed to just one with pegcetacoplan," Dr. Abbey says. "Some people may feel that since ACP didn't have to pool its data to achieve significance, it could mean C5 inhibition is a better data-driven option. However, I'll point out that in ACP's trial, it was administered monthly, so you have to consider that amount of burden on the patient. And just like pegcetacoplan, we did see that signal again with an increased rate of the neovascularization and conversion to wet AMD in the patients who were receiving ACP."

As the field watches other trials progress, Dr. Kovach notes that oral therapy would be particularly appealing. She's currently a principal investigator for danicopan (Alexion Pharmaceuticals), an oral factor D inhibitor that's currently in a Phase II trial. Cognition Therapeutics also has an oral therapy in development, consisting of a "small molecule sigma-2 (σ-2) receptor modulator designed to penetrate the blood-retinal barrier and bind selectively and saturably to the σ-2 receptor complex" in Phase II of the MAGNIFY study, according to the company. Cognition says this therapy may protect RPE cells from key drivers of underlying disease.

"It would be great to have an oral medication to treat GA in both eyes and obviate the need for intravitreal injections," adds Dr. Kovach.

Gene therapy may also prove beneficial, she continues. "Janssen has developed a gene therapy drug, JNJ-81201887, that expresses CD59 and that inhibits MAC formation. It's administered via a single intravitreal injection, and it was well-tolerated in a 24-month Phase I clinical trial. We'll have to see how it performs in the subsequent studies. There are many other investigational treatments moving through the clinical trial pipeline, so hopefully in the next couple of years we'll have more treatment options in our armamentarium," Dr. Kovach says.

Pearls for the General Ophthalmologist

Retina specialists feel there are some important elements for the general ophthalmologist to know and consider regarding these new therapies and the patients who may benefit.

"There should be a discussion of who's an ideal patient to start on Syfovre (and eventually on Zimura as well, if it gets approved)," says Dr. Abbey. "That's important because the comprehensive ophthalmologists are going to be the gatekeepers for a lot of these patients. Most of the time, they're following these patients and not typically referring them to retina specialists because there was no available treatment for them in the past."

It's hard to define who the ideal patient is, but identifying certain characteristics of GA is essential. "Snellen vision often can't capture how devastating geographic atrophy is for patients," notes Dr. Kovach. "A patient can have significant functional vision limitations and still retain good central Snellen vision." Retina specialists rely on fundus photography and OCT to detect and diagnose GA.

"GA can be a devastating disease," she continues. " The ability to diagnose GA early and refer patients to retina specialists for evaluation and possible treatment can positively alter their disease course. Early treatment with the goal of slowing GA progression can give patients the opportunity to benefit from even more effective future next-generation therapies." ◀

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AN UPDATE ON OFFICE-BASED SURGERY

Ophthalmologists discuss the pros and cons of office-based surgery suites.

MICHELLE STEPHENSON
CONTRIBUTING EDITOR

Office-based cataract surgery continues to gain popularity and proponents say it offers some benefits over procedures performed in ambulatory surgery centers; however, safety concerns remain.

According to Lance Kugler, MD, who is in practice in Omaha, Nebraska, office-based surgery is the way of the future and is better for patients, surgeons and payers. "We've been performing in-office cataract surgery since 2017. At that time, there were a handful of centers across the country, and now there are at least 150 or 200 that I know of, and more are coming onboard every week. There is clearly momentum in that direction," he says.

However, some ophthalmologists have expressed concerns about safety. Dr. Kugler and colleagues recently published an article that addresses the safety of office-based cataract surgery.[1] The study found that the rate of adverse events for office-based cataract or refractive lens surgery is similar to or less than the reported adverse event rate for cataract surgery in the ASC setting. The study reviewed 18,005 cases of office-based cataract or refractive lens surgery performed at 36 clinical sites. The rate of postoperative endophthalmitis, toxic anterior segment syndrome, and corneal edema were 0.028 percent, 0.022 percent and 0.027 percent, respectively. Unplanned anterior vitrectomy was performed in 0.177 percent of patients. Additionally, 0.067 percent of patients returned to the OR, and 0.011 percent of patients were referred to the hospital. Dr. Kugler says the case count is now more than 30,000.

Patients

Surgeons performing in-office surgery say that there are benefits for patients. "Patients love it because it's more comfortable and less intimidating. They are already comfortable with the office and the staff," Dr. Kugler says.

Jason Stahl, MD, who is in practice in Overland Park, Kansas, agrees. His office has been performing office-based IOL surgery since January of 2020. "It's a very similar experience to LASIK surgery," he says. "Patients are familiar with the staff on the day of LASIK because it's the same staff who worked them up in the clinic. It's at the office, and so patients walk into surgery and walk out. The in-office IOL surgery, whether it's refractive lens exchange or refractive cataract surgery, is very similar. It's very familiar and comfortable for the patients, and they've embraced it. We've had patients who, for whatever reason, have had one eye done in an ASC and then the other eye done in-office, and they all comment on how much more comfortable they were with the experience in-office. That's not to say that you can't have a good experience in an ASC."

Dr. Kugler adds that it can be anxiety-provoking for patients to have surgery in a hospital or ASC with IV anesthesia. "When a patient comes into a traditional surgery operating room, like an ASC or a hospital, he or she is immediately put in a gown, an IV is placed, and there are monitors on the wall indicating that he or she is about to have a big surgery.

This article has no commercial sponsorship.

Dr. Kugler is medical director of in-office surgery company iOR Partners. **Drs. Stahl and Cotter** have no related financial disclosures.

Jason Stahl, MD

Surgeons say that office-based cataract surgery, such as this shown here, can be less anxiety-inducing for the right patients, and can allow the surgeon to have more control over the cost and equipment, compared to an ASC or hospital.

That causes a tremendous amount of anxiety, and I didn't fully appreciate what it was doing to patients until we started using our office-based surgery center where we can perform surgery under oral anesthesia a majority of the time. Oral anesthesia without an IV is much more comfortable for patients. They are more relaxed, and they do better in that environment than they do with IV anesthesia," he says.

Dr. Kugler's center is class B certified, so there is a CRNA who can administer IV anesthesia, if necessary, but he says that it's rarely needed.

Dr. Stahl says that patients with any significant health issues need to be operated on in an ASC that's staffed by nurse anesthetists just in case there's an issue. "These include cases that are maybe a little bit more complex, if the patient isn't as healthy, or if the patient has enough anxiety to need IV sedation. We do not offer that in-office, so these are all reasons why I would elect to schedule someone at the ASC. I have plenty of colleagues who will do in-office cataract surgery on patients who require IV sedation and will have nurse anesthetists available. We would like to just stay with the class A certification where we only provide oral sedation," he explains.

Dr. Stahl's office trained its LASIK staff to assist in-office cataract surgery. "We trained them to do everything. Obviously, there's a learning curve with anything, but they've done an amazing job. We were able to just train our current laser surgery staff to work in the cataract suite with us," he says.

Dr. Kugler's office added staff to provide office-based cataract procedures. "We added some staff and retrained some existing staff," he says. "To run a successful in-office suite, you don't need to have registered nurses as part of your team, but if you want to be able to offer class B level with IV anesthesia, then you do need to have registered nurses on the team. You also need well-trained surgical technicians, so we trained a couple of surgical techs and also hired a couple of already well-trained surgical techs, so we have four surgical techs now as part of our team."

When asked about the potential for complications, Dr. Stahl says that the in-office procedures performed in his office have been routine. "We take this very seriously. We all have training, we have a crash cart, and everyone has their basic life support training. We are prepared to handle something if it were to happen," he says.

Other benefits include control and cost savings. "You're in your own facility, where you can control the environment, the cost, the schedule, and the equipment," Dr. Kugler says. "Additionally, it's less expensive for payers. They can save money because many of the expenses associated with other facilities may not be necessary, such as anesthesia. Particularly for premium cataract surgery where there is a cash-pay portion, you can really save on expenses by performing surgery in an office-based surgery center rather than going to an ASC. The cost savings that's passed on to the patient can be tremendous."

The Price of Moving to Office-Based Surgery

According to Frank Cotter, MD, who is in practice in Roanoke, Virginia, cataract surgery migrating from the hospital to the ASC was likely to occur, because it was lower in cost and provided greater efficiency and quality. "This was done without any sacrifice in quality because the ASCs had to adhere to 600 conditions for coverage by Medicare," he says. "Nurse anesthesia was by the patient's side. You could take advantage of all the cost savings and convenience, without sacrificing patients' safety. Some people believe that the further natural evolution is moving cataract surgery from the ASC to the office. While office-based cataract surgery maintains the convenience and cost improvement compared to hospitals, there are several problems related to quality, patient safety, and patient comfort. Regarding quality, ASCs have personnel dedicated solely to the execution of eye surgery. Office-based surgery enlists clinic personnel to multitask by assisting with surgery. The lack of staff focus, training and experience in the office-

based surgery setting results in lower quality. However, the biggest quality decrease is the fact that you don't have nurse anesthesia."

He believes that cataract surgery is too intense to be performed in the office. Of the 3,600 procedures that Medicare reimburses for in an ASC, cataract surgery was ranked 6th in intensity per unit time.[2] "This means that you can't turn your attention away from what you're doing to address an anesthesia need or a patient problem," Dr. Cotter says. "You must stay focused on what you're doing because you can't just take all the instruments out of the eye and manage a problem. Procedures deemed less intense than cataract surgery include ventriculoperitoneal shunt, total knee, radical prostatectomy, rotator cuff and total hip. No one would consider performing them in the office."

He notes that office-based surgery would benefit surgeons in that it makes it easier to create a venue for surgery. "Number one is the very onerous, very strict certificate-of-need laws in some states that prevent people from opening up enough ASCs to do all of our volume of cataract surgery," Dr. Cotter says. "It's very difficult to open a new ASC. Some ASCs are restrictive as to ownership, so it can be difficult and expensive for a young surgeon to get in. However, you always have to look first and foremost at what you are doing to the patient. I think if the patient realized that if he or she were to develop pain, discomfort or anxiety during the procedure that there was no nurse anesthetist there to manage it, he or she would not choose to have the procedure in that setting."

Dr. Cotter adds that another concern is that there's no requirement to have a back-up generator for office-based surgery. "Many of these procedures are performed in high rises where you can't have a back-up generator. If the power goes out due to a storm or any other reason, you're stuck. There are also the issues of air quality, water quality and infection control. There are 600 conditions for coverage that are designed for patient safety that these office-based surgeries are not required to maintain. While they must be accredited by the same bodies as ASCs, they don't have the same accreditation criteria. They're accredited as offices; ASCs are accredited as ASCs. It's a totally different set of criteria," he explains.

"Some patients in Virginia have had nightmare experiences during office-based surgery. If you develop a complication or a problem in an office-based setting and there's no nurse anesthetist there, the patient's going to go through abject misery," Dr. Cotter avers. "Once patients are educated and informed about the comfort and safety advantages of ASCs, I just don't think office-based cataract surgery is going to evolve. But, there are going to be great efforts to make office-based procedures grow. iOR is very convincing with young doctors."

He also notes that there's no Medicare reimbursement for office-based procedures. "Surgeons are only reimbursed for the IOL. There is no prospect of being reimbursed for the entire procedure. The earliest that could possibly happen is 2027," Dr. Cotter adds.

For these reasons, Dr. Cotter doesn't believe that office-based surgery is where we're headed. "I've been doing this for a lot of years, and I've never seen anything pan out long-term that wasn't in the best interest of the patient," he says. "I think state legislators are going to slowly start loosening their certificate-of-need laws for ophthalmology because 80-plus percent of cataracts are now performed in an ASC setting. They will loosen up for cataract surgery so that it's easier to open up an ASC. I think that's the future." ◀

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WHITHER PRESBYOPIA EYE DROPS?

Vuity is struggling on the market, but it might not be the end of presbyopia-correcting eye drops. Here's a look at the current market and pipeline.

ANDREW BEERS
ASSOCIATE EDITOR

The presbyopia marketplace is growing, but physicians and patients aren't satisfied with some of the latest advancements in presbyopic treatments. Allergan offers the first presbyopia-correcting eye drop in the market, Vuity, and yet prescriptions have been trailing off since its release. Why is Vuity struggling to satisfy patients, and how can the pharmaceutical market bounce back?

John Hovanesian, MD, an ophthalmologist at Harvard Eye Associates in Laguna Hills, California, explains why Vuity struggled to meet the needs of presbyopic patients. "Two factors that are responsible for it's less-than-expected performance: One factor is that there are side effects that patients are less prepared for than most of us expected. It's not unusual to have a headache or pain in patients especially at the beginning of the dosing regimen," he says. "Patients have to take it for a period of time before they may overcome that, and most do, but it can be a surprise initially for patients, particularly if they're unprepared for having those side effects."

For the Phase III VIRGO trial, Allergan reported that 14.04 percent of participants in the Vuity group (n=114) experienced adverse effects such as eye irritation and headache, as opposed to 3.45 percent of participants in the vehicle group (n=116) who experienced similar effects.

"Second," Dr. Hovanesian continues, "I think that doctors prescribing these drops often may not always take time to prepare their patients for those side effects and everything involved. Every treatment has its limitations, but if we don't prepare patients for these, they may not have the best experience, and that can affect our readiness to prescribe the treatment again. Additionally, there's no financial incentive for doctors to recommend an eye drop for presbyopia. That doesn't mean they won't prescribe it, but the enthusiasm with which they prescribe it is not going to be the same as it would for, say, a drop for glaucoma that's potentially going to save the patient's sight."

Allergan

Vuity is the only presbyopia-correcting eye drop available in the market. Patients can take it once-daily for six hours of near vision, or twice-daily for nine hours. The second dose should be administered after six hours if needed.

Gil Kliman, MD, an ophthalmologist and managing partner at InterWest, a health care investment firm, is the co-founder and program director of Eyecelerator. During a

This article has no commercial sponsorship.

Drs. Hovanesian and **Kliman** have no financial interests to disclose.

presentation in 2021, Dr. Kliman provided the statistics for the most likely blockbuster product advancement for ophthalmic innovation. According to an Eyecelerator poll from industry and physicians, 40.6 percent of participants (n=105) agree that the first FDA approval of pharmacological therapy for presbyopia was the greatest advancement.

"As an investor in the area at InterWest, we didn't invest in any of the presbyopic companies initially. At first, we regretted that decision when we saw all the excitement around Allergan. Now, we're glad to be on the sidelines watching how it's going to play out and maybe get involved at a later point," says Dr. Kliman. "It was seen as a positive that Allergan would have the first drug because they would develop the market and increase both patient and eye-care provider awareness, and then other companies could take advantage of that as kind of fast followers. That actually had the opposite effect, which was a surprise to everyone. The side effects of developing retinal detachments was unexpected. That wasn't really seen as a major issue in the clinical trials by Allergan, and they did a very good trial of thousands of people."

It's unclear if Vuity is the direct cause, however. "Pilocarpine has in its labeling a warning that it can be associated with retinal tears or retinal detachment," Dr. Hovanesian continues, "and there were a few cases of patients taking Vuity who developed retinal tears or detachments. It may not be fair to attribute those effects to pilocarpine. There's no way to say that Vuity caused that.

"From a legal perspective, someone taking Vuity who has a detachment could blame the drug for it, and if they weren't properly warned about that possibility, there could be liability questions for the doctors," Dr. Hovanesian explains. "These few cases led to some doctors saying, 'I don't want to prescribe a drop that could land me in trouble because it's associated with retinal detachment.' Even if a retinal detachment had nothing to do with the drop, the risk is still a deterrent."

Patient satisfaction and safety is leading to the issues in the presbyopia-correcting eye drop market, but understanding how to fit these drugs into the pharmacological space could potentially boost prescriptions. Dr. Kliman explains how companies and physicians should be approaching these products. "I think it's a multichannel process because first companies have to get the providers comfortable with the idea that these are going to be good things to prescribe. And this is an interesting market in that it's probably going to be primarily optometrically driven. Most people with presbyopia are probably going to see an optometrist first rather than an ophthalmologist if they're just [plano presbyopes]."

Dr. Hovanesian notes that there's a specific patient demographic who'll receive favorable effects from presbyopic eye drops, including plano presbyopes. "Seems to me that the patients who probably do best with it are maybe around age 50 or older, those who definitely have presbyopia who don't have much other refractive error, and those who are fully committed to glasses even if they can't make it work another way. I have patients who are younger than that, or who aren't affected as much by presbyopia, and they're just not likely to commit to both the effort and the cost, because there's also an out-of-pocket cost to use the medication.

"The patients who are significantly older than that often have cataracts playing a role, and if you have cataracts in the eye and you constrict the pupil, sometimes you can make the vision worse and not get the amount of depth of focus that you'd like to have," continues Dr. Hovanesian. "Cataract and presbyopia are, sort of, part of the same process of maturing of the lens of the eye."

Both Drs. Hovanesian and Kliman have some ideas on which products in the presbyopia-correcting drop pipeline seem promising. Dr. Kliman says, "The highest profile companies behind Allergan are Lenz Therapeutics, Visus Therapeutics and Orasis Pharmaceuticals. They're all venture-capital backed, and they're moving forward with a single product. I'm excited for them because they could have better efficacy and better side effect profiles than Vuity."

Dr. Hovanesian agrees that products from Lenz Therapeutics and Visus are potentially promising. "Visus has a carbachol product, and Lenz Therapeutics has an aceclidine product, and those are different types of pupil constrictors," he says. "They

Lenz Therapeutics

LNZ100 and LNZ101 are the first and only eye drops in the pipeline to use the compound aceclidine. Like pilocarpine and carbachol, acecldine is a muscarinic agonist originally used to treat glaucoma.

work by different mechanisms of action, and the companies hope that they'll work better [than their competitors]. Visus combines their carbachol with brimonidine, which improves the longevity of the effect. It improves the efficacy of the carbachol, and they probably have the best clinical trial results for duration of effect of any of the companies, lasting out well past 12 hours, meaning most patients wouldn't have to dose more than once a day with their product, Brimochol. However, they're not approved, and we don't know yet what the real-world side effect profile will look like."

Current FDA Pipeline

There are five compounds in the FDA pipeline for presbyopia-correcting drops, each completing FDA trials for market release. "There can be more than one winner, which is important, because there's a lot of entrants here in the market," says Dr. Kliman. "So, it's like a big horse race."

Here are the eye drops in the pipeline currently:

• ***Brimochol (Visus Therapeutics).*** Carbachol and brimonidine tartrate make up the solution for Visus' presbyopia-correcting eye drop, Brimochol. Visus explains that carbachol is a miotic agent that constricts the pupil, and brimonidine tartrate prevents the pupil from dilating. This reduces the pupil's size and creates a pinhole effect similar to pilocarpine solutions. Visus uses brimonidine to potentially mitigate side effects from carbachol as well as increase the longevity of the solution.

Brimochol's Phase III trials, BRIO-I and BRIO-II, are currently underway. The Phase III trial will measure the percentage of participants with three-line improvement in near visual acuity without the loss of at least one line in distance visual acuity. Participants will be administered different compounds to assess the effects of the solution in Brimochol. Brimonidine tartrate, carbachol and Brimochol are all going to be administered separately in different groups. In previous trials, researchers discovered that Brimochol is significantly superior to reducing pupil diameter than brimonidine tartrate or carbachol, creating a 2-mm pupil as opposed to a nearly 3-mm pupil from the separate compounds. As Dr. Hovanesian stated before, this product hasn't completed FDA trials and physicians have to wait for a profile on the side effects after approval.

• ***LNZ100/LNZ101 (Lenz Therapeutics).*** There are two eye drops in development from Lenz Therapeutics: LNZ100 and LNZ101. Both solutions include the compound aceclidine, but LNZ101 introduces brimonidine to improve the bioavailability of aceclidine. Lenz Therapeutics explains that aceclidine doesn't overstimulate the ciliary muscle, provides a sub 2-mm pupil and avoids impacting distance vision. They also mention that LNZ101 has the added benefit of eye whitening.

Lenz's Phase II INSIGHT trial met its primary endpoint of a ≥ three-line gain in near visual acuity without losing ≥ one-line of distance vision, with 71 percent (LNZ100) and 56 percent (LNZ101) of participants achieving this at one hour. The duration of both solutions was examined at 10 hours, which found 37 percent (LNZ100) and 48 percent (LNZ101) of participants achieving the primary endpoint. The secondary endpoint pushed for ≥ two-line gain in near visual acuity without losing ≥ one-line of distance, which 86 percent (LNZ100) and 78 percent (LNZ101) achieved this at one hour, and 55 percent and 58 percent at 10 hours.

• ***CSF-1 (Orasis Pharmaceuticals).*** In February, Orasis Pharmaceuticals announced that the FDA approved for review the NDA for CSF-1, the company's 0.4% pilocarpine solution. The Phase III, NEAR-1 and NEAR-2 (n=613) trials' primary endpoints attempted to find the percentage of participants with a ≥ three-line gain in DCNVA at 40 cm and no loss in BDCVA ≥ five letters at 4 m on the eighth day of the trial. The secondary endpoint attempted the same results on the first, eighth and 15th day of the trial.

According to Orasis, both trials met their primary and secondary

Eyenovia

Eyenovia is developing Optejet to include smart technology. It can connect with a smart device to track dosing and alert patients when they need a dose or refill. Eyenovia proposes the potential of sharing this information with a patient's doctor to improve treatment decisions.

endpoints on day eight. Forty percent and 50 percent of participants from the NEAR-1 and NEAR- 2 trials received a three-line gain in DCNVA with no loss of one line or more in BDCVA after one-hour post-dose. Participants achieved statistically significant three-line improvement on days one and 15. On Day 15, participants achieved statistically significant three-line or more improvement in DCNVA as early as 20 minutes and up to eight hours post-dose. Researchers reported that 6.8 percent and 5.8 percent of participants from the NEAR-1 and NEAR-2 trials experienced side effects such as headaches and eye irritation. Overall, 2.6 percent of participants reported moderate treatment-related adverse effects.

• ***MicroLine (Eyenovia).*** Eyenovia offers 1% and 2% pilocarpine solutions that would be administered using their OpteJet dispenser. This product is meant to regulate the dispensing of their pilocarpine solution, MicroLine. Eyenovia notes that traditional eye drops are approximately 40 µL in volume, which exceed the absorption capacity of the eye. OpteJet dispenses an 8 µL dose of medication, which is the approximate absorption capacity of the eye. This dispenser is the driving force for Eyenovia's latest drugs in the pipeline.

The Phase III, VISION-2 trial for MicroLine isn't completed, but Eyenovia researchers completed the VISION-1 trial. The primary endpoint for the VISION-1 was to have a ≥ three-line gain in DCNVA at 45 cm after one-hour post-dose. Participants were administered MicroLine and a vehicle (placebo). Participants who received MicroLine reported improvement in their near vision as opposed to the vehicle group (2:1). The MicroLine group reported side effects such as moderate hyperemia, instillation discomfort, and brow ache, while zero participants in the vehicle group reported side effects. Eyenovia states that MicroLine improves vision for three to four hours.

> **Every treatment has it's limitations, but if we don't prepare patients for these, they may not have the best experience, and that can affect our readiness to prescribe the treatment again.**
>
> ***— John Hovanesian, MD***

• ***Nyxol (Ocuphire Pharmaceuticals).*** Ocuphire's Nyxol is being developed for presbyopia as well as mydriasis and dim light vision disturbances. The presbyopia eye drops, unlike the products for mydriasis and DLD, are made up of 0.4% pilocarpine and 0.75% phentolamine. Nyxol is currently undergoing Phase III trials. Phase II trials for the presbyopia eye drops showed that Nyxol can sustain its effect for an 18-hour period. Pilocarpine is meant to reduce the pupil size along with the phentolamine. Ocuphire uses this compound to work alongside pilocarpine in order to relax muscles and reduce IOP.

"[Presbyopia-correcting eye drops] can change the future of treatment profoundly," says Dr. Hovanesian. "We have drugs that the market recognizes are really improving lives. I'm still optimistic for the future of drugs like this. It has a large impact, and I would encourage my colleagues to consider and try each of these products as they become FDA approved. Give them a reasonable chance, educate patients properly, screen patients properly for who might have the best outcome, and give them a chance to succeed, because if they were approved in an FDA trial, then they probably have some value to patients." ◀

Presbyopia-correcting Eye Drops Approved and in the Pipeline

Name	Company	Active Ingredient	Mechanism of Action	Approval Status
Vuity	Allergan	Pilocarpine 1.25%	Miotic	FDA approved
CSF-1	Orasis Pharmaceuticals	Sub-glaucoma dose pilocarpine with proprietary vehicle	Miotic	Phase III completed
MicroLine	Eyenovia	Pilocarpine 1%, 2%	Miotic	First of two Phase III trials completed
Brimochol	Visus Therapeutics	Carbachol + brimonidine	Miotic	Phase III initiated
LNZ100, LNZ101	Lenz Therapeutics	Aceclidine 1.75%, aceclidine 1.75% + brimonidine	Miotic	Phase III initiated
Nyxol + low-dose pilocarpine	Ocuphire Pharma	Phentolamine ophthalmic solution 0.75% + low-dose 0.4% pilocarpine	Miotic	Phase III initiated

Antithrombotics and Glaucoma Surgery

Weighing the pros and cons of altering therapy involves several factors. Here's guidance for management.

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PHILADELPHIA

With the aging population and the increasing prevalence of cardiovascular disease in the United States, it's become more common for patients to be on some kind of antithrombotic medication such as aspirin or warfarin. These medications are vital for managing long-term comorbidities such as atrial fibrillation and venous thromboembolism, but their blood-thinning effects also increase the risk for bleeding and bleeding-related complications during glaucoma surgery.

Determining whether or not to discontinue or alter antithrombotics perioperatively is challenging. Here, I'll discuss the risk stratification process and the effects of these drugs on glaucoma surgery.

Classes of Anti-thrombotic Drugs

There are three classes of antithrombotic therapy (*Table 1*):

• ***Antiplatelets.*** Antiplatelet agents inhibit platelet function by blocking the production of a chemical involved in aggregation of platelets. Aspirin is the most commonly used antithrombotic drug, used daily in about half of adults over the age of 65. Both Aspirin and clopidogrel (Plavix) are recommended to be stopped about seven to 10 days before surgery if they are to be held. They may be restarted about one to two days after surgery. Like clopidogrel, dipyridamole, used for high-risk stroke and heart attack prevention, can be taken with aspirin.

Clopidogrel requires a functional copy of the active cytochrome P450 2C19 (CYP2C19) enzyme for efficacy, and many Chinese and Pacific Islander individuals lack this. Individuals who have two loss-of-function copies of CYP2C19 gene—approximately 2 percent of Caucasians, 4 percent of African Americans, 14 percent of Chinese, and 57 percent of Pacific Islanders—are considered CYP2C19 poor metabolizers.

• ***Anticoagulants.*** Anticoagulants inhibit the various coagulation pathways, preventing clot formation and growth. Vitamin K antagonists such as warfarin (Coumadin) block the synthesis of coagulation factors II, VII, IX and X and proteins C and S. Because of its variable half-life (20 to 60 hours), warfarin requires regular blood tests to monitor clotting time (i.e., International Normalized Ratio). Patients must remain within a fairly narrow therapeutic window, which is typically between 2 and 3 INR, depending on therapeutic indication. (Patients not on anticoagulant therapy usually have an INR of 1.) As clinicians know, fluctuations in INR are very common and can be influenced by a host of commonly used medications (e.g., NSAIDs, antifungals, antibiotics and antidepressants) and other factors such as dietary changes (including alcohol use) and illness. It's recommended that warfarin be stopped about five to six days before surgery and restarted up to one day after surgery if it is to be held.

In outpatient settings, low molecular weight heparins are typically used for bridging warfarin therapy in high-risk patients.

• ***Direct oral anticoagulants.*** Direct oral anticoagulants are a newer class of medications consisting of direct factor Xa inhibitors, which include apixaban (Eliquis), rivaroxaban (Xarelto), edoxaban (Savaysa) and betrixaban (Bevyxxa), and direct thrombin inhibitors, such as dabigatran (Pradaxa). These medications can be stopped about two to five days before surgery and restarted up to one to three days after if they are to be held.

Direct oral anticoagulants don't require monitoring or bridging, making them very popular in the outpatient setting. The three most commonly used agents (apixaban, rivaroxaban and dabigatran) have reversal agents. Idarucizumab (Praxibind) is approved for the reversal of dabigatran; andexanet alfa (Andexxa) is approved for the reversal of apixaban and rivaroxaban.

It's important to ask patients

This article has no commercial sponsorship.

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

TABLE 1. RECOMMENDED PERIOPERATIVE USE OF ANTIPLATELET AND ANTICOAGULANT AGENTS

Medication	Mechanism of Action	Typically Stopped	Typically Restarted
Aspirin	COX-1 inhibitor	Seven to 10 days before surgery	One to two days after surgery
Clopidogrel (Plavix)	P2Y12 receptor inhibitor	Seven to 10 days before surgery	One to two days after surgery
Warfarin (Coumadin)	Vitamin K antagonist	Five to six days before surgery	Up to one day after surgery
Apixaban (Eliquis) Rivaroxaban (Xarelto) Edoxaban (Savaysa) Betrixaban (Bevyxxa)	Direct factor Xa inhibitors	Two to four days before surgery	One to three days after surgery
Dabigatran (Pradaxa)	Direct thrombin inhibitor	Two to five days before surgery	One to three days after surgery

why they're using a particular type of antithrombic medication—if an antithrombotic is being used prophylactically by an individual with low thrombotic risk, temporarily discontinuing its use perioperatively may be less of an issue versus if the patient is on the medication for atrial fibrillation, for example. Patients should also be asked about the use of supplements with blood-thinning properties such as *Ginkgo biloba*, vitamin E or fish oil. These substances have been associated with increased bleeding risk during surgery, and it's recommended that they be stopped before the procedure.

Minimizing Bleeding Risk: Surgical Factor

Potential bleeding-related complications in glaucoma surgery include vitreoretinal hemorrhage, hyphema and choroidal hemorrhage. These may be more likely to occur in patients on antithrombotics, so it's important to consider how to minimize bleeding risk.

Certain ocular factors such as high preoperative intraocular pressures and low postoperative IOP, aphakia, the presence of an AC-IOL and prior ocular surgery put eyes at higher risk for bleeding. Systemic factors such as arrhythmia, high blood pressure, ischemic heart disease and respiratory disease also put patients at higher risk of bleeding.

There's a fair amount of literature on antithrombotic use with trabeculectomies and tube shunt procedures. Increased bleeding risk is well-documented for these procedures. A retrospective review of 367 consecutive trabeculectomies demonstrated a higher risk of hyphema with antithrombotic therapy. Aspirin significantly increased hyphema risk (p=0.0015) but didn't appear to affect surgical outcome, while warfarin use was associated with hemorrhagic complications and trabeculectomy failure.[1]

A case-control study of 347 anticoagulated patients who underwent trabeculectomy and tube shunt procedures reported a statistically significant increase in the rate of hemorrhagic complications with chronic anticoagulation or antiplatelet therapy compared with controls (10.1 percent versus 3.7 percent, p=0.002).[2] Patients on anticoagulants had a higher rate of hemorrhagic complications compared with patients on antiplatelet agents (22.9 percent versus 8 percent, p=0.003). The highest rate of hemorrhagic complications (31.8 percent) was found in patients who continued anticoagulation therapy prior to surgery. Postop complications were associated with preoperative anticoagulation therapy, arrhythmia and higher preop IOP.

Glaucoma surgeries involving scleral manipulation such as trabeculectomy and viscocanaloplasty, and a history of deep vein thrombosis or peripheral arterial occlusive disease may also increase the risk for bleeding complications, according to a prospective study of 89 eyes.[3] This study, however, found no significant increase in severe intraoperative bleeding events associated with concomitant use of antiplatelet or anticoagulation therapies.

Interestingly, tube shunt procedures carry the greatest risk for bleeding with antithrombotics. A retrospective case-control study of 2,752 glaucoma surgeries reported a 1-percent (29 cases) incidence of delayed suprachoroidal hemorrhage after glaucoma surgery.[4] Of these 29 hemorrhage cases, tube shunt implantation resulted in a significantly greater incidence of delayed suprachoroidal hemorrhage compared with trabeculectomy (p<0.0001; OR 3.4, 95% CI: 1.9 to 5.4). Significantly associated risk factors included low postop IOP (≤3 mmHg), aphakia, prior intraocular surgery, hypertension, anticoagulation therapy, ischemic heart disease, and respiratory disease.

Similarly, another retrospective case-control study of delayed suprachoroidal hemorrhage after glaucoma filtration surgery reported that this complication occurred

more frequently after tube shunt implantation than trabeculectomy (p<0.0001, OR 3.2). Of the 2,285 patients who underwent glaucoma surgery, there were 66 cases (2.9 percent) of delayed suprachoroidal hemorrhage. Trabeculectomies without antimetabolite use had a 1.5-percent incidence (nine of 615 cases); whereas the incidence was 2.4 percent with antimetabolites (30 of 1,248 cases). Valved tube shunts had a 2.8-percent incidence (two of 72 cases) and nonvalved tube shunt implantation had a 7.1-percent incidence (25 of 350 cases). Risk factors included white race, anticoagulation therapy, severe postop hypotony and aphakia/AC-IOL. Patients with hemorrhages had significantly poorer visual outcomes than controls (p<0.009).

In comparison, we have limited guidance when it comes to MIGS surgeries. What we can say, based on existing literature, is that little evidence suggests antithrombotic therapy alter the risk of bleeding. We know that certain procedures such as GATT, compared with other MIGS procedures, have a higher risk of bleeding. Other procedures like the iStent have a very low risk of bleeding, with reportedly no effect on IOP control when combined with phaco.[5]

Right now, we don't know enough about the significance of systemic ocular risk factors in antithrombotic management with respect to MIGS. In one retrospective study of 435 eyes of 333 patients who underwent trabecular bypass microstent surgery with iStent (n=331), iStent inject (n=71) and Hydrus (n=33), hyphema was found to be associated with stent type and female sex.[6] Hyphema occurred in 19.3 percent of eyes (n=84; 41 on antithrombotics and 43 not on antithrombotics)—36.4 percent with Hydrus, 19.9 percent with iStent and 8.5 percent with iStent Inject. The authors suggested that the higher hyphema rate seen with the Hydrus may be related to its relatively larger size and greater amount of Schlemm's canal involvement. The authors noted that the small Hydrus sample size (due to the recent FDA approval of the device) accounts for its lack of significance in the multivariate model. Hydrus wasn't associated with IOP spikes

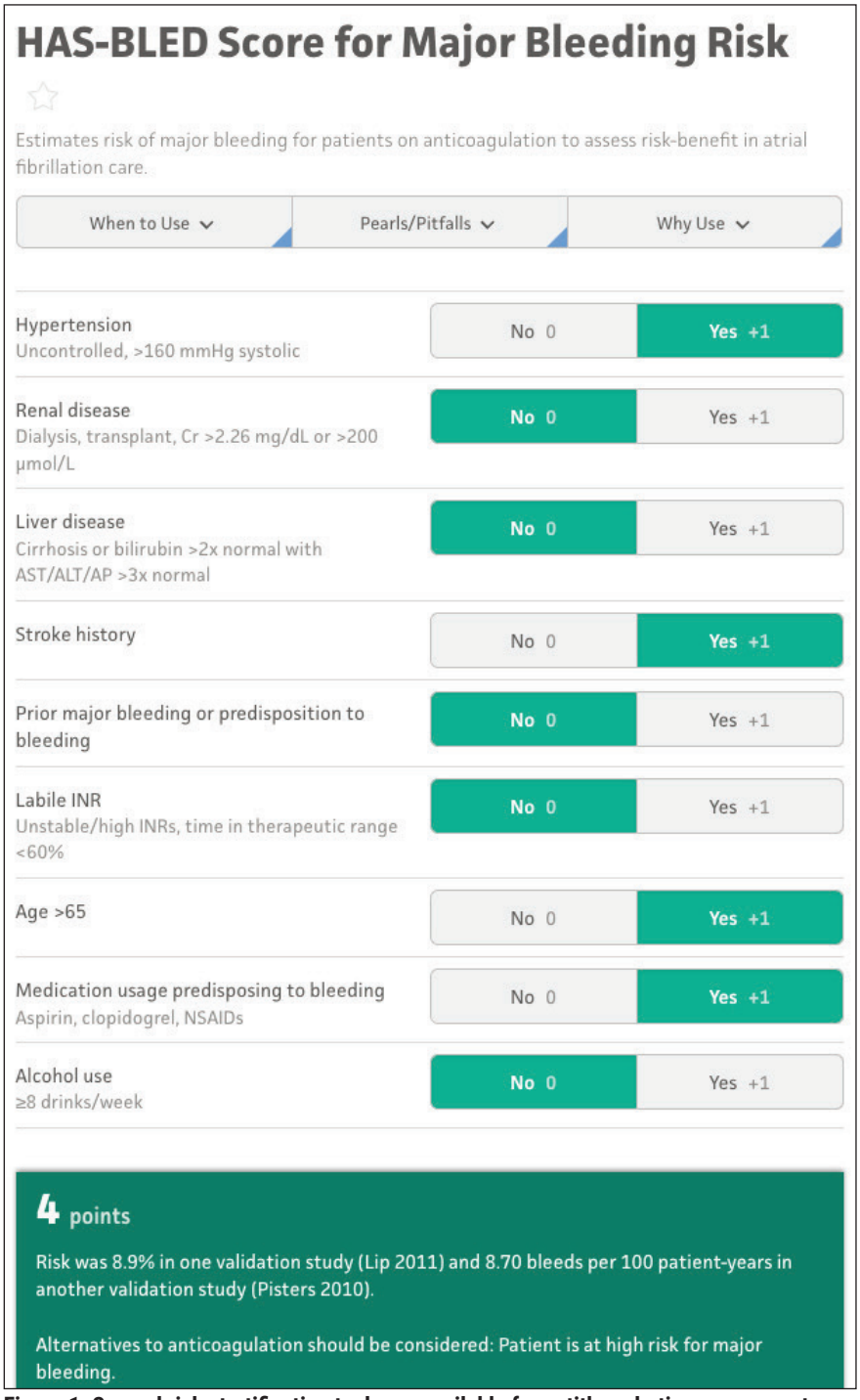

Figure 1. Several risk stratification tools are available for antithrombotic management. The Hypertension, Abnormal liver/renal function, Stroke history, Bleeding predisposition, Labile INR, Elderly, Drug/alcohol usage (HAS-BLED) risk score calculator for our example patient is shown here. These free tools can help clinicians identify appropriate approaches for glaucoma surgery and perioperative medication management. (*Source: mdcalc.com*)

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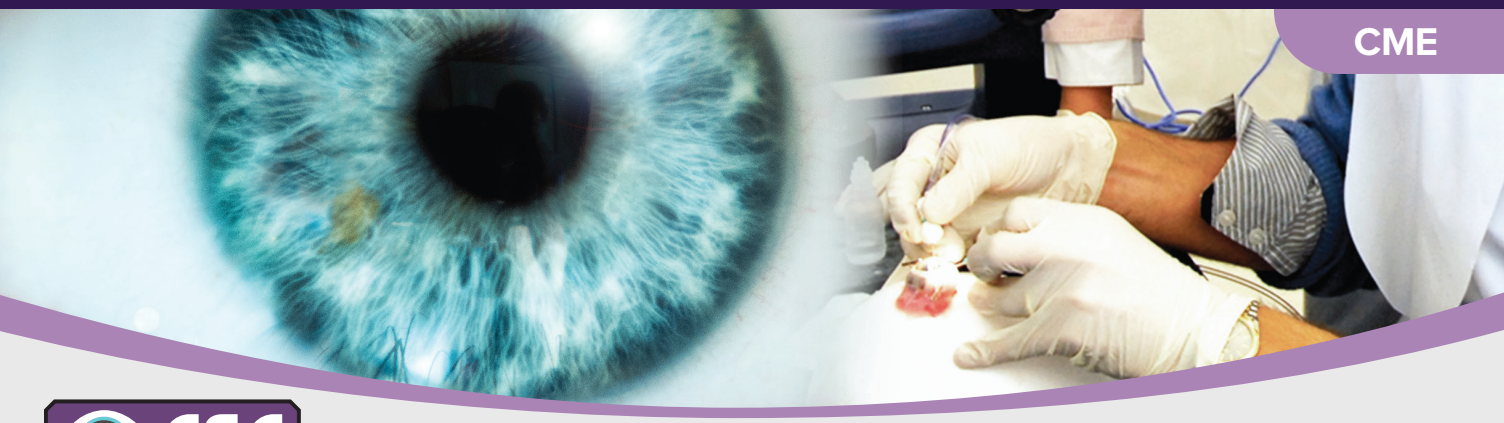

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in the study, possibly because of its greater outflow facility.

Antithrombotic therapy didn't increase the risk of bleeding after Kahook Dual Blade excisional goniotomy in a single study of 202 eyes of 145 patients, but the authors noted further research is warranted in this area.[7] Hyphema occurred in 8.4 percent of patients at one day postop, and was significantly associated with male sex, angle closure glaucoma and postop pressures ≤12 mmHg.

For *ab interno* trabeculotomy (using the Tanto microhook) combined with cataract surgery, a small retrospective case-control study of 44 patients reported a higher rate of hyphema and IOP spikes in those who continued antithrombotic therapy versus those who discontinued before surgery (43 percent versus 10 percent).[8] Discontinuation of antithrombotics resulted in better IOP-lowering effects and fewer postoperative complications.

In conclusion, based on existing literature, we can say that tube shunt procedures and trabeculectomies carry the greatest risks for bleeding; GATT poses a moderate risk, and other MIGS are generally low risk.

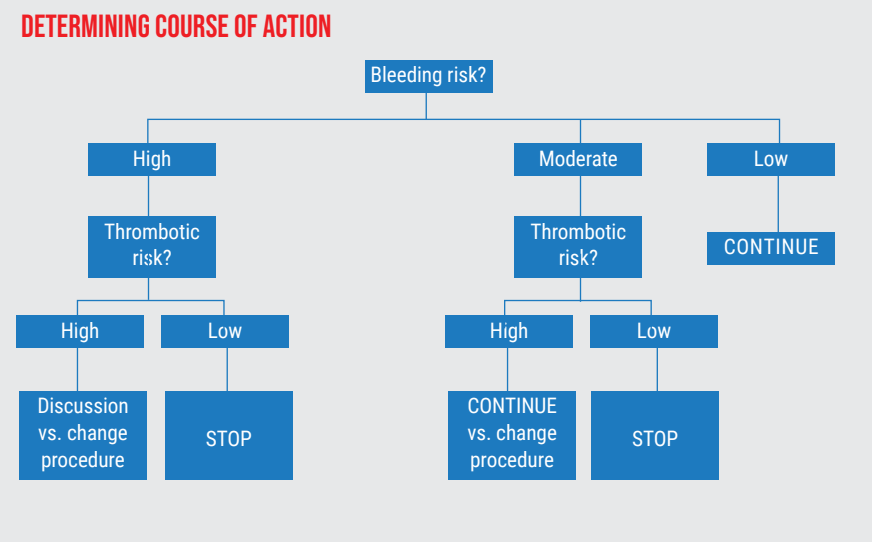

Figure 2. This flowchart can be used to determine the appropriate course of action based on the planned procedures, as well as a patient's risk for bleeding and thromboembolism.

For the case example described below, the surgical factor is moderate with the proposed GATT procedure, and the HAS-BLED calculator (patient factor) shows a high bleeding risk, putting the patient on the left-hand side of the flowchart. His thromboembolism risk calcuated using the CHA^2DS^2-VASc Score is high. This leads to the option: "Discussion vs. change procedure." It's important to discuss the risks and benefits with the patient to facilitate an informed decision. Changing the planned GATT procedure to one with lower bleeding risk may be an option.

Minimizing Bleeding Risk

Consider this case example: A 75-year-old man with open-angle glaucoma and cataracts is scheduled for cataract surgery and GATT. He's taking Eliquis for a stroke (CVA x 2) in the setting of atrial fibrillation and high blood pressure.

The patient factor can be calculated using a host of very handy, readily available online risk-score calculators. One option is the Hypertension, Abnormal liver/renal function, Stroke history, Bleeding predisposition, Labile INR, Elderly, Drug/alcohol usage (HAS-BLED) calculator (available at www.mdcalc.com/calc/807/has-bled-score-major-bleeding-risk or as a part of the iPhone/Android app MD+Calc). This calculator estimates the risk of bleeding for patients on anticoagulation to assess the risk-benefit of anticoagulation in somebody with atrial fibrillation. According to the HAS-BLED calculator, the patient in our case example scores four points, which puts him in the high-risk category, with an 8.9-percent chance of a major bleed (*Figure 1*).

Minimizing Thromboembolism Risk

The second patient factor to consider is the risk for thromboembolism. Two options for calculating this risk include using the CHA_2DS_2-VASc Score for stroke risk in patients with atrial fibrillation (available at www.mdcalc.com/calc/801/cha2ds2-vasc-score-atrial-fibrillation-stroke-risk) or the Caprini Score, for surgical venous thromboembolism risk. The patient in our case example scored five points on the CHA^2DS^2-VASc Score, which is moderate-high risk.

This score can then be input into a flow chart to assess a particular patient's risks (*Figure 2*). Our patient's bleeding risk is moderate-high, so that puts him on the left-hand side of the flowchart. His thrombotic risk is also high, leading to the option: Discussing the risks and benefits with the patient to facilitate an informed decision and/or changing the planned GATT to one with lower bleeding risk.

As you might expect, there isn't an easy solution in many cases. This patient's situation is tricky and there's no clear answer, but using these tools, we know a detailed and nuanced discussion with the patient is ultimately what's necessary. It may also be necessary to involve the prescribing provider to talk about the risks of

surgeries and the risks and benefits of stopping or continuing the antithrombotic agent. One thing to consider is whether GATT is still appropriate for this patient. If he's at high risk for bleeding, perhaps a different MIGS surgery would be a better option.

What Do Colleagues Do?

While there are recommended guidelines for stopping and restarting antithrombotics in the literature, a consensus is lacking among surgeons regarding antithrombotic management for glaucoma surgery.[9] Thirty percent of respondents in a U.K. study said they discontinued either warfarin or aspirin for four to seven days prior to surgery, respectively,[10] whereas 80 percent of surveyed Brazilian Glaucoma Society (BGS) members said they discontinued warfarin or aspirin prior to surgery (typically seven days prior, resuming one day post-surgery).[11]

In the BGS study, about half of respondents reported that they experienced hemorrhagic complications that could have been related to antithrombotics, including subconjunctival hemorrhage (29.6 percent), hyphema (25.9 percent), increased postoperative bleeding (29.6 percent), and hemorrhagic choroidal detachment (7.4 percent). Ninety percent of the respondents said they referred patients to a preoperative appointment with a cardiologist or general practitioner.

Additionally, 88.5 percent of respondents said they didn't change their usual anesthetic planning (73 percent preferred injectable anesthesia, 23 percent preferred topical anesthesia and 3.8 percent preferred general anesthesia). About 87 percent of respondents said they preferred a particular incision type in patients using antithrombotics while 13.5 percent reported that they didn't change their technique.

At this year's American Glaucoma Society meeting in Austin, Texas, Tejus Pradeep, MD, a resident physician at the Scheie Eye Institute, presented anonymized survey findings from our study on antithrombotic practice patterns for MIGS among AGS members.[12]

As might be expected, management preferences varied, depending on procedure type and surgeon preference. For example, approximately half of survey respondents preferred to defer antithrombic management to a primary care provider most or all of the time whereas the other half preferred to defer only either some of the time or never.

> **When appropriate, I highly recommend using the risk stratification tools available online, as well as involving the prescribing physician in decision making in antithrombotic management.**
>
> ***—Qi N. Cui, MD, PhD***

In summary, it's important to pay close attention to the patient's antithrombotic management when considering glaucoma surgery. In these situations, here are the three questions I always ask myself:

1. What is the bleeding risk of the procedure?
2. What is the bleeding risk for the patient?
3. What is the thromboembolic risk for the patient?

When appropriate, I highly recommend using the risk stratification tools available online, as well as involving the prescribing physician in decision making in antithrombotic management. Finally, a detailed conversation with the patient regarding the pros and cons of both the procedure and antithrombotic medications is critical. ◀

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ABOUT THE AUTHOR

Dr. Cui is an assistant professor of ophthalmology and leads the Cui Lab for glaucoma research at the Scheie Eye Institute, University of Pennsylvania in Philadelphia. She has no related financial disclosures.

A Review of Genetic Testing and Counseling

A look at the current state of genetic counseling, the methods that are available, and what might be coming in the future.

REBECCA A. PROCOPIO, MS, CGC
PHILADELPHIA

I'm on the phone with the daughter of a patient affected by autosomal dominant TIMP3-associated Sorsby fundus dystrophy, the onset of which is in the fourth or fifth decade of life and vision loss is rapidly progressive.[1] I explain the natural history of the condition to the woman, who's in her early 20s and considering predictive genetic testing. She has 20/20 vision and reports no signs of retinal disease on her last examination.

As we speak, I concentrate on the inflection of her voice, on high alert for signs of distress. If she tests positive, having this information won't change her surveillance or management at this moment, but it would allow her to prepare. We carefully and thoroughly delve into the obvious, and the more nuanced, risks, including the possible psychological impact and the limitations of the Genetic Information Nondiscrimination Act (GINA). The testing can be completed using a cheek swab that's sent to her in the mail—simple, and physically harmless. Over the phone, it can be difficult to build rapport, but I ask her to imagine how she may feel in each scenario; the one in which she tests positive, and the one in which she is negative. I ask her to contemplate how this information will affect not only her, but also others in the family. Although there isn't currently a treatment for her mother's condition, the number of clinical trials for inherited retinal diseases is growing, and there's optimism about targeted therapeutics. I explain that there's reason to believe this part of our conversation may sound different in a few years.


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After a brief pause, she states that she would like to proceed with testing. There's no treatment, but the information will make a difference. She explains that she wants to travel, and to have her own children; knowing whether she inherited the TIMP3 variant is a piece that will factor into her timing and decision-making. And if she were positive, she could stay informed about clinical trials and new interventions. Together, we plan to proceed with the test.

Logistically, it's easier than ever to complete genetic testing. Extracting DNA used to require a blood draw, but now it can be isolated from cheek swabs. Even better, the cheek swabs are nicely packaged in a small cardboard box and delivered to a doorstep along with the next-day Amazon delivery. Several genetic testing panels for ophthalmologic indications are sponsored by pharmaceutical groups, and are therefore "free" to families. Genetic counseling can happen via telehealth, or over the telephone.

However, the conversation and the decision-making aren't always linear. The anticipated outcome, or the anticipated feeling about the outcome, may not align when the results are returned. Sometimes, results are extraordinarily complicated, and other times they reveal unexpected information, uncovering new risks, or syndromic diagnoses. That's the nature of re-

This article has no commercial sponsorship.

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

ceiving genetic information: The raw human experience remains constant despite our advancements in technology and care.

Genetic counseling is crucial in this uniquely delicate part of medicine. As access to testing and new technologies surface, the profession must continuously evolve while maintaining the human connectivity at its core. Genetic diagnosis is now a pillar in the model of precision health. As centers move toward patient-centered care, further integration of genetic testing and counseling into practice is inevitable.

This article will explain how the current approaches to genetic testing work, and take a look at new testing technologies that we may be using in the future.

Genetic Counseling in Retina

Genetic counselors are allied health care professionals trained to evaluate and discuss genetic testing options, interpret results and communicate with families to facilitate decision-making. Classically housed in prenatal, cancer and pediatric centers, genetic counselors can now be found working in specialty care, including ophthalmology.

Inherited retinal diseases (IRD) are the some of the most common ocular genetic conditions. There is phenotypic overlap in IRD, which makes genetic diagnosis critical for prognosis and potential treatments as gene therapy and clinical trials continue to emerge. Ophthalmologists specialized in retina need to be able to order and interpret genetic testing accurately to provide essential patient care. In many centers, they work in conjunction with genetic counselors, however, access continues to be limited.[2]

At Wills Eye Hospital, we've implemented genetic counseling as a standalone service, available to all physicians in every subspecialty. We're implementing an efficient and cost-effective model of care with the option of telehealth and telephone counseling, as telemedicine appointments have increased in frequency and popularity over recent years.[4,5] This delivery model has also been adopted for the practice of genetic counseling in various subspecialties for residents of Pennsylvania and neighboring states (with plans to expand), since encounters don't require a physical examination. In ocular genetics, this has been deemed effective and safe, as visual impairment can lead to difficulties with transportation to health-care facilities.[5] Patients can also be referred for post-test counseling from outside institutions that lack genetic counselor support. Although the number of ocular genetic counselors continues to grow, they're still relatively hard to come by, and are mostly employed at large ophthalmology centers with specialized care. In 2019, there were fewer than 5,000 genetic counselors in the United States, and very few with expertise in ophthalmology.[3]

Whole Exome Sequencing in IRD

By implementing genetic counseling for each patient undergoing genetic testing on our retina service, we've been able to identify candidates for and complete reflex whole exome sequencing (WES) when gene panels are non-diagnostic. Studies show that gene panel-based testing identifies a diagnosis in 70 to 80 percent of cases that are highly suspicious for IRD; however, when researchers completed WES in the remaining families, the yield increased to 92 percent.[2] Obtaining whole exome sequencing requires careful attention to ordering details and informed consent. When parental testing is included, the diagnostic rate increases further. Therefore, it's beneficial to organize sample collection and consent with parents or other family members.

Genetic testing is notoriously expensive and often not covered by insurance. However, with proper prior authorization, affordable self-pay rates, and financial assistance programs, even WES is attainable for most families.

Gene panel testing isn't always the best first tier test, nor the only genetic test, needed for each patient with a retinal indication. Gene panel content is undergoing constant updating, to keep up with the ever-changing landscape of molecular diagnosis in retinal diseases. Physical examination that provides detailed phenotypic information along with differential diagnoses is essential to genetic test selection and genetic testing pipelines. Next generation sequencing (NGS) technologies aren't always validated to perform identification of all types of genetic anomalies. This includes copy number variant analysis and conditions that are caused by trinucleotide repeats, such certain forms of spinocerebellar ataxia, which can be associated with retinitis pigmentosa.

The interpretation of genetic variants and reporting varies between laboratories. Although two labs may include the same gene on their panel, application of variant classification systems may produce different results and inclusion of variants of uncertain significance can result in discrepancies.

Genes with pseudogenes and highly repetitive sequences can be difficult for NGS technology to capture. When evaluating gene panels, one must pay close attention to the coverage of these genes, or the ability of the lab to identify variants with the "problem" area. Reading the fine print is necessary when completing genetic testing to avoid missing a diagnosis due to limitations in technology.

Emerging Technology

Although WES can increase the diagnostic yield in inherited retinal disease, identifying causative genetic results is still imperfect in Mendelian disorders overall.[6] When using whole genome sequencing (WGS) instead of whole exome sequencing, the yield only increases by a small percentage. There are regions of DNA

that are difficult to analyze using the current next-generation sequencing technology (NGS), which performs "short read" sequencing (SRS).

New technology called long-read sequencing has the potential to capture multiple types of genetic variants, which currently require several genetics tests, in a single NGS based platform. Not only can LRS analyze tandem repeat sequences, segmental duplications, and other areas of the genome that are "problems" for SRS based testing, it can also obtain phase data from sequencing a proband alone (a proband is the first person in a family to bring concern of the genetic condition to a medical professional). Phase data in IRD is extremely valuable, as many of these diseases are autosomal recessive. Targeted testing of parents or children is needed to confirm that two disease causing variants are in trans configuration, or on opposite copies of the gene, as opposed to on the same copy, called cis configuration. Confirming trans configuration is needed to completely confirm a diagnosis. In some cases, phase testing can clarify the meaning of a variant of uncertain significance. However, family members aren't always available for, or willing to complete, testing. LRS has the potential to change the landscape of genetic testing in retina by removing these extra steps and allowing for a shorter time to diagnosis. Despite this, there are pitfalls, including lower depth of coverage, leading to lower accuracy when compared to short sequencing.[7] LGS isn't clinically available currently but is a promising advancement.[6,7]

Treatments and Clinical Trials

When clinicaltrials.gov is searched for "retinitis pigmentosa," 166 recruiting and soon-to-be recruiting interventional studies are returned. Increasing availability of genotype-specific treatments and clinic trials in inherited retinal disease drives up the demand for genetic services.[8] This breadth of trials and possible avenues for treatment are vast in comparison to other areas of genetic diagnosis, providing optimism for families and providers alike.

Increasing availability of trials also presents challenges, as decision-making with respect to determining eligibility and enrollment can be complicated. Genetic counselors may assist, as we often facilitate decision making about genetic testing. This skillset can be applied to clinical trial participation as well. As more clinical trials become available, genetic counselors may increase their knowledge base and change their practice to include discussion on such options. Evaluating eligibility criteria in relation to a patient can also be achieved by a genetic counselor, although input from a physician will continue to be integral.

On the other hand, we may begin to see the inclusion of genetic counselors on the backend of clinical trial development and enrollment. If a genetic test is necessary to confirm eligibility for patients with specific clinical findings, counselors can ensure the right test is ordered and obtain patient consent. Expertise in genetics and genetic conditions may be invaluable in this setting.

In conclusion, we finally got the long-anticipated result for the daughter of the patient who was TIMP3-positive. Predictive testing results for known, familial variants in asymptomatic individuals carries a unique amount of weight. As I scroll through the report, I bite my thumbnail, a nervous habit and an uncomfortable reminder of what the patient might feel when I call, though just a fraction as intense. If she's positive, I'll wait until the end of a workday to call, and certainly not on a Friday. I'll set up an appointment to review the results in more detail a few days later. The initial digestion of the information is largely emotional, and questions will often come later once there's time to process it. Most importantly, I recognize my plan as tentative; I can never fully predict how someone will react, or what they will need.

I scroll to reveal the remainder of the report: negative. I breathe out. It's good news. When I call later that day, I get right to the point, and over the phone I hear her exhale in relief.

Genetic testing will continue to bring us to new places, as we're able to reach diagnoses more often and faster than ever before. We'll continue to fill more of our results notes and take-home packets with information on trials and treatments. Our consent conversations will extend to cover new technology with lower cost. But genetic testing will also bring us here, to a place where patient care must be deeply individualized, autonomous and rooted in compassion. ◀

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Patient Education: Just a Click Away

Develop patient education experiences in the waiting room, exam room and at home with these online resources.

ANDREW BEERS
ASSOCIATE EDITOR

You spend years studying pharmacological treatments, surgical procedures and technology used in eye surgery, but their knowledge and terminology doesn't always translate well when communicating with your patients. Having educational ophthalmic resources can help inform patients about their options before undergoing a procedure. Fortunately, ophthalmologists don't have to create their own unique patient education program. There are many companies and organizations that offer credible resources to educate patients. Here's a list of some educational programs that can help physicians prepare their patients for surgery.

AAO Products and EyeSmart

For decades, the American Academy of Ophthalmology has been offering a product line of print materials and videos to assist ophthalmologists with patient education. The AAO shop features booklets, brochures, videos and online animations in both English and Spanish to ease the educational process for a larger patient demographic. Alternatively, the AAO created an entire website called EyeSmart dedicated to patient information that features articles, videos and an ophthalmic dictionary for patients.

"Our role is to make sure the Academy interfaces with the public in ways that keep them reasonably informed about ophthalmologic problems, conditions and treatments," says J. Kevin McKinney, MD, ophthalmologist and chair of AAO's Patient Education Committee. He's been using the AAO's educational materials for 25 years and currently works with a team of volunteer ophthalmologists to continue to generate and maintain credible content for both EyeSmart and the patient education product line.

EyeSmart includes free online resources that AAO encourages ophthalmologists to use. It offers a guide on how to embed educational videos and links from EyeSmart onto a physician's website. They also provide details explaining search engine optimization (SEO), how to make an accessible medical website, and the various approaches to promoting content online. "A large portion of our patient population, especially younger patients, are using social media. So, an ophthalmologist putting their materials online or in social media increases their visibility. It reaches the population with relevant material more effectively, and it allows for the possibility of the information going viral," says Dr. McKinney.

Kierstan Boyd, director of patient education at the AAO, explains the difference between the content featured in the product line and on EyeSmart, "The website content is designed for the person who is doing their research either prior to or after an office visit, and the products are meant to be given to the patient when they've been given a diagnosis, or if they know they're going to need a certain treatment.

"With regard to accessibility of our content, there are a couple of things that we address. We write our content to be compliant with health literacy standards," says Ms. Boyd. Health literacy standards are set by the Plain Language Action and Information Network through the Federal Plain Language Guidelines. These guidelines were built on the Plain Act of 2010, which established clearly written government documents to enhance citizen access to information and services.

Dr. McKinney explains further, "The reading literacy rate in the U.S. is rather low and simple printed materials don't get to every patient. We use a health literacy process to make sure our materials are written at an eighth-grade level, given that the average health literacy level in the U.S. is at that level. There are still some people who aren't going to grasp what they need to, even from our written materials. So, if you can supplement with video or audio, that really helps the retention rate."

Rendia

Video-based media has been proven to be an effective educational tool in ophthalmology, and it can help boost patient satisfaction.[1] Rendia offers three subscription packages that allow the user to access a library of videos and graphics for their website, waiting room and/or exam room. For physicians who want all three packages or a custom package, Rendia provides consultations and quotes.

This article has no commercial sponsorship.

Dr. McKinney is the chair of American Academy of Ophthalmology's Patient Education Committee. **Ms. Boyd** is the director of patient education at the American Academy of Ophthalmology. **Dr. Lord** is the chief editor for Eye Handbook and Eye Patient. **Dr. Meier** has no financial interests to disclose.

"We use Rendia in several different ways. When somebody schedules a cataract visit, we get their email and send them a playlist of videos about cataract surgery and the different lenses," says Edward Meier, MD, ophthalmologist at the Cincinnati Eye Institute. "When someone comes in for their cataract evaluation, we have an educator who patients meet with first. They show patients the same playlist of videos describing cataract surgery. We find reinforcement is key to truly educating patients on their choices. Our educator will also use the Outcome Simulator to give patients a view of what their vision might look like with the different lens options."

According to Dr. Meier, the Cincinnati Eye Institute uses all three Rendia packages. Although the institute's IT manager handles the waiting room and website graphics, Dr. Meier is familiar with Rendia's exam room capabilities. "I use Exam Mode when I'm trying to explain something where the patient really needs to understand the eye's anatomy," he says. "Narrow-angle glaucoma is a very common condition that I would use Rendia to explain. It shows what the condition is, how it can cause a narrow angle glaucoma attack, and how a peripheral iridotomy helps to treat the condition."

Dr. Meier says he appreciates Rendia's organization of content and ease-of-use. "When you're using it in Exam Mode, it's broken up into anatomic features, disease processes, and treatments," he explains. "If a patient asked what a cataract is, you could look under diseases, click on 'Cataracts' and it immediately shows the lens of the eye going from clear to yellow-cloudy. If they say, 'What is cataract surgery?' Then you can hit the button that shows the patient how the old lens is coming out and a new one is going in. It's very easy to use in Exam Mode."

All the packages Rendia offers start at $199 a month, while the Full Suite package, which includes website, waiting room and exam room accessibility, is priced at $249 a month. The Website package includes more than 1,000 videos accessible to embed online or post onto social media. Physicians can also send videos to patients, but they can't communicate directly with patients through Rendia since it isn't HIPAA-compliant. The Waiting Room package allows the user to customize video playlists for the waiting-room screen. Lastly, the Exam Room package provides the user with the aforementioned Outcome Simulator and Exam Mode, in addition to 3D anatomy visuals. Physicians who own a tablet can use the Exam Room features with a stylus to better write and highlight notes in Rendia.

Eye Handbook/Eye Patient

After the original iPhone was released, Ken Lord, MD, and Vinay Shah, MD, brought together a team of developers – Cloud Nine Development – to design an app for ophthalmologists and optometrists. Eye Handbook (EHB) features eye tests, calculators, ophthalmic codes, media and online forums to assist eye care professionals with basic day-to-day operations. Years after the development team launched EHB, the team decided to create an app for ophthalmic patients.

"We realized that there was a need to develop a comprehensive app that was more patient facing. Not only are apps in front of a patient every day, but there was a clear need to develop something that was more than one little bite," says Dr. Lord, an ophthalmologist and chief editor for EHB. "I think there's a lot of apps in the store that target eye patients, but we felt like we were in the best position to build a comprehensive one that met many needs."

Cloud Nine Development

Side-by-side comparison of EHB (left) and Eye Patient (right). Physicians can register on each app to communicate with other physicians and notify their patients about upcoming appointments.

Eye Patient is Cloud Nine's latest app that's equipped with features similar to EHB. "So, the goal of Eye Patient is fourfold: vision monitoring; patient education; physician connection; and treatment adherence. Those four tenets are kind of the goals of Eye Patient and what we're trying to achieve," says Dr. Lord. "Every few months we come up with another feature that could be useful not only to patients but for doctors to provide to their patients, and if you go through it, you can see there's a lot of different functionalities."

The four tenets refer to the key features in the app. Eye Patient offers vision tests to users to ensure vision monitoring, and a library of definitions, articles, videos and images make up the patient education aspect of the app. If a user is struggling to find a physician online, then they can search for one using the Eye Doctor Directory. After visiting with a doctor, the user might receive a prescription or a follow-up appointment. In that case, registered users can store their vision and/or medicine prescription in the app and set appointment reminders.

Physicians around the world can register to join the Eye Doctor Directory through the physician-facing Eye Patient website. Physicians and patients can take advantage of the different simulation tools by trying on new glasses, selecting an IOL or taking a vision test. However, Cloud Nine added a disclaimer to both apps stating that the tests aren't FDA approved and results shouldn't substitute a doctor's diagnosis. Clinical discretion is advised.

"A number of things on the road map: we're always trying to get a little more user-friendly. I mean, you have a ton of information you're trying to deliver onto this little, tiny screen," notes

Dr. Lord. "Also, we want to make it so patients who don't have great vision can navigate and get the same benefit out of the app that people who do have normal vision get. As physician developers we always look for improvements to help the doctor and the patient."

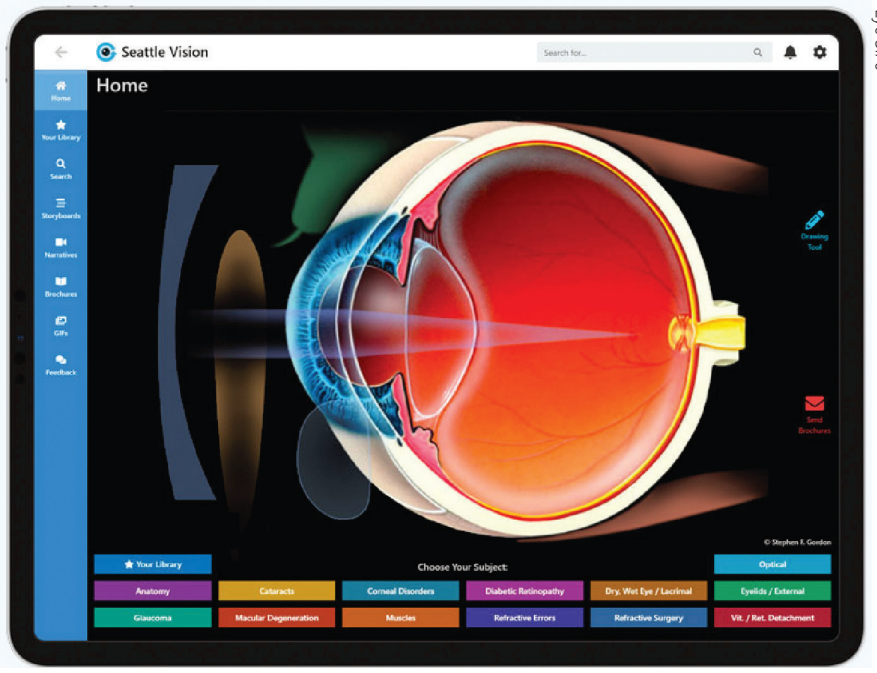
Eye GIFs

Art enthusiasts who are familiar with the work of medical artist Stephen F. Gordon will appreciate this program. Eye GIFs was created to catalogue animated visual aids for eye-care professionals based off of the conceptual images from Gordon's Eye Flip Charts. As an online resource, Eye GIFs provides digital content such as storyboards, brochures, narratives and animated GIFs.

According to the app, Eye GIFs' storyboards are collections of related GIFs that assist with patient consultations. Each animation can be added or removed to a physician's personal Eye GIFs library, and offices can embed the clips onto their website. Storyboards come with drawing and editing tools to allow the user to annotate and edit content. For patients with hearing issues, closed captions can be toggled on and off as well as edited to meet the patient's needs.

Storyboards go hand-in-hand with brochures. When presenting a storyboard, physicians can access an associated brochure to read more about a treatment or disease. Brochures can also be edited and embedded onto a website. If a physician needs to communicate the material to a patient, then they have the options to either send an email or text that includes the brochure. Also, Eye GIFs provides downloadable QR codes as another way to present their brochures to patients.

Narratives are meant to be shown to patients in the waiting room. Patients can access associated brochures and storyboards in correspondence to the narrative. This tool is used to explain high-level concepts to patients through a narrator and text captions.



Eye GIFs

"Your Library" can be accessed through the Eye GIFs menu. Here is where physicians can store animations to later present to their patients. Physicans can access this feature online and in the app.

Physicians are able to edit the captions and animations shown during the narrative depending on what concepts they determine are necessary to show their patient.

There are three subscription plans to choose from: Solo Doctor; Solo Practice; and Group Practice. The Solo Doctor plan is priced at $9.99 a month, the Solo Practice plan is priced at $19.99 a month, and the Group Plan is priced at $29.99 a month. Each plan includes access to the entire library of animated GIFs, but other features are limited depending on which plan the user chooses. The Solo Doctor plan doesn't allow the user to embed videos onto their website, nor does it allow them to access brochures. The Solo Practice plan allows up to 10 user accounts to embed videos and access brochures. The Group Practice plan provides a broader range of usability by allowing a single sign-on and unlimited user accounts.

ViewMedica

As stated previously in the article, video-based media is an effective educational tool, and ViewMedica has an extensive library of digital media for health-care professionals. Although the program doesn't focus solely on ophthalmology, they provide several videos on care, management and ophthalmic conditions.

ViewMedica's On-Demand service features content specifically for a health-care website or the exam room. Physicians can select from a catalogue of medical videos and topics to support their practice, and then they have the option to present those resources in a multitude of ways. One of the ways physicians can use the videos is by downloading them and presenting them on the ViewMedica app. The app and desktop program work similarly in that physicians can access ViewMedica's library and their downloaded content. By using Markup Mode, physicians can draw, highlight and add text labels to videos online or in the app.

Another service ViewMedica offers is VMcast, a content creation tool for the waiting room. This service allows physicians the opportunity to create their own unique loop of slides for

their waiting room. Physicians can add themes, QR codes, social media account information, weather updates and more to create a personalized channel to better inform and educate their patients. If users don't want to implement videos from the ViewMedica library, then they can download accessible content from the CDC and other health centers to boost their waiting room channel's watchability. For pediatric ophthalmologists, ViewMedica partnered with Health Nuts Media, a producer of animated health content, to provide engaging pediatric cartoons.

ViewMedica offers both services in various plans. Depending on the plan, ViewMedica will limit the number of videos a user can download for patient education. The cheapest plans for On-Demand and VMcast cost $85 a month and limits the user to 25 videos. If physicians need access to the entire library of ViewMedica videos, then they can opt into the all-inclusive plan that provides them access to over 2,000 videos, which costs $1,665 a month.

iHealthSpot

There are clinics and offices across the country that have used iHealthSpot Interactive to develop their websites. iHealthSpot is a medical web developer and health-care marketing company that provides patient education materials during the web design process. Instead of using a third-party program to embed content, physicians can work with iHealthSpot to embed content prior to launching their website. Their patient education content covers an extensive field of medical practices, including ophthalmology and optometry. All their content is generated and edited by a medical editorial team at iHealthSpot as well as the Health on the Net Foundation, a non-profit promoting reliable and transparent health information. These patient education materials aren't standalone products and can't be accessed without partnering with iHealthSpot for website development or marketing.

"[The best way to educate patients with materials is] by giving it at an appropriate level of understanding, so at a health-literate level," says Dr. McKinney. "You should use the method of asking the patient to repeat back to you what you've said or what they've read to confirm that they actually understand. Also, provide that information via more than one method, so provide verbal communication, but also hand them written communication, or give them a link to a video that they can watch online or provide them with access through your website." ◀

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ADVERTISER INDEX

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EDITED BY COLLIN ROZANSKI, MD
WILLS EYE RESIDENT CASE REPORT

A 63-year-old with vision loss presents at Wills Eye Hospital.

ERIK MASSENZIO, MD, CHRISTIAN PONDER, MD, AND MARK MOSTER, MD
PHILADELPHIA

Presentation

A 63-year-old Caucasian female is referred to the Wills Eye Emergency Room after six days of vision loss in her right eye. She complains of pain with right eye movements, and notes she had a headache two weeks ago which has since resolved. She denies diplopia, jaw claudication, weight loss, scalp tenderness, polymyalgia, systemic neurologic symptoms or snoring.

History

The patient had no significant past ocular history or past medical history. Past surgical history was significant for right rotator cuff repair three years ago. Family history was non-contributory. The patient had never smoked tobacco and didn't use alcohol. The patient wasn't on any medications.

Examination

Ocular examination demonstrated visual acuity of 20/400 in the right eye and 20/30 in the left. A 2+ APD was noted in the right eye without anisocoria. Intraocular pressure was 20 and 19 mmHg in the right and left eyes, respectively. Confrontation visual fields were full in both eyes, but Amsler grid testing revealed a central scotoma in the right eye. Extraocular motility was full bilaterally. Color plates were 4/8 in the right eye, and 8/8 in the left. Anterior segment examination was notable for 1+ nuclear sclerosis bilaterally.

Dilated fundus examination of the right eye demonstrated 360 degrees of blurred disc margins without obscuration of vessels, hemorrhage or pallor. The left optic disc was sharp without edema, pallor or hemorrhage. There was no vitritis noted in either eye.

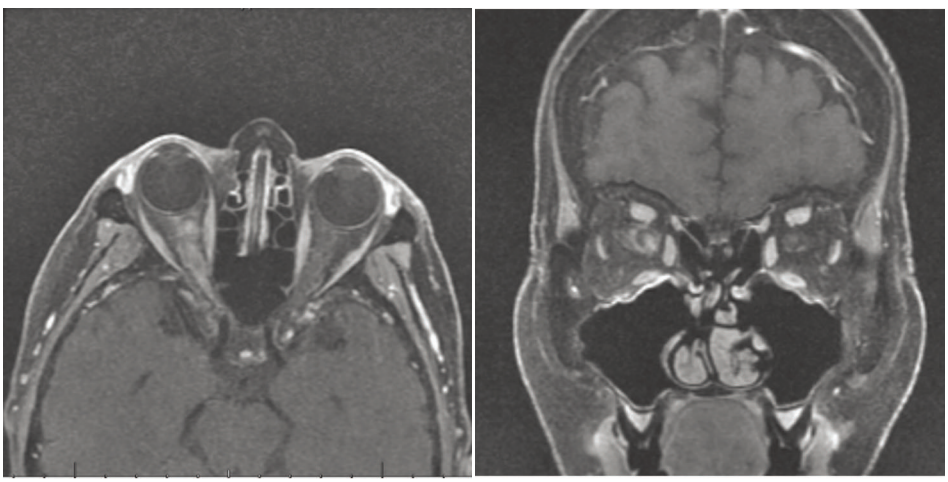

Figure 1. Magnetic resonance imaging revealing long segment hyperintense T1 signal abnormality and enhancement of the intraorbital right optic nerve and optic nerve sheath, characteristic of MOG antibody associated optic neuritis.

What's your diagnosis? What work-up would you pursue? The diagnosis appears on the opposite page.

Work-up, Diagnosis and Treatment

MRI brain and orbits with and without contrast revealed long segment hyperintense T2 signal abnormality and enhancement of the intraorbital right optic nerve *(Figure 1)*. The patient's symptoms, exam findings and imaging supported the diagnosis of acute optic neuritis of the right optic nerve. The differential diagnosis of this patient included ischemic optic neuropathy, inflammatory, infectious, and neoplastic etiologies. Vascular etiologies include giant cell arteritis, Sjögren's syndrome. Inflammatory etiologies include multiple sclerosis-associated optic neuritis, neuromyelitis optica and myelin oligodendrocyte glycoprotein (MOG) antibody disease. Infectious etiologies include *Bartonella*, Lyme, tuberculosis, syphilis, and HSV or VZV.

The lab work-up for targeted vascular, autoimmune, infectious and infiltrative diseases (ESR, CRP, Platelets, ACE, Quant-Gold, Syphilis, Lyme, *Bartonella*) were negative, and MOG and NMO were pending.

The patient was admitted to Wills Eye Hospital for intravenous, pulse-dose steroids. During admission, her visual acuity improved from 20/400 to 20/30, and her color plates improved from 4/8 to 7/8. She was discharged on an oral prednisone taper. Her MRI C/T spine showed no spinal lesions. She returned to clinic a week later, and her visual acuity and improved to 20/25, and her color plates were 8/8. Optical coherence tomography and B-scan ultrasound images were obtained. OCT demonstrated right-sided optic disc edema with decreased thickening of the retinal nerve fiber layer in the right eye *(Figure 2)*. Her Humphrey visual field testing was normal in the left eye and revealed a small residual paracentral scotoma in the right eye. Her MOG testing returned positive 1:40, and her NMO was negative. She has continued to improve on subsequent follow-up visits without recurrence over four months.

Discussion

Inflammatory demyelinating optic neuritis can result from three main diseases: multiple sclerosis; NMO; and MOG antibody disease. These diseases are distinguished by the presence of specific autoantibodies in the serum that target different antigens in the central nervous system. Anti-aquaporin-4 (AQP4) antibodies are characteristic of NMO, while anti-MOG antibodies are specific for MOG antibody disease. Anti-AQP4 antibodies have the capacity to induce demyelination by themselves, whereas anti-MOG antibodies require additional factors to cause tissue damage.[1] This is one reason why it's believed that anti-AQP4 positivity is associated with disease activity, while anti-MOG antibody levels persist even after the resolution of the acute phase.[2,3]

MOG antibody disease manifests as demyelinating lesions in the cerebral hemispheres, brainstem and spinal cord that sometimes resemble those of multiple sclerosis. Optic neuritis in MOG is more likely to affect both eyes simultaneously and present with more profound visual loss than MS-associated optic neuritis. Ophthalmoscopic examination in MOG reveals optic disc swelling more frequently than in MS. Moreover, magnetic resonance imaging in MOG antibody disease shows longer seg-

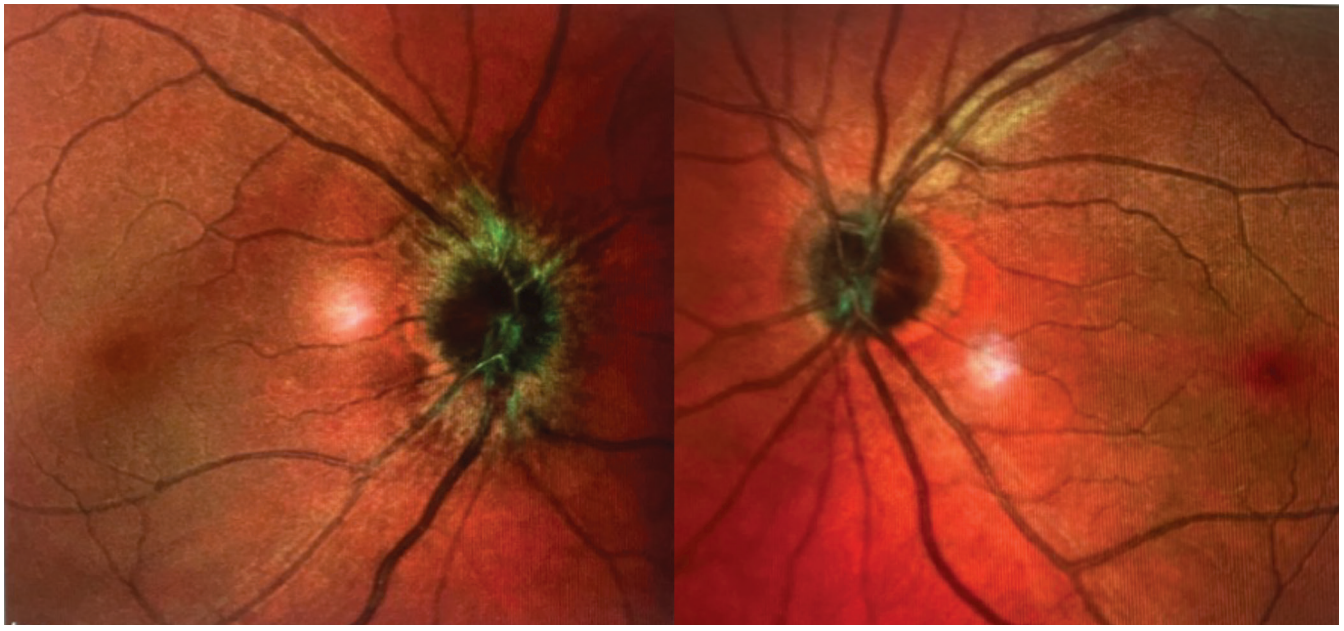

Figure 2. En face multicolor optical coherence tomography revealing optic disc edema of the right eye.

ments of optic nerve enhancement anterior to the optic chiasm, whereas multiple sclerosis typically presents with a short segment of retrobulbar enhancement.[4] Despite the more severe initial presentation of optic neuritis in MOG compared to MS, both conditions generally have favorable visual outcomes and respond well to steroids.[5] This contrasts with NMO, which is associated with a poorer visual prognosis.[6]

The patient in this case had several features suggestive of MOG antibody disease. She didn't match the typical age profile for optic neuritis associated with multiple sclerosis. The patient's visual acuity was 20/400, which is worse than the usual range for optic neuritis associated with MS. The patient exhibited optic disc swelling, perineural enhancement and a long segment of optic nerve enhancement on MRI. Furthermore, the patient experienced a prodromal headache preceding the onset of optic neuritis, which has been reported in up to half of cases of MOG optic neuritis.[7] In cases of optic neuritis that deviate from the common presentation, it is essential to consider the differential diagnosis of MOG or NMO and to monitor visual acuity closely in case plasma exchange is required in addition to high-dose corticosteroid therapy.[8,9] ◀

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(Continued from p. 27)

Refractive Lens Exchange

keratoectasia and I was looking for a visual-quality solution, we can use a small aperture lens to help correct some of the irregular astigmatism and it works almost like a therapeutic clear lens surgery. Not only can it help their lifestyle, but helps treat some of the pathology that's there. Furthermore, if somebody has been using Vuity eyedrops or pupil modulating eyedrops and really likes the small aperture vision and is used to that but is tired of taking the drops, the IC-8 could be considered. I would do a modified monovision with a monofocal in one eye and a small aperture lens in the other eye."

Patients may ask what their options are if their eyes continue to change. "I tend to tell them that the main thing that changes over time is the eye's natural lens as it's developing a cataract," says Dr. Wiley. "The fact that we're removing their natural lens typically removes the main variable that was changing over time. While there's a chance that you miss the target, that would show itself right away—within the first month or so—but if they're pretty good within that first month, chances are that the vision is going to maintain over time."

Dr. Hura considers a few factors in the event of a refractive miss. "If a patient has a virgin cornea—they've never had laser refractive surgery—and there's a refractive miss after RLE, it can be corrected with LASIK, SMILE or PRK," he says. "But if that refractive miss is significant and noted immediately after surgery, I feel the best way to correct it is to address the issue at the source. This might mean IOL exchange for a different power lens or rotating a toric IOL to the intended axis if postoperative rotation has taken place."

The Keys to Success

Ultimately, a surgeon's success with RLE comes down to patient selection and knowledge. "The surgeon really needs to understand the lenses inside and out," says Dr. Hura. "It's not enough to know that multifocal lenses give glasses-free vision, you really have to understand the nuances of the optics of all the lens implants because there's no perfect lens and each one has trade-offs. It also goes without saying, but you have to be a good surgeon and get good surgical results because patients are paying out of pocket for this premium surgery, it's all elective. You have to be able to deliver the desired outcome." ◀

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ABOUT THE AUTHOR

Dr. Hura is a consultant and speaker for Alcon, Rayner, Zeiss, Staar and AcuFocus/B + L. **Dr. Wiley** is a consultant for Alcon, Johnson & Johnson, Staar and Zeiss.

VABYSMO™
faricimab-svoa injection 6 mg

VABYSMO™ (faricimab-svoa) injection, for intravitreal use

This is a brief summary. Before prescribing, please refer to the full Prescribing Information

1 INDICATIONS AND USAGE

VABYSMO is a vascular endothelial growth factor (VEGF) and angiopoietin 2 (Ang-2) inhibitor indicated for the treatment of patients with:

1.1 Neovascular (wet) Age-Related Macular Degeneration (nAMD)

1.2 Diabetic Macular Edema (DME)

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

VABYSMO is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

VABYSMO is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

VABYSMO is contraindicated in patients with known hypersensitivity to faricimab or any of the excipients in VABYSMO. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, erythema, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections have been associated with endophthalmitis and retinal detachments *[see Adverse Reactions (6.1)]*. Proper aseptic injection techniques must always be used when administering VABYSMO. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management *[see Dosage and Administration (2.6) and Patient Counseling Information (17)]*.

5.2 Increase in Intraocular Pressure

Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of intravitreal injection, including with VABYSMO *[see Adverse Reactions (6.1)]*. IOP and the perfusion of the optic nerve head should be monitored and managed appropriately *[see Dosage and Administration (2.6)]*.

5.3 Thromboembolic Events

Although there was a low rate of arterial thromboembolic events (ATEs) observed in the VABYSMO clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

The incidence of reported ATEs in the nAMD studies during the first year was 1% (7 out of 664) in patients treated with VABYSMO compared with 1% (6 out of 662) in patients treated with aflibercept *[see Clinical Studies (14.1)]*.

The incidence of reported ATEs in the DME studies from baseline to week 100 was 5% (64 out of 1,262) in patients treated with VABYSMO compared with 5% (32 out of 625) in patients treated with aflibercept *[see Clinical Studies (14.2)]*.

6 ADVERSE REACTIONS

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

- Hypersensitivity *[see Contraindications (4)]*
- 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 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 other clinical trials of the same or another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to VABYSMO in 1,926 patients, which constituted the safety population in four Phase 3 studies *[see Clinical Studies (14.1, 14.2)]*.

Table 1: Common Adverse Reactions (≥ 1%)

Adverse Reactions	VABYSMO		Active Control (aflibercept)	
	AMD N=664	DME N=1,262	AMD N=662	DME N=625
Cataract	3%	15%	2%	12%
Conjunctival hemorrhage	7%	8%	8%	7%
Vitreous floaters	3%	4%	2%	3%
Retinal pigment epithelial tear[a]	3%		1%	
Intraocular pressure increased	3%	4%	2%	3%
Eye pain	3%	3%	3%	3%
Intraocular inflammation[b]	2%	1%	1%	1%
Eye irritation	1%	< 1%	< 1%	1%
Lacrimation increased	1%	1%	1%	< 1%
Ocular discomfort	1%	1%	< 1%	< 1%

[a]AMD only
[b]Including iridocyclitis, iritis, uveitis, vitritis

Less common adverse reactions reported in < 1% of the patients treated with VABYSMO were corneal abrasion, eye pruritus, ocular hyperemia, blurred vision, sensation of foreign body, endophthalmitis, conjunctival hyperaemia, visual acuity reduced, visual acuity reduced transiently, vitreous hemorrhage, retinal tear and rhegmatogenous retinal detachment.

6.2 Immunogenicity

The immunogenicity of VABYSMO was evaluated in plasma samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to VABYSMO 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 VABYSMO with the incidence of antibodies to other products may be misleading.

There is a potential for an immune response in patients treated with VABYSMO. In the nAMD and DME studies, the pre-treatment incidence of anti-faricimab antibodies was approximately 1.8% and 0.8%, respectively. After initiation of dosing, anti-faricimab antibodies were detected in approximately 10.4% and 8.4% of patients with nAMD and DME respectively, treated with VABYSMO across studies and across treatment groups. As with all therapeutic proteins, there is a potential for immunogenicity with VABYSMO.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of VABYSMO administration in pregnant women.

Administration of VABYSMO to pregnant monkeys throughout the period of organogenesis resulted in an increased incidence of abortions at intravenous (IV) doses 158 times the human exposure (based on C_{max}) of the maximum recommended human dose *[see Animal Data]*. Based on the mechanism of action of VEGF and Ang-2 inhibitors, there is a potential risk to female reproductive capacity, and to embryo-fetal development. VABYSMO should not be used during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus.

All pregnancies have a background risk of birth defect, loss, and 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 is 2%-4% and of miscarriage is 15%-20% of clinically recognized pregnancies.

Data

Animal Data

An embryo fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received 5 weekly IV injections of VABYSMO starting on day 20 of gestation at 1 or 3 mg/kg. A non-dose dependent increase in pregnancy loss (abortions) was observed at both doses evaluated. Serum exposure (C_{max}) in pregnant monkeys at the low dose of 1 mg/kg was 158 times the human exposure at the maximum recommended intravitreal dose of 6 mg once every 4 weeks. A no observed adverse effect level (NOAEL) was not identified in this study.

8.2 Lactation

Risk Summary

There is no information regarding the presence of faricimab in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Many drugs are transferred in human milk with the potential for absorption and adverse reactions in the breastfed child.

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

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 following the last dose of VABYSMO.

Infertility

No studies on the effects of faricimab on human fertility have been conducted and it is not known whether faricimab can affect reproduction capacity. Based on the mechanism of action, treatment with VABYSMO may pose a risk to reproductive capacity.

8.4 Pediatric Use

The safety and efficacy of VABYSMO in pediatric patients have not been established.

8.5 Geriatric Use

In the four clinical studies, approximately 60% (1,149/1,929) of patients randomized to treatment with VABYSMO were ≥ 65 years of age. No significant differences in efficacy or safety of faricimab were seen with increasing age in these studies. No dose adjustment is required in patients 65 years and above.

17 PATIENT COUNSELING INFORMATION

Advise patients that in the days following VABYSMO administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the patient to seek immediate care from an ophthalmologist *[see Warnings and Precautions (5)]*.

Patients may experience temporary visual disturbances after an intravitreal injection with VABYSMO and the associated eye examinations *[see Adverse Reactions (6)]*. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

VABYSMO™ [faricimab-svoa]
Manufactured by:
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U.S. License No.: 1048

M-US-00013249(v2.0) 2/23

Start with the power of 2

VABYSMO™ (faricimab-svoa) is the only treatment that delivers powerful **first-line efficacy** with **1–4 month dosing**[1-5*†]

*Primary endpoint of non-inferiority vs aflibercept was defined as the mean change from baseline in BCVA (measured by the ETDRS letter score) to 1 year (average of weeks 40, 44, and 48 in nAMD and weeks 48, 52, and 56 in DME) and was tested for non-inferiority using a margin of 4 letters.[1]
†After 4 or 6 monthly loading doses.[1] Please see below for more information.
‡Verana Health data from Q1–Q4 2022.[6]

Discover 2 years of DME data at vabysmo-hcp.com/start

†Dosing Information:
DME dosing: at least 4 monthly loading doses followed by extensions ≤4 weeks or reductions ≤8 weeks based on OCT and visual acuity evaluations OR 6 monthly loading doses followed by Q8W. Q4W dosing may be needed (no added benefit). nAMD dosing: 4 monthly loading doses followed by OCT and visual acuity evaluations 8 and 12 weeks later to inform Q16W (weeks 28 and 44), Q12W (weeks 24, 36, and 48), Q8W (weeks 20, 28, 36, and 44), or Q4W (no added benefit) dosing.[1]

INDICATIONS

VABYSMO (faricimab-svoa) is a vascular endothelial growth factor (VEGF) inhibitor and angiopoietin-2 (Ang-2) inhibitor indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (nAMD) and Diabetic Macular Edema (DME).

IMPORTANT SAFETY INFORMATION

Contraindications

VABYSMO is contraindicated in patients with ocular or periocular infection, in patients with active intraocular inflammation, and in patients with known hypersensitivity to faricimab or any of the excipients in VABYSMO. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, erythema, or severe intraocular inflammation.

Warnings and Precautions

Endophthalmitis and Retinal Detachments
Intravitreal injections have been associated with endophthalmitis and retinal detachments. Proper aseptic injection techniques must always be used when administering VABYSMO. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management.

Increase in Intraocular Pressure
Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of intravitreal injection, including with VABYSMO. IOP and the perfusion of the optic nerve head should be monitored and managed appropriately.

Thromboembolic Events
Although there was a low rate of arterial thromboembolic events (ATEs) observed in the VABYSMO clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

The incidence of reported ATEs in the nAMD studies during the first year was 1% (7 out of 664) in patients treated with VABYSMO compared with 1% (6 out of 662) in patients treated with aflibercept.

The incidence of reported ATEs in the DME studies from baseline to week 100 was 5% (64 out of 1,262) in patients treated with VABYSMO compared with 5% (32 out of 625) in patients treated with aflibercept.

Adverse Reactions
The most common adverse reactions (≥5%) reported in patients receiving VABYSMO were cataract (15%) and conjunctival hemorrhage (8%).

Pregnancy, Lactation, Females and Males of Reproductive Potential
Based on the mechanism of action of VEGF and Ang-2 inhibitors, there is a potential risk to female reproductive capacity, and to embryo-fetal development. VABYSMO should not be used during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VABYSMO and any potential adverse effects on the breastfed child from VABYSMO. Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment and for at least 3 months following the last dose of VABYSMO.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.

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

References: 1. VABYSMO [package insert]. South San Francisco, CA: Genentech, Inc; 2023. **2.** Beovu® (brolucizumab-dbll) injection [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2022. **3.** Eylea® (aflibercept) [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2022. **4.** LUCENTIS® (ranibizumab) [package insert]. South San Francisco, CA: Genentech, Inc; 2018. **5.** SUSVIMO™ (ranibizumab injection) [package insert]. South San Francisco, CA: Genentech, Inc; 2022. **6.** Data on file. South San Francisco, CA: Genentech, Inc.

BCVA=best corrected visual acuity; ETDRS=Early Treatment Diabetic Retinopathy Study; OCT=optical coherence tomography; Q4W=every 4 weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks.

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