Wills Eye Resident Series: A patient presents with vision problems after refractive surgery, *p .77*

REVIEW® of OPHTHALMOLOGY

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RE-ENERGIZE YOUR PRACTICE

New tools, techniques and ways of thinking that can snap you out of a pandemic stupor.

Not an actual patient.

*In some patients with continued daily use. One drop in each eye, twice daily (approximately 12 hours apart).[3]

†Xiidra is an LFA-1 antagonist for the treatment of dry eye disease. Pivotal trial data: The safety and efficacy of Xiidra were assessed in four 12-week, randomized, multicenter, double-masked, vehicle-controlled studies (N=2133). Patients were dosed twice daily. Use of artificial tears was not allowed during the studies. The study end points included assessment of signs (based on Inferior fluorescein Corneal Staining Score [ICSS] on a scale of 0 to 4) and symptoms (based on patient-reported Eye Dryness Score [EDS] on a visual analogue scale of 0 to 100).[3] A larger reduction in EDS favoring Xiidra was observed in all studies at day 42 and day 84. Xiidra reduced symptoms of eye dryness at 2 weeks (based on EDS) compared to vehicle in 2 out of 4 clinical trials. Effects on signs of dry eye disease ICSS (on a scale from 0-4; 0=no staining; 4=coalescent) was recorded at each study visit. At day 84, a larger reduction in inferior corneal staining favoring Xiidra was observed in 3 of the 4 studies.[3]

Indication

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

Important Safety Information

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

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

Important Safety Information (cont)

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

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

References: 1. US Food and Drug Administration. Code of Federal Regulations, Title 21, Volume 5 (21CFR349). Accessed April 17, 2020. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=349&showFR=1 **2.** Jones L, Downie LE, Korb D, et al. TFOS DEWS II Management and Therapy Report. *Ocul Surf.* 2017;15(3):575-628. **3.** Xiidra [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; June 2020.

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

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

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

6 ADVERSE REACTIONS

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

- Hypersensitivity *[see Contraindications (4)]*

6.1 Clinical Trials Experience

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

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

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

6.2 Postmarketing Experience

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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NEWS

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Glaucoma Study Identifies New Genetic Markers

In the largest study of its kind ever completed, researchers from Australia, the United Kingdom, The Netherlands, Finland, Germany, Singapore, Japan, Nigeria, Ghana, South Africa, Switzerland, Tanzania and the United States—led by principal investigator, Janey L. Wiggs, MD, PhD, associate chief of ophthalmology clinical research at Mass Eye and Ear, and the Paul Austin Chandler Professor of Ophthalmology and vice chair of clinical research at Harvard Medical School—compared the genes of 34,179 people with glaucoma to the genes of 349,321 control subjects. Their goal was to identify previously unknown gene loci (specific locations on a given gene) associated with the disease. Primary open-angle glaucoma is highly inheritable, making genetic variants a valuable treatment target.

This study, which included 10 times more glaucoma cases and controls than previous studies conducted by the group, uncovered 44 new genetic variants present only in the subjects with glaucoma. It also confirmed 83 genetic loci that had previously been identified.

One of the shortcomings of similar previous studies was a focus on people of European ancestry. Because of that narrow focus, it remained unclear whether the findings of those studies applied to other races—a notable irony given that rates of glaucoma are highest among people of African-American and Asian ancestry. For the first time in a study of this kind, the participants included members of all three groups, allowing the study to determine whether the same genetic variants appear in all groups.

Remarkably, the data revealed that the majority of genetic variations associated with glaucoma were present in all three groups. "Seventy to 80 percent of the genetic associations had similar effects across all ancestries," notes Dr. Wiggs. Asked whether the researchers believe the 20-percent difference between the groups might account for the difference in their disease rates and severities, Dr. Wiggs indicates it may be too early to know the answer. "The genetic associations that are not the same [between groups] are of interest," she acknowledges. "This would be a fruitful area of investigation in the future."

The study authors report that in addition to revealing new potential treatment targets, the new data suggest the presence of previously unknown biological processes that may contribute to the development of the disease. "Those new processes include vascular function and development," explains Dr. Wiggs. "Blood vessels and blood flow have been thought to be important [in the development of glaucoma], but these results support a more primary role for vascular development and function in some patients. Additionally, some of the vascular-related genes, such as TEK and ANGPT1,

(Continued on p. 16)

IN BRIEF

Breaking News: Rayner RayOne EMV IOL Receives FDA Approval
At press time, Rayner announced U.S. Food and Drug Administration approval of its new RayOne "enhanced monofocal" intraocular lens, which is purported to give greater range of vision without the use of diffractive or extended-depth-of-focus optics. *(See "IOL Review: 2021 Newcomers," p. 38, for more information.)*

Visus Announces FDA Acceptance of IND for Presbyopia-correcting Eye Drop
Visus Therapeutics announced that the FDA has accepted the company's Investigational New Drug Application to proceed with the clinical development program for Brimochol, a proprietary combination of carbachol and brimonidine tartrate, designed to be a once-daily eye drop to compensate for the loss of near vision associated with presbyopia. Under this IND, Visus will initiate its planned Phase II clinical trial in the United States.

Foundation Aims to Improve Eye Care Through Education
The newly incorporated Ophthalmology Foundation, a "nonprofit organization that supports ophthalmic education to preserve and restore vision for people of all nations," is laying the groundwork to improve global eye care and ophthalmic practice, particularly in low-resource and underserved countries. Led by a global board of ophthalmologists, ophthalmology professors and industry leaders, the foundation's mission is to "create opportunities for ophthalmic education around the world."

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FIRST AND ONLY
FDA-APPROVED TREATMENT FOR THYROID EYE DISEASE

In the treatment of Thyroid Eye Disease (TED),

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

TEPEZZA is proven to[1-4]:

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

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

INDICATION

TEPEZZA is indicated for the treatment of Thyroid Eye Disease.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

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

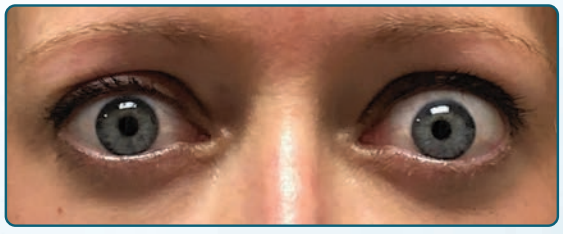
Preexisting Inflammatory Bowel Disease: TEPEZZA may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

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

TEPEZZA®
teprotumumab-trbw

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

SEE THE TEPEZZA DIFFERENCE[7*]



BASELINE
Proptosis: 19 mm OD, 20.5 mm OS

OD, oculus dexter; OS, oculus sinister.

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

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

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

TEPEZZA
83%
TEPEZZA (n=41)

vs

Placebo
10%
Placebo (n=42)

P<0.001 at Week 24

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

» See more before and after photos

Adverse Reactions

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

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

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

HORIZON

TEPEZZA™
teprotumumab-trbw

For injection, for intravenous use

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

INDICATIONS AND USAGE

TEPEZZA is indicated for the treatment of Thyroid Eye Disease.

WARNINGS AND PRECAUTIONS

Infusion Reactions

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

Exacerbation of Preexisting Inflammatory Bowel Disease

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

Hyperglycemia

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

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

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

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

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

Immunogenicity

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

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

Data

Animal Data

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

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

Contraception

Females

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

Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

Geriatric Use

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

OVERDOSAGE

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

PATIENT COUNSELING INFORMATION

Embryo-Fetal Toxicity

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

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

Infusion-Related Reactions

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

Exacerbation of Inflammatory Bowel Disease

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

Hyperglycemia

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

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HORIZON

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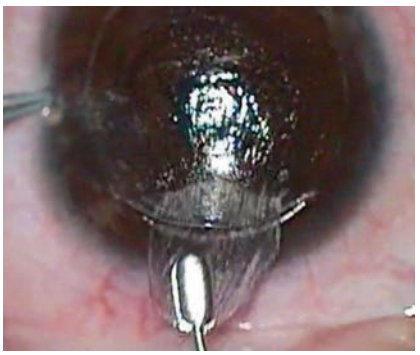

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EDITOR'S PAGE

Holding a Positive Charge

Many years ago (long enough that the internet was still known only as "that computer thing with the web pages"), a 20-something friend of mine went to buy his first car, a used Honda Accord. My friend is a reader, a researcher, and besides vetting the car for its roadworthiness, had calculated what his monthly payment would be based on a certain amount of loan interest over a certain amount of time. So, when the big moment came and he sat down with the car dealership's finance officer to sign on the dotted line, he looked at that weird, abnormally oblong auto financing contract and his brow furrowed. The monthly payment was higher than he'd calculated by $10.

After a fleeting moment of self-doubt, my friend pointed out the error. To his surprise, rather than a debate ensuing over whose loan calculations were correct, the loan officer just kind of made a half-hearted apology, opened his desk drawer, and produced a contract with the correct monthly amount. The other contract vanished into the drawer during the process, like a playing card in a sleight-of-hand trick. *We'll get the next guy.*

I think about my friend's story a lot, including over the course of the pandemic, in which—despite it being the worst crisis of our lifetime—tricks continued to be played.

Early on in the crisis, as small businesses like ophthalmology practices were faced with the prospect of laying off employees or even shutting their doors, multi-million dollar organizations like Shake Shack and the Los Angeles Lakers were shouldering the small fry out of the way and scooping up the Paycheck Protection Plan loans for themselves. Only when watchdogs called them on it did they reach back into that desk drawer and return the money.

More recently, AstraZeneca, who no doubt assiduously followed every patient and *p* value in its study of its coronavirus vaccine, cited data that stated the vaccine was 79 percent effective. However, when the data-monitoring board questioned the "completeness" of the data in a message to the U.S. government, AZ reached into the old desk drawer and produced the more applicable, and slightly less impressive, data.

Amid a pandemic, when spirits are already low, it might be easy to focus on such negative tricks and traps, but I won't. Instead, let's focus on the positive stories: The ophthalmologists who reconfigured their practices with the help of PPP loans to enable their employees to have an income and their patients to receive care; and the clinicians who re-engineered the way they examined patients—moving screenings to the parking lots and patients' homes via telemedicine. They stared into the gaping maw of the pandemic and survived.

Imagine what we could accomplish if we eliminated all the negative impulses and focused solely on the positive? If we didn't see our fellow human as a mark to be duped but instead someone worthy of respect?

We might keep that desk drawer closed forever.

— Walter C. Bethke
Editor in Chief

Alcon

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Glaucoma Study Identifies Genetic Markers

(Continued from p. 5)

are needed for Schlemm's canal development, which is known to be a modified lymph vessel.

"A second interesting area is ocular development," she says. "We've known that mutation in the genes needed for ocular development can cause severe forms of childhood glaucoma, but several of these genes also appear to be able to contribute to adult-onset forms of glaucoma such as POAG."

One possible use of this kind of genetic data would be to identify associations between specific genes and different types of glaucoma. "This was a study of POAG only," notes Dr. Wiggs. "Other types of glaucoma weren't included. However, we're investigating associations with the high-tension and low-tension subgroups in the study, as well as some glaucoma-related ocular traits, such as IOP and cup-to-disc ratio." Dr. Wiggs says it may take some time to uncover the purpose of the newly discovered genetic loci. "For some of these genetic associations we have some insight into mechanism and function," she notes. "However, for the most part the role of these genes in disease pathogenesis is still unknown."

In addition to suggesting new targets for therapeutic intervention, this type of data has been used to develop polygenic risk scores, making it possible to estimate the likelihood that someone will manifest the disease. Adding the new list of genetic loci should make it possible to increase the specificity of that risk score significantly. The study authors are planning additional studies to see how individuals with higher risk scores, calculated with the addition of the new data, do in the real world. Hopefully this will provide guidance for clinicians in terms of deciding whether more proactive treatment is called for.

Of course, it would be exciting if this information were able to lead to direct genetic manipulation via current techniques such as CRISPR, preventing the disease from occurring or effecting a cure. However, Dr. Wiggs urges patience. "Some of these genes may be targets for new therapies—even gene-based therapies using approaches such as CRISPR/Cas9," she says. "However, research using animal and cell models would be needed to demonstrate efficacy and safety. Furthermore, POAG is genetically complex, so a single gene isn't responsible for the majority of these cases. That means that treatment of a single gene would be unlikely to be curative for all patients."

BCBS Changes Eylea Stance

After pressure from the American Academy of Ophthalmology, Blue Cross/Blue Shield has decided to continue to cover treatment with aflibercept (Eylea, Regeneron) for patients who have lost three lines of vision.

Initially, BCBS's policy was to deny coverage to such patients, which stirred the AAO and its members into action.

"Blue Cross Blue Shield has based its exclusion of Eylea treatment on two studies that were conducted to determine the drug's efficacy prior to approval from the FDA," the AAO said in a statement when the original policy was announced. "The insurer ignores the hundreds of studies completed after FDA approval that reflect the results seen in real-world ophthalmology practice and that are the basis for the treatment of patients." ◀

PAUL M. LARSON, MBA, MMSC, COMT, CDE, CPC, CPMA

MEDICARE Q&A

The 2021 E/M Data Area—Updated Already!

It didn't take long for there to be an update to the new 2021 coding regulations: On March 9, 2021, the American Medical Association released a small update (https://www.ama-assn.org/system/files/2019-06/cpt-office-prolonged-svs-code-changes.pdf) that affected the coding for the brand-new, outpatient, office-based 2021 Evaluation and Management (E/M) exam codes. Though many other questions about the new system remain, in this review we'll concentrate on the updates to the Data area (which refers to such things as orders for outside testing, as well as the outside tests and/or exam notes that had to be reviewed, etc.).

An Overview of the Changes

Some of the changes in the latest AMA update actually don't affect eye care, and most of these clarifications and small changes affect the Data area of the commonly used Medical Decision Making (MDM) reimbursement option. Under MDM are three areas defined by the new rules: Problems; Data; and Management, and they're equally weighted. A level of service is selected via the "two-out-of-three meet-or-exceed" principle and the lowest of these three isn't counted. Most often, Problems and Management are the two highest ones and the Data area gets dropped when determining the code level. In a few cases, however, the Data area might be important and the recent update helped clarify some early questions that arose.

As we explained in a recent installment of this column, the new rules for 992xx series exam codes only went into effect a couple of months ago. Although providers can also select a code based on the time required to treat a patient (designated as "Time" in the codes), instead of the more typical MDM route, that'll be unusual. The AMA updated the Time option for E/M 2021 as well, but the update is small. Importantly, the Eye exam codes (920xx) are unaffected.

Q What did the AMA change as it relates to the Time-based code option for E/M?

A The clarification here relates to what does not count for Time. The AMA noted the following don't count in your time calculation when coding using this option: other services that are reported separately; travel; and teaching that is general and not required for the management of a specific patient.

Example: Let's say you have 45 minutes recorded in your chart for Time on an established patient, but that calculation included some services like a billed test interpretation and some general teaching unrelated to the conditions being treated on that day. If your exam lasted 40 minutes, this would mean you could use 99215 under the new rules. However, the clarification means that if the test work and general teaching added up to 10 minutes, your actual time used for calculating the level of service is only 35 minutes, and that means only a 99214 can be used.

Q What are the changes related to categorizing the ordering of tests under the Data area when using MDM instead of time?

A The AMA notes that ordering a test doesn't count if you're doing the interpretation yourself. It appears that some people have been misinterpreting the prior version of the guidelines and felt that you could count all tests that you order when determining the level of services, even if you asked to be paid separately for them. The association notes "… The ordering and actual performance and/or interpretation of diagnostic tests/studies during a patient encounter aren't included in determining the levels of E/M services when the professional interpretation of those tests/studies is reported separately by the physician reporting the E/M service."

In essence, the AMA is emphasizing that tests you order, interpret and bill shouldn't be counted at all in the exam level determination.

This article has no commercial sponsorship.

Mr. Larson is a senior consultant at the Corcoran Consulting Group and is based in Tucson, Arizona. He can be reached at plarson@corcoranccg.com.

Q What's the AMA's determination on what constitutes 'independent interpretation' under the Data area, as opposed to a "review of test"?

A In the same area of the new document as the information covered in the question discussed above, the AMA notes, "Tests that do not require separate interpretation (e.g., tests that are results only) and are analyzed as part of MDM do not count as an independent interpretation, but may be counted as ordered or reviewed for selecting an MDM level."

This clarification means that if you're reviewing prior results of outside tests when taking care of your patient at a visit, and use those results today, that review alone doesn't constitute "independent interpretation." Instead, this review still counts as a Data element, but generally at a different (much lower) level when it's by itself. "Independent interpretation" when such a level is reached, yields the much higher moderate level under the Data area of MDM. Miscounting the test here could have raised the Data level artificially and thereby caused you to select a code that placed you at risk for overpayment.

Q Do the letters I send to the primary care doctors of my diabetic patients count as "Discussion" under the Data area of MDM so that I could have the "Moderate" level?

A It's now very clear that a one-way transfer of information doesn't meet the intent for Discussion. In the new guidance, AMA notes "Discussion requires an interactive exchange. The exchange must be direct and not through intermediaries (e.g., clinical staff or trainees). Sending chart notes or written exchanges that are within progress notes does not qualify as an interactive exchange."

In that statement, the AMA clarified that other forms of communication such as text and email between providers is allowed, but "interaction" is key. When you meet the definition of Discussion, you receive the moderate Data level, so you want to be sure you're compliant. Naturally, even if you do meet it via text or email, be sure you don't inadvertently create a HIPAA violation by including protected health information (PHI) in a non-secure mode of communication!

Q Are there any other important clarifications to the Data area?

A Yes, there is one, and it relates to what can constitute an "Independent Historian" in this area of MDM. It's already clear that getting a history from someone other than the patient counted as the "limited" level under Data. CPT Guidance had noted that an "Independent Historian" is: "An individual (e.g., parent, guardian, surrogate, spouse, witness) who provides a history in addition to a history provided by the patient who is unable to provide a complete or reliable history."

The clarification makes the point that the historian doesn't have to be physically present with the patient as long as providers obtain the information themselves on the day of the exam. Document the person you speak with in order to support this potentially higher level of Data.

Q I often get referrals from outside doctors in my glaucoma practice and they include old visual fields and OCTs of the nerve. How do I categorize them?

A Before the new guidance, you would have counted every OCT and VF individually at that visit. The clarification subtly changes this. The AMA notes, "When multiple results of the same unique test (e.g., serial blood glucose values) are compared during an E/M service, count it as one unique test." If you had two OCTs of the nerve and two visual fields, it's clear this is only two tests reviewed (not four as in the former guidance). ◀

Need the Normal Be New?

Musings on life, ophthalmology and global pandemics.

BY MARK H. BLECHER
CHIEF MEDICAL EDITOR

I'm back. There may be some of you who remember my monthly column here from decades past, usually railing at the wind, the Fates and our regulatory overlords. Interspersed were vignettes from life in a small private practice. Lest you think I had run out of screeds, life had gotten very busy. Turns out it's not so easy to build and run a practice, teach, advocate and have a home life. But I'm sure many of you already knew that.

It really was more work every year, much of it just to keep it all together. So many fingers to point. Where to start … EMR, MIPS, private equity, predatory insurance companies, reimbursement cuts ... I could go on. And just when you thought there wasn't a fresh hell to visit upon us, COVID arrived. As you all know, ophthalmology has been the most significantly impacted specialty in all of medicine. Sure, why not? Bring it on. What doesn't kill you makes you stronger—or kills you.

COVID has caused the demise of practices, careers and an entire way of life—but not for everyone. For some, life goes on as usual. For the vast majority of us, though, this past year has been beyond challenging. It's been life- and career-changing. In polling for *Review of Ophthalmology* early on in the pandemic, it became clear that private practices were more severely stressed than those in academia or private equity. Some private practices have closed, and some have been acquired under duress. The impending death of private practice seems not to have been exaggerated, but accelerated.

But let's get to the core of this lament: Is all this bad? Can't change be unexpected, painful, but, inadvertently, good? It may not be the path we thought we would take, but given our impressive skill set as ophthalmologists, can't we redirect our energies and plans in new directions? Is this kind of redirection even needed? Perhaps perseverance is the answer. Finding our way to our "new normal" may entail something new, or it may simply be a realization that what we had—what we had planned—remains our best path forward. If only we can get there.

2020 was always going to be a year of transition for me personally. I had long planned to move from high-volume, full-time private practice and managing partner to something less stressful— less Sisyphean—as I pushed the practice up that never-ending hill. Little did I know that COVID would put a huge exclamation point on my last year. In the end, I didn't change my plans: I stepped down from my practice and from full-time clinical. And after a short sabbatical this winter, I'll return to teaching, staying surgically sharp and working with industry. These are the things I've enjoyed the most.

It does pain me to see how the delivery of eye care is changing, but really, when hasn't it? So, like many of you, it's time to just put one foot in front of the other, make the best decisions possible and continue to find employment, enjoyment and gratification in the best specialty in medicine: Ophthalmology.

As we see the beginning of the end of the pandemic, I'm hoping all of you are finding your direction, whether new or established. I'll be back periodically to shake my fist at the sky, give you updates on how my new normal is working out, and commiserate when the next crisis arises.

Be safe, be well, be vaccinated. ◀

This article has no commercial sponsorship.

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

Phaco Update: Getting The Right Setting

An evidence-based, expert guide on how to go beyond what the company reps dial into your machine.

BY SEAN MCKINNEY
SENIOR EDITOR

Like many technologies today, state-of-the-art phacoemulsification machines offer more ways of using them than most users think about or, in some cases, even understand. In this practical guide, experts advise you on what you might be missing. Find out how to optimize safety and efficiency with IOP, vacuum, aspiration, phaco-tip motion, power modes, continuous irrigation, chopping, quadrant removal, polishing, viscoelastic, infusion fluidics, ultrasound, phaco burst, phaco pulse and other functions. You'll also learn strategies for avoiding and managing complications.

Beyond Routine: Uncertainty

Lisa Park, MD, an associate professor of ophthalmology at Columbia University College of Physicians and Surgeons in New York City, points out that most of her colleagues are pretty familiar with many of their phaco machines' settings, but could always learn a new trick or two.

"Every cataract surgeon knows how to use the technology of phaco, of course," acknowledges Dr. Park. "However, when it comes to the specifics of making adjustments to the settings on the machine? Surgeons typically set up parameters when they initially buy a new phaco machine. Then, because the machines and the surgeons are so good, many surgeons don't necessarily feel a need to make any changes from that point on."

To get the most out of phaco, Dr. Park recommends following the basic principle of "less is more." She notes: "Remember that the primary goal during cataract surgery is to perform nuclear disassembly efficiently, using just the right amount of phaco energy," she says. "Using too much ultrasound can result in endothelial cell loss, corneal edema and, in the worst cases, wound burn. Yet, setting the ultrasound settings too low may result in capsular bag movement and zonular stress, difficulty with disassembly and using too much irrigation fluid during needlessly long surgeries."

She notes that longitudinal energy is the traditional phaco modality. The phaco needle moves in a forward and backward motion, creating mechanical impact in a jackhammer fashion. Cavitation bubbles appear, implode and propagate energy waves, which break up the lens material. Increasing phaco power is achieved by increasing the stroke length.

Continuous, Pulse and Burst

You can also make phaco more efficient by modifying the timing or duration of ultrasound power, according to Dr. Park. The basic power settings available include continuous, pulse and burst modes.

In continuous mode, the degree of delivered power is determined by depressing the foot pedal, which increases energy until it reaches a preset maximum, if the mode is set to "linear." For the pulse setting, according to Dr. Park, "after each pulse of energy, no energy is delivered for a brief 'off' period, within a preset maximum limit. By alternating on and off periods, there's time to cool the phaco needle and reduce heat and energy that are delivered into the eye."

The ratio of the total phaco-on and phaco-off time is expressed as a percentage. A 50-percent duty cycle, for

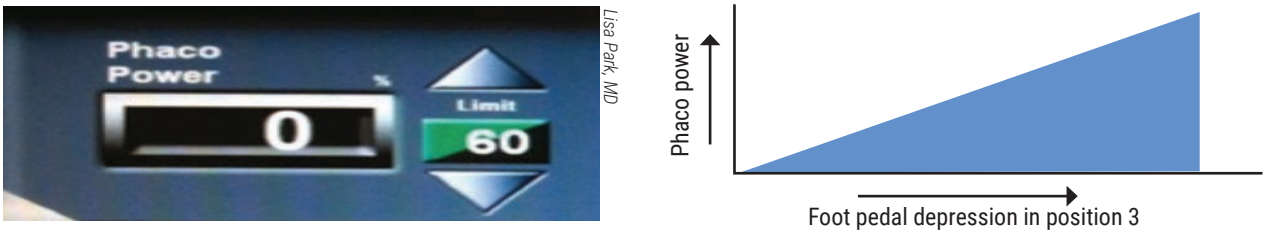


Figure 1. Continuous phaco power provides a predictable flow of energy that increases to a preset limit when you depress the foot pedal.

This article has no commercial sponsorship.

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

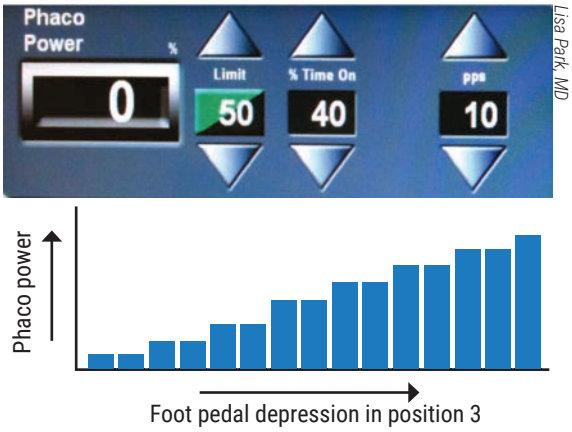
example, means that the power is on half the time and off the other half, according to Dr. Park. "To be clear, then, increasing or decreasing the number of pulses per second doesn't change the total amount of energy delivered," she continues. "If you compare a setting of 50 pulses per second to a setting of 200 pulses per second and if the duty cycle remains at 50 percent, the phaco energy will still be delivered 50 percent of the time for both settings."

However, she adds, you can alter the duty cycle to change the on-and-off times. For example, you can program your machine to provide a 20-percent duty cycle, which results in 20 milliseconds of energy followed by 80 milliseconds of no energy in each cycle. "During the extended off time, while no energy is being delivered, the nuclear fragments can easily be aspirated," says Dr. Park. "Therefore, you can still have 200 pulses, but the amount of energy delivered in this duty cycle would be 20 percent of continuously delivered phaco energy."

Managing the Pulse Rate

Dr. Park emphasizes selecting the right pulse rate and duty cycle for the right circumstances. During sculpting, for example, energy creates a groove and, therefore, higher pulse rates tend to work better because the narrower time intervals between pulses produce a smoother delivery of ultrasound energy. For quadrant removal, she says, a lower duty cycle tends to be a better choice most of the time because a long interval between pulses allows for the aspiration of nuclear fragments.

Burst, the third mode, also helps in special situations. "Each burst has the same power," says Dr. Park. "The interval between each burst decreases as the pedal is depressed. The more the pedal is depressed, the shorter the off period is between each burst. In other words, the bursts of energy are delivered more rapidly as the pedal is depressed. At the maximum point of depression, the time between bursts becomes infinitely smaller and essentially constitutes a continuous delivery of energy."



Lisa Park, MD

Figure 2. In phaco pulse mode, the time between pulses, known as the off time, allows the phaco needle to cool, reducing the heat and energy delivered into the eye.

Dr. Park says the burst mode allows for "true" phaco-assisted aspiration of the lens nucleus. The vacuum and fluidics of the phaco machine are used to aspirate the cataract fragments and give small bursts of power only when necessary, she notes. "Because we can program these bursts to be as quick as a few milliseconds, we can give hundreds of tiny bursts each second," she points out. However, in these situations, she notes that the surgeon doesn't have linear control of the phaco power that's delivered.

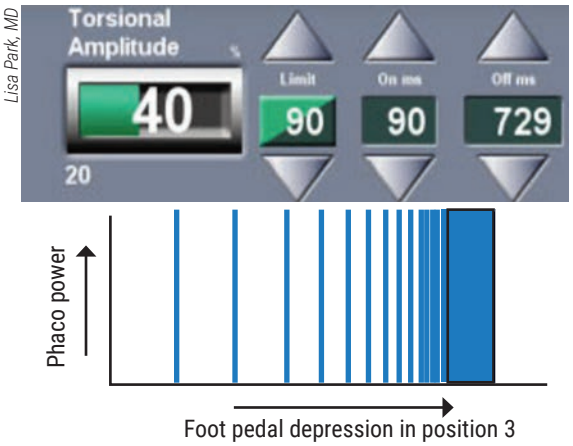
"Our ability to program timing and duration in combination with the directional modes, such as transverse and torsional phaco, can result in highly elegant control and precise ultrasound power delivery," says Dr. Park.

Besides reducing heat and energy, "pulse and burst modes can theoretically improve followability and improve efficiency," says James D. Auran, MD, professor of ophthalmology at the Columbia University Irving Medical Center. "Micropulse mode uses a pulse of 4 to 10 milliseconds in duration. Long pulse mode is a 30-to-60 millisecond pulse duration."

Remember Your Parameters

Dr. Auran, also the surgical curriculum director for the Columbia University ophthalmology residency program, says intelligent use of phaco parameters is essential. "Intraocular pressure, for example, is a valuable tool," he says. "Pressure pushes the capsular bag posteriorly and makes it taut, decreasing the risk of inadvertent capsular aspiration and rupture. Increased IOP also stabilizes the chamber, especially in the presence of high aspiration and vacuum or when leaking incisions are involved. We can minimize post-occlusion surge in these situations.[1] However, be alert, because increased IOP can also cause endothelial damage[2] and, of course, higher IOP is less comfortable, especially in high myopes."

Dr. Auran points out that, according to *in vitro* data, increasing the IOP to as high as 110 mmHg in the Alcon Centurion system can make the machine more efficient.[3] Another study found that, in the Whitestar Signature Pro system (Johnson & Johnson Vision), increasing bottle height to 110 cm increases efficiency in the peristaltic continuous mode.[4] However, another study involving



Lisa Park, MD

Figure 3. In the phaco burst mode, bursts of equal levels of energy are delivered more rapidly as the pedal is depressed.

YOUR PATIENTS WITH DME ARE READY FOR A CHANGE

The power of EYLEA improved and sustained outcomes in the largest phase 3 anti-VEGF clinical trials completed to date in DME (N=862), with improved visual acuity at 52 and 100 weeks.[1]

IMPORTANT SAFETY INFORMATION AND INDICATIONS

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

EYLEA IMPROVED AND SUSTAINED VISION GAINS THROUGH 52 AND 100 WEEKS IN DME[1-3]

	EYLEA 2 MG EVERY 4 WEEKS[§]	EYLEA 2 MG EVERY 8 WEEKS[‖]	CONTROL
VISTA	(n=154)	(n=151)	(n=154)
MEAN CHANGE IN BCVA (52 WEEKS,* 100 WEEKS[†])	+12.5, +11.5 LETTERS	+10.7, +11.1 LETTERS	+0.2, +0.9 LETTERS
PROPORTION GAINED ≥15 LETTERS (52 WEEKS,[‡] 100 WEEKS[†])	41.6%, 38.3%	31.1%, 33.1%	7.8%, 13.0%
VIVID	(n=136)	(n=135)	(n=132)
MEAN CHANGE IN BCVA (52 WEEKS,* 100 WEEKS[†])	+10.5, +11.4 LETTERS	+10.7, +9.4 LETTERS	+1.2, +0.7 LETTERS
PROPORTION GAINED ≥15 LETTERS (52 WEEKS,[‡] 100 WEEKS[†])	32.4%, 38.2%	33.3%, 31.1%	9.1%, 12.1%

VISTA and VIVID study designs: Two randomized, multicenter, double-masked, controlled studies in which patients with DME (N=862; age range: 23-87 years, with a mean of 63 years) were randomized and received 1) EYLEA 2 mg administered every 8 weeks following 5 initial monthly doses; 2) EYLEA 2 mg administered every 4 weeks; or 3) macular laser photocoagulation (control) at baseline and then as needed. Protocol-specified visits occurred every 28 (±7) days. In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at week 52, as measured by ETDRS letter score.
Efficacy of both EYLEA groups was statistically superior vs control at 52 and 100 weeks ($P<0.01$).
*Primary endpoint.
[†] Prespecified exploratory endpoint.
[‡] Secondary endpoint.
[§] Last observation carried forward; full analysis set.
[‖] Following 5 initial monthly doses.
The results of exploratory endpoints require cautious interpretation and could represent chance findings, as a multiplicity adjustment has not been applied.
anti-VEGF = anti–vascular endothelial growth factor; BCVA = best-corrected visual acuity; DME = Diabetic Macular Edema; ETDRS = Early Treatment Diabetic Retinopathy Study.

See more at HCP.EYLEA.US

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

INDICATIONS

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

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

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

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

08/2020
EYL.20.07.0057

EYLEA® (aflibercept) Injection
For Intravitreal Injection

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

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

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

4 CONTRAINDICATIONS

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

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

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

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments.
Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [*see Patient Counseling Information (17)*].

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS.

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

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

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

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

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

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

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

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

REGENERON

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

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

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

EYL.19.07.0306

James D. Auran, MD

Figures 4 and 5. When performing an anterior vitrectomy during cataract surgery, James D. Auran, MD, recommends removing the vitreous at 4,000 cuts per minute and aspirating fluid in the third pedal position. For lens removal with the vitrector, make careful adjustments to draw the lens pieces away from vitreous (without aspirating the vitreous) while slowing the cut rate to 100 to 200 cuts per minute, he says. This opens the cutter port enough to produce sufficient aspiration and vacuum to engage the lens pieces.

the Catahrex 3 phacoemulsification system (Oertli) found that bottle height had little influence on efficiency or chatter.[5]

Dr. Auran notes that vacuum varies when the phacoemulsifier is turned on, requiring you to use vacuum for aspiration only. "Control of the nuclear fragments with the vacuum is best achieved with the tip embedded in the nucleus," he adds. "If your hold on a nuclear fragment is tenuous, wait until you can drag the fragment centrally, away from the capsule, to visualize an adequate amount of nucleus in front of the phaco tip. Quick taps of the tip will advance the tip deeper into the nuclear fragment, enabling a firmer hold."

Keep in mind that tip occlusion is required to reach a preset maximum vacuum power (for example, 400 to 700+ mmHg) when using a peristaltic pump but not a venturi. Dr. Auran says you can ensure the best use of vacuum to hold a lens, capsule or iris against the instrument tip. Increasing vacuum can also increase phaco efficiency in some machines, to some extent. Meanwhile, a very high vacuum setting decreases efficiency,[6] but does allow for the aspiration of soft and medium pieces of the nucleus, which can be aspirated with minimal or no phaco power, notes Dr. Auran. "Harder pieces can be mashed against the tip of a second instrument," he says. "Our choices depend on the texture of the individual fragment we're handling." He lists, for example:

1. hold in place (lower vacuum);
2. drag (slightly higher vacuum);
3. hard nucleus phaco, (higher vacuum);
4. soft and medium nucleus aspiration (higher vacuum).

Meanwhile, when you increase aspiration you increase phaco efficiency, Dr. Auran points out, noting that high aspiration can help with sticky material, such as the epinucleus and cortex, and for viscoelastic removal. However, high aspiration can also be risky. For example: A column of cohesive nucleus, epinucleus and/or cortex can draw the posterior capsule into the tip from 1 to 2 mm away in 300 microseconds.[7] "So, avoid excessive aspiration," he says. "Lower aspiration (20 to 24 ml/min) can help if events occur too quickly, such as when you're removing a soft cataract, and you don't want to pull materials toward the tip while grooving or during vitrectomy capsule polishing.[7] Low aspiration can also help ensure protection of the endothelium, such as in cases of Fuchs' dystrophy."

Appreciating Variable Power

Dr. Auran says increasing phaco power generally increases efficiency. "But you'll see less of an efficiency gain from incremental increases at higher powers, as well as decreased efficiency (in part due to chatter) at the highest powers in some situations," he says. "Also, keep in mind that low power (for example, 20 percent) may be best for some situations, such as soft cataracts. Higher power can increase the risk of corneal injury, wound burn, iris damage and capsular rupture."

Are there any other approaches to increase efficiency? One example, Dr. Park points out, is limiting power to prevent excessive heat build-up. She also urges you to use the innovations in phaco technology that augment longitudinal phaco, when indicated. These innovations "enable us to deliver power through lateral and rotational motions in two modes known as transversal and torsional ultrasound," she says. Remember that transversal ultrasound helps emulsify the nucleus in more than one direction, increasing cutting efficiency. The main advantage of torsional phaco is increased energy efficiency, but the main disadvantage is significant tip movement. (Note that transverse and torsional phaco are proprietary. Transversal ultrasound [Ellips] is employed by Johnson & Johnson Vision in the Whitestar Signature Pro and torsional ultrasound [Ozil] is found in Alcon machines, such as the Infiniti and the Centurion vision systems.)

Meanwhile, remember that specific phaco units perform differently. For example, efficiency in the Centurion increases, using up to 100 percent of continuous power with a longitudinal-torsional balanced tip, set at IOP, 50 mmHg; aspiration, 50 mL/min; and vacuum, 500 mmHg.[8] When using a torsional-Intrepid balance tip and 550 mmHg of vacuum, efficiency improves up to 60 percent.[9]

"When you alternate longitudinal

with torsional modes, efficiency rises linearly, with an increase of longitudinal power up to 100 percent," Dr. Auran adds. "But 60-percent torsional optimizes efficiency and minimizes chatter.[10] Alternative approaches, such as manual mashing and chopping mechanisms to minimize the risk of damage, can sometimes be safer."

The Whitestar Signature Pro, when used with longitudinal power and a 30-degree bevel straight tip, increases efficiency up to 100 percent. Efficiency is optimal at 90 percent power in the transverse mode with a 100 cm bottle height and vacuum at 600 mmHg.[4] Efficiency is also optimal in the Whitestar at 90-percent power with transverse elliptical tip movement, aspiration at 50 mL/min, bottle height at 100 cm and vacuum set at 600 mm Hg.[4]

James D. Auran, MD

Figure 6. When performing peripheral iridotomy during cataract surgery, you'll need to choose from a range of one cut per minute to one cut every one to two seconds.

Avoiding Trouble

Dr. Auran explains how phaco modes can help keep your surgeries safe, efficient and responsive to the needs of varied patients.

"The sculpt mode is really for scraping off nucleus," says Dr. Auran. "You don't want nucleus drawn to the tip, so you should use low vacuum and low aspiration, but as much power as you need longitudinally. Unlike torsional or transverse power, longitudinal power will likely draw the nucleus toward the tip."

The chop mode is for holding the lens, he continues. "This requires more vacuum and more aspiration, depending on the nuclear consistency," says Dr. Auran. "The power is only employed to drill the hole to begin chopping. Some surgeons go right to quad, drawing pieces of the lens toward the phaco tip, relying on increased aspiration and vacuum and as much phaco power as needed. The torsional or transverse modes, less likely to repel nuclear particles, might be best."

Epinuclear settings are for handling the rubbery outer layer of the nucleus, again with moderate to high vacuum and aspiration, as needed, with minimal or no phaco power and high IOP to push the capsule posteriorly, as appropriate, he notes.

"Cortex can be very adherent to the capsule, which may tend to prolapse forward into the aspiration port during cortex removal," he says. To prevent this, elevate the IOP, pushing the capsule bag back and making it taut. "When it's like a drumskin, it's much less likely to be drawn into the port. When engaging and stripping cortex in the periphery, use moderate vacuum and high aspiration. Once cortex has been drawn into a safe area in the center at the iris level, increase aspiration and vacuum to aspirate cortex."

Polish is best used with a silicone tip, according to Dr. Auran. It involves very low settings while you keep the pressure high and capsule taut. Very low vacuum and aspiration are indicated to gently remove cells while minimizing the risk of aspirating capsule material. Viscoelastic can be used to viscopolish the lens capsule. Removing viscoelastic requires the same settings as for the epinucleus, including high IOP (to keep the capsule away from your tip) and increased vacuum and aspiration to remove the viscoelastic.

When Things Go Wrong

Dr. Auran emphasizes the need to prepare for an unexpected complication. "If vitreous gets pulled into the instrument tip, whether it's because of a broken bag, zonular dehiscence or some other factor, if vitreous prolapses forward, your first response should always be to freeze your instrument, stop phacoemulsification and kick your pedal in the appropriate direction to reflux fluid and clear the tip," says Dr. Auran. "If that doesn't work, inject viscoelastic directly into the barrel of the probe or amputate the material with Chang scissors. Lower the IOP to nearly zero before withdrawing the tip. Halt all irrigation. Wiggle your sideport instrument sideways within the incision to potentiate controlled fluid egress from the sideport. Then withdraw the phaco tip quickly through the main incision, taking care not to depress the base or lift the roof of the incision while withdrawing the instrument."

For an anterior vitrectomy, Dr. Auran repeats common words of caution: Never pull on the vitreous. "A very rapid cut rate is required, along with very low vacuum and aspiration settings," he says. "Using 4,000 cuts per minute, the cutter is mostly closed, and nothing happens until you're in the third pedal position and aspirating fluid. These settings allow you to apply minimal traction to the vitreous."

For lens removal with the vitrector, Dr. Auran recommends drawing the lens pieces away from vitreous. You may need to apply the vitrector port directly against the lens piece (using irrigation only), then apply vacuum and aspiration to engage the piece, carefully pulling it into a safe zone, he says. Lens removal requires a much slower cut rate (100 to 200 per minute), allowing the cutter port to open wide enough to produce sufficient aspiration and vacuum to engage the lens pieces. "Sometimes a higher cut rate is necessary to be efficient for removal of the lens material," he acknowledges. "But efficiency with the vitrector is extremely low for removing the material. If possible, it's best

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to use viscolastic to trap the lens pieces and perform phacoemulsification in the quad setting with a very low flow."

For a peripheral iridotomy, Dr. Auran says you'll need to choose a range of one cut per minute to one cut every one to two seconds. "To control the cut you make, use fairly high vacuum and low aspiration," he advises. "Make sure the port is pointed down over the iris location where you want to make the iridotomy, then make one cut to see what you've got." Knowing which way to kick to get reflux and keep the iris from being drawn into the tip is also very important, according to Dr. Auran. "Know your machine," he adds.

For a peripheral iridotomy, Dr. Auran says you'll need to choose a range of one cut per minute to one cut every one to two seconds. "To control the cut you make, use fairly high vacuum and low aspiration," he advises. "Make sure the port is pointed down over the iris location where you want to make the iridotomy. Also make one cut to see what you've got." It's also very important to know which way to kick your footpedal to activate the reflux mode, keeping the iris from being drawn into the tip. "Know which direction your machine requires you to kick in," he says.

Other Potential Challenges

A few other potential challenges might include a chamber collapse in a normal-pressure eye, Dr. Auran says. "Check your equipment, looking for bad tips and problems with connections to the tips," he says. "You can increase IOP, consider continuous irrigation or decrease aspiration. A lot of fluid escapes through the sideport, so removing or angling your sideport instrument may help. Matching the diameter of your sideport instrument with the sideport as well as hydrating or suturing the incisions may also help."

Watch out for high phaco power, as well, he warns. "At high power, we need to continuously irrigate the incision," says Dr. Auran. "Immediately stop phaoemulsification when the tip occludes, as indicated by a white cloud of debris appearing over the tip or an audible occlusion signal sounding. A wound burn can occur in a half a second. You can get into real trouble real fast."

In the presence of a small pupil, Dr. Auran recommends raising the IOP to around 100 to 110 mmHg, pressing the lens diaphragm back and dilating the pupil. "This can be helpful, although it's uncomfortable for the patient," he says.

And for those cases that start to get out of control? "Things may be happening too fast," Dr. Auran admits. "Lens particles are flying around, the iris and the lens capsule are snapping at you." He recommends decreasing aspiration (flow) and power but increasing IOP. "Also consider using viscoelastic to manipulate the nucleus and cortex," he says. "Viscoelastic is an excellent tool to use instead of your phaco tip."

Iris prolapse is always possible, of course, but recognizing its onset can help you keep it from getting serious, according to Dr. Auran. "Don't withdraw your instruments until you've addressed IOP and flow," he says. "Like vitreous, the iris will follow the pressure gradient.

Again, halt all irrigation and wiggle your sideport instrument within the sideport to gently allow fluid egress. Once IOP drops close to zero, withdraw the phaco tip quickly (without pressing on or lifting the incison) to minimize fluid/iris egress. Then, hydraulically reposit or visco-reposit the iris, if possible. You may need iris retractors (posterior to or bracketing the main incision) to reposition the iris and hold it in the eye. Whatever you do, avoid manipulating the iris with metal,

since it frays easily."

Infusion Fluidics

One aspect of phacoemulsification that doesn't get a lot of attention is the infusion side of the machine, says Kevin M. Miller, MD, chief of cataract and refractive surgery at the David Geffen School of Medicine at the University of California, Los Angeles.

"When the aspiration pump of a phaco machine is turned on," he continues, "fluid is pulled from the eye. To compensate, irrigation fluid must flow passively from the BSS reservoir into the eye. Under this greater-than-zero-inflow condition, IOP no longer equals bottle height. Because there's flow through the resistive infusion tubing, IOP drops in proportion to the amount of flow."

It's important to keep in mind that the infusion flow rate equals the aspiration flow rate as long as the incisions don't leak, he continues. With aspiration rates varying throughout a procedure, IOP also fluctuates significantly, he says. While trying to operate at a nominal IOP of 55 mmHg with a variable aspiration flow rate, actual IOPs might range from a high of 80 mmHg to a low of 30 mmHg, according to Dr. Miller.

"If you started surgery with an IOP of 50 mmHg at zero inflow and ran the aspiration flow up to 60 cc/min, the IOP would drop to zero and the anterior chamber would collapse," he says.

Options for compensating for lost pressure and avoiding a chamber collapse are varied. "The surgeon can raise the bottle height during the procedure to compensate," he observes. "However, you might find yourself needing to raise it by several feet, which can be challenging. A negative consequence of this approach, of course, is reduced patient comfort."

An alternative approach is injecting air into the infusion bottle. "Essentially, pressurized air injection does the same thing as raising the bottle height," says Dr. Miller.

Manufacturers of phaco machines employ a variety of features to address fluidics issues. One solution, available through the Alcon Centurion Vision System, is the use of active infusion fluidics. A feedback system continuously measures pressure in the irrigation and aspiration lines, as well as flow rate, and commands a motor-controlled plate to respond to changes. The plate applies pressure to a bag of BBS to increase flow and releases pressure on the bag to decrease flow, enabling IOP to remain constant while irrigation and aspiration flow rates vary, Dr. Miller says.[13,14]

Other phaco machines do some things on the aspiration side of the system that are noteworthy. Johnson & Johnson Vision's Whitestar Signature Pro features what it calls "on-demand fluidics," offering a peristaltic pump for "holdability" and intraoperative control, and a venturi pump for followability and improved efficiency.[15] The company says the ability to switch between pumps is made possible with the press of the footpedal.

In its Stellaris Elite phaco system, Bausch + Lomb offers what it calls adaptive fluidics, which integrate automated aspiration control with dynamic infusion compensation. This helps stabilize IOP, creating a responsive and controlled surgical environment, according to the company.

Oertli says its CatarRhex 3 relies on a system that controls flow in 0.1-ml steps. A vacuum sensor integrated into the tubing system "monitors everything without delay," according to a company brochure. DORC says its EVA Phaco-Vitrectomy System provides enhanced fluidics. A new system called VacuFlow VTi offers, among other features, "automatic infusion compensation" for IOL stabilization and a precise flow that the company says eliminates pulsation.

Keeping It Together

Staying on top of infusion fluidics, avoiding complications, managing complications when they develop, respecting aspiration, understanding phaco parameters and mastering varied power settings are just some of the ways you can safely and efficiently optimize phacodynamics for your patients' benefit. Keep these insights handy, and surgeons say you'll find yourself operating more effectively and confidently. ◀

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DISCLOSURES

Dr. Miller is a consultant to Alcon and LensAr and an investigator for Johnson & Johnson Vision. **Drs. Auran** and **Park** report no financial interest in any product mentioned in this article.

THE COVID CHRONICLES: PAST, PRESENT & FUTURE

The pandemic has impacted every practice differently, but the changes it's wrought may last a long time.

BY CHRISTOPHER KENT
SENIOR EDITOR

The arrival of the COVID-19 pandemic plunged the field of ophthalmology—along with the rest of the world—into a sea of challenges, changes and stress. Now that we're a year into this saga, the initial shock has worn off; people are more able to look at what's happened with some perspective.

Here, ophthalmologists share three dramatically different stories about how the pandemic affected their practices; what they've learned from this experience; and what they believe may happen in the coming months and years. In addition, practice management experts share a few of their observations and predictions.

In the Eye of the Storm

One of the most remarkable aspects of this is how differently practices in different parts of the country were affected. To illustrate how different those experiences were, we spoke with James C. Tsai, MD, MBA, the Delafield-Rodgers Professor and chair of the Department of Ophthalmology at the Icahn School of Medicine at Mount Sinai and president of the New York Eye and Ear Infirmary of Mount Sinai, who witnessed firsthand the devastation when New York was overwhelmed with the virus; Karl Stonecipher, MD, medical director for Laser Defined Vision and Physicians Protocol in Greensboro, North Carolina, and a clinical associate professor of ophthalmology at the University of North Carolina, who watched how COVID impacted his two very different vision centers; and John D. Kirk, MD, FACS, who practices at the Kirk Eye Center in Loveland, Colorado.

New York City was the epicenter of the pandemic in America for several weeks. Dr. Tsai describes the experience as "harrowing." "We faced an onslaught," he says. "It was far more traumatic than what many practices in the U.S. faced—it was more like what happened in Italy."

Dr. Tsai says the worst month of 2020 was March. "Everything happened all at once," he says. "I'd been to the American Glaucoma Society's annual meeting a couple of weeks before the shutdown. Everyone at the meeting was still shaking hands or fist bumping and not wearing masks; no one realized that COVID would be so devastating and so easily transmissible. But the day after I returned from the meeting, the first COVID-positive patient was found in New York. Within two weeks the number of COVID patients exploded.

"What followed happened very suddenly," he notes. "We were abruptly told that everything was shutting down within the next day or two. So we suddenly had postop patients who couldn't come in; we had to evaluate them from their homes. Then we started having fatalities. Meanwhile, some of our residents were training at Elmhurst hospital in Queens, and that was part of the epicenter, so our residents were at the front lines in the ER. At the same time, some of our staff, including nurses and anesthesiologists, were redeployed within the Mt. Sinai Health System (including Mt. Sinai Brooklyn) to help care for COVID patients. Our ophthalmologists were helping out in the emergency department. On top of that,

This article has no commercial sponsorship.

Dr. Stonecipher is a consultant for Alcon. **Drs. Tsai** and **Kirk** and consultants **Pinto** and **Wohl** report no financial ties to anything discussed in the article.

there was a shortage of providers because physicians, nurses and staff were getting infected, calling in sick, or were barred from work because they'd been exposed to COVID-positive patients.

"Even by mid-March, when they first locked down New York, we were scrambling to get the appropriate N-95 masks," he continues. "We had to fight to have ophthalmologists and ear, nose and throat doctors prioritized to get them. After all, we examine patients up close. We had to point out that in China, two of the first doctors affected by COVID were ophthalmologists. It was extremely challenging."

Dr. Tsai says the next thing that happened was that all elective surgeries were shut down. "Ophthalmology was heavily impacted by this because most of our surgeries are elective," he points out. "We struggled to find ways to care for patients without seeing them in person. We had to very quickly get creative and ramp up tele-ophthalmology strategies. We had to figure out how patients could download visual acuity charts so they could communicate to us their vision. We got creative about telling patients how to do tactile tonometry. We described to them what their eye should feel like after glaucoma surgery, so they could alert us if their eye felt firm or too soft.

"Here at New York Eye and Ear we have busy walk-in eye clinics," he says. "We wanted to remain committed to that, but we were told that we should reduce our schedules to the smallest number of patients possible, only handling emergencies. So we started a tele-ophthalmology screening service to meet with patients before they even came into our building.

"Then, our revenues plummeted, and we had to furlough our staff," he continues. "Luckily, the federal government implemented the COVID unemployment supplement, which was applicable for both full and partial unemployment. We ended

John D. Kirk, MD, FACS

Practices are likely to leave many safety precautions such as plexiglass breath shields in place indefinitely.

up working with the state to manage how we handled our staffing crisis. At the same time, we still had to see patients who needed emergency eye surgery. And, we had to get them tested for COVID to keep everyone safe, which was a challenge."

Dr. Tsai says that through this entire crisis, he and other senior management came into the hospital in person every day. "We knew that a lot of people were feeling despair," he says. "We wanted to be visible. If the hospital and department leaders are doing Zoom calls from home, that doesn't engender a lot of confidence. So we managed the hospital and clinics by walking around and being available. We made sure the residents, fellows, attending physicians, nurses and staff knew they were not alone on the front lines."

Reinventing the Status Quo

Dr. Tsai says the crisis forced them to come up with new ways to handle patients who have become reluctant to come into the city, which is now perceived as risky. "If patients have glaucoma, we may send them to one of our satellite locations outside the city to get their visual fields, OCTs and pressure measurements done by a technician," he says. "Then, we do a tele-ophthalmology consultation via Zoom a week later. We also don't want our retina patients waiting around in our very busy retina center and being exposed to COVID, just to be informed that their OCT didn't show any appreciable change. So we've employed a similar strategy in our retina center: Patients come in for their OCT or other retinal imaging; then several days or a week later, they can speak to their doctor via a video visit to discuss whether or not they need to come in for a intravitreal injection."

Dr. Tsai says the concept of "lean" strategies came to the fore. "The 'lean' strategies are all about reducing waiting time and waste," he says. "Patients of ophthalmology practices spend a lot of time waiting for things like dilated exams and imaging tests. Part of what COVID taught us is that patients don't want to wait around, especially in a crowded waiting room during a pandemic. So it's forced us to practice more efficiently to make patients feel safe.

"We realized that even if patients were healthy, they were concerned about coming in," he continues. "COVID has changed patient expectations. They want to feel safe and they want to feel that we're taking the waiting-time issue seriously. So, we created videos showing patients what we've done to increase safety. The videos show how we clean the rooms between patients, and that our waiting rooms aren't crowded. We show how we're using disposables everywhere.

"In essence," he says, "COVID has forced us to create an environment that's more efficient and makes the patient feel comfortable about coming in, and then forced us to make sure our patients know about these quality and safety

changes. Otherwise, we risk losing more patient visits, which isn't sustainable when we're already facing financial challenges because of the pandemic crisis."

Dr. Tsai adds that one of the lessons they've learned is the importance of tele-ophthalmology. "Because of the intense learning we went through, my colleagues and I published a paper about using telemedicine at the height of the pandemic," he says.[1] "In addition to discussing the ins and outs of virtual visits and how these visits may affect the field of ophthalmology, we shared a lot of our telemedicine strategies in that paper—strategies that we're still employing."

A Dual Perspective

Dr. Stonecipher, in North Carolina, experienced the consequences of the pandemic from multiple perspectives, because he runs two different practices: One provides cataract surgery, the other laser vision correction. "The laser vision correction practice was part of a chain, but in late March of last year, the pandemic caused the parent company to not only close the practice, but also declare that they weren't planning to reopen it," Dr. Stonecipher explains. "They let all the employees go.

"Ironically, this turned out to be a huge opportunity for me," he says. "I already owned most of the equipment, so I went to the company and negotiated a licensing agreement. I said, 'I'll maintain the center if you provide some of the information technology services.' We agreed that I'd pay them a licensing fee so I could still use their software and call center and keep the company's name on the door. They agreed, so on May 5th I rehired the majority of the staff—at least as many as I could with minimal patient visits. (We were still seeing mainly postop patients and emergencies because at that time the state still wasn't allowing elective surgery.)

"By May 12th we were able to start doing laser surgery again," he says. "Surprisingly, a lot of people still wanted to have surgery, even during the pandemic, because at least in the short run they were getting more money not working than they usually got when working. As a result, a lot of these people had extra income. They wanted LASIK because their COVID masks were fogging up their glasses!"

Dr. Stonecipher says his LASIK center ended up having a good year. "I used PPP money during the first months of the crisis to support the employees that I had," he notes. "That helped me be able to bring staff back. But this year, in January, when I applied for PPP money again, my accountant told me that we'd done too well in 2020 to qualify. It was partly timing, because to qualify we had to have lost 20 percent of our income in a quarter, and our losses were spread is such a way that no quarter had that big a loss. That was ironic, but I can't complain when so many other practices had a far worse year than we did."

Dr. Stonecipher's other practice offers primarily cataract surgery, and his experience there was quite different. "We separated the cataract business from the LVC business years ago," he explains. "When the

WILL PRACTICES RECOUP THEIR LOSSES?

James C. Tsai, MD, MBA, president of the New York Eye and Ear Infirmary of Mount Sinai, says he doesn't expect they'll make up for all of the patients who postponed or canceled appointments during the pandemic. "Some of our patients have now permanently left New York City," he notes. "Before the pandemic, people felt that it was ideal to come into the city from New Jersey, Connecticut and Long Island to get health care because there are so many specialists concentrated in Manhattan. Now, New York City has been stigmatized; people see coming here as putting themselves at risk."

Dr. Tsai says this is forcing practices in the city to rethink everything. "We're looking at partnering with physicians in nearby communities," he says. "We do have some satellite offices in Long Island and Westchester County, and we're trying to grow these locations. Our whole strategy has changed."

Karl Stonecipher, MD, medical director for Laser Defined Vision and Physicians Protocol in Greensboro, North Carolina, is optimistic. "I suspect we'll make back any losses eventually," he says. "The number of COVID cases has recently been dropping. The more people are vaccinated, the closer we'll get to 'herd immunity,' and the more people will return to our offices." He suspects that the upcoming months may go very differently for cataract and LASIK providers, however. "I think the cataract market may bounce back, because the people who didn't get cataract surgery will still need to get it done. On the other hand, fee-for-service offerings like LASIK may be hit hard again."

John Pinto, president of J. Pinto & Associates, an ophthalmic practice management consulting firm, says his average ophthalmologist client practice lost 10 to 15 percent of topline revenue last year, and 25 to 30 percent of normal profits. "That's obviously an unpleasant experience," he says, "but it's not like owning a restaurant and going out of business and walking away from your lease. Almost all independent private ophthalmology practices have stayed in business. Our average client is now back to 80 to 95 percent of historic patient visits and revenue.

"Before the pandemic, demand for eye care was going up about 5 percent per year," he points out. "Everyone's expectation is that the U.S. GDP is going to grow at least 5 percent in 2021, and unless there are some real surprises with the COVID variants, it would be reasonable to forecast that the trajectory of practice revenue and patient volumes in 2021 will pretty much mirror that. We should be getting back to at least 5 percent annual growth—perhaps closer to 8 or 9 percent growth. I hope that 2021 will be all the time it takes to make up for the step back we took in 2020."

—CK

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IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- Alpha-adrenergic agonists as a class may impact blood pressure. Advise Upneeq patients with cardiovascular disease, orthostatic hypotension, and/or uncontrolled hypertension or hypotension to seek medical care if their condition worsens.
- Use Upneeq with caution in patients with cerebral or coronary insufficiency or Sjögren's syndrome. Advise patients to seek medical care if signs and symptoms of potentiation of vascular insufficiency develop.
- Upneeq may increase the risk of angle closure glaucoma in patients with untreated narrow-angle glaucoma. Advise patients to seek immediate medical care if signs and symptoms of acute narrow-angle glaucoma develop.
- Patients should not touch the tip of the single patient-use container to their eye or to any surface, in order to avoid eye injury or contamination of the solution.

ADVERSE REACTIONS

Adverse reactions that occurred in 1-5% of subjects treated with Upneeq were punctate keratitis, conjunctival hyperemia, dry eye, blurred vision, instillation site pain, eye irritation, and headache.

DRUG INTERACTIONS

- Alpha-adrenergic agonists, as a class, may impact blood pressure. Caution in using drugs such as beta blockers, anti-hypertensives, and/or cardiac glycosides is advised. Caution should also be exercised in patients receiving alpha adrenergic receptor antagonists such as in the treatment of cardiovascular disease, or benign prostatic hypertrophy.
- Caution is advised in patients taking monoamine oxidase inhibitors which can affect the metabolism and uptake of circulating amines.

To report SUSPECTED ADVERSE REACTIONS or product complaints, contact RVL Pharmaceuticals at 1-877-482-3788. You may also report SUSPECTED ADVERSE REACTIONS to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Reference: 1. Upneeq® (oxymetazoline hydrochloride ophthalmic solution), 0.1%. [Prescribing Information].

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BRIEF SUMMARY: The following is a brief summary only; see full Prescribing Information at https://www.upneeq.com/Upneeq-PI.pdf for complete information.

1 INDICATIONS AND USAGE

UPNEEQ is indicated for the treatment of acquired blepharoptosis in adults.

2 DOSAGE AND ADMINISTRATION

Contact lenses should be removed prior to instillation of UPNEEQ and may be reinserted 15 minutes following its administration.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least 15 minutes between applications.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Potential Impacts on Cardiovascular Disease

Alpha-adrenergic agonists may impact blood pressure. UPNEEQ should be used with caution in patients with severe or unstable cardiovascular disease, orthostatic hypotension, and uncontrolled hypertension or hypotension. Advise patients with cardiovascular disease, orthostatic hypotension, and/or uncontrolled hypertension/hypotension to seek immediate medical care if their condition worsens.

5.2 Potentiation of Vascular Insufficiency

UPNEEQ should be used with caution in patients with cerebral or coronary insufficiency, or Sjögren's syndrome. Advise patients to seek immediate medical care if signs and symptoms of potentiation of vascular insufficiency develop.

5.3 Risk of Angle Closure Glaucoma

UPNEEQ may increase the risk of angle closure glaucoma in patients with untreated narrow-angle glaucoma. Advise patients to seek immediate medical care if signs and symptoms of acute angle closure glaucoma develop.

5.4 Risk of Contamination

Patients should not touch the tip of the single patient-use container to their eye or to any surface, in order to avoid eye injury or contamination of the solution.

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.

A total of 360 subjects with acquired blepharoptosis were treated with UPNEEQ once daily in each eye for at least 6 weeks in three controlled Phase 3 clinical trials, including 203 subjects treated with UPNEEQ for 6 weeks and 157 subjects treated with UPNEEQ for 12 weeks. Adverse reactions that occurred in 1-5% of subjects treated with UPNEEQ were punctate keratitis, conjunctival hyperemia, dry eye, blurred vision, instillation site pain, eye irritation, and headache.

7 DRUG INTERACTIONS

7.1 Anti-hypertensives/Cardiac Glycosides

Alpha-adrenergic agonists, as a class, may impact blood pressure. Caution in using drugs such as beta-blockers, anti-hypertensives, and/or cardiac glycosides is advised.

Caution should also be exercised in patients receiving alpha adrenergic receptor antagonists such as in the treatment of cardiovascular disease, or benign prostatic hypertrophy.

7.2 Monoamine Oxidase Inhibitors

Caution is advised in patients taking MAO inhibitors which can affect the metabolism and uptake of circulating amines.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on UPNEEQ use in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, there were no adverse developmental effects observed after oral administration of oxymetazoline hydrochloride in pregnant rats and rabbits at systemic exposures up to 7 and 278 times the maximum recommended human ophthalmic dose (MRHOD), respectively, based on dose comparison. [see Data]. The estimated background risks of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Effects on embryo-fetal development were evaluated in rats and rabbits following oral administration of oxymetazoline hydrochloride during the period of organogenesis. Oxymetazoline hydrochloride did not cause adverse effects to the fetus at oral doses up to 0.2 mg/kg/day in pregnant rats during the period of organogenesis (28 times the MRHOD, on a dose comparison basis). Oxymetazoline hydrochloride did not cause adverse effects to the fetus at oral doses up to 1 mg/kg/day in pregnant rabbits during the period of organogenesis (278 times the MRHOD, on a dose comparison basis). Maternal toxicity, including decreased maternal body weight, was produced at the high dose of 1 mg/kg/day in pregnant rabbits and was associated with findings of delayed skeletal ossification.

In a rat prenatal and postnatal development study, oxymetazoline hydrochloride was orally administered to pregnant rats once daily from gestation day 6 through lactation day 20. Maternal toxicity was produced at the high dose of 0.2 mg/kg/day (28 times the MRHOD, on a dose comparison basis) in pregnant rats and was associated with an increase in pup mortality and reduced pup body weights. Delayed sexual maturation was noted at 0.1 mg/kg/day (14 times the MRHOD, on a dose comparison basis). Oxymetazoline hydrochloride did not have any adverse effects on fetal development at a dose of 0.05 mg/kg/day (7 times the MRHOD, on a dose comparison basis).

8.2 Lactation

Risk Summary

No clinical data are available to assess the effects of oxymetazoline on the quantity or rate of breast milk production, or to establish the level of oxymetazoline present in human breast milk post-dose. Oxymetazoline was detected in the milk of lactating rats. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for UPNEEQ and any potential adverse effects on the breastfed child from UPNEEQ.

8.4 Pediatric Use

Safety and effectiveness of UPNEEQ have not been established in pediatric patients under 13 years of age.

8.5 Geriatric Use

Three hundred and fifteen subjects aged 65 years and older received treatment with UPNEEQ (n = 216) or vehicle (n = 99) in clinical trials. No overall differences in safety or effectiveness were observed between subjects 65 years of age and older and younger subjects.

10 OVERDOSAGE

Accidental oral ingestion of topical intended solutions (including ophthalmic solutions and nasal sprays) containing imidazoline derivatives (e.g., oxymetazoline) in children has resulted in serious adverse events requiring hospitalization, including nausea, vomiting, lethargy, tachycardia, decreased respiration, bradycardia, hypotension, hypertension, sedation, somnolence, mydriasis, stupor, hypothermia, drooling, and coma. Keep UPNEEQ out of reach of children.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Instructions for Use).

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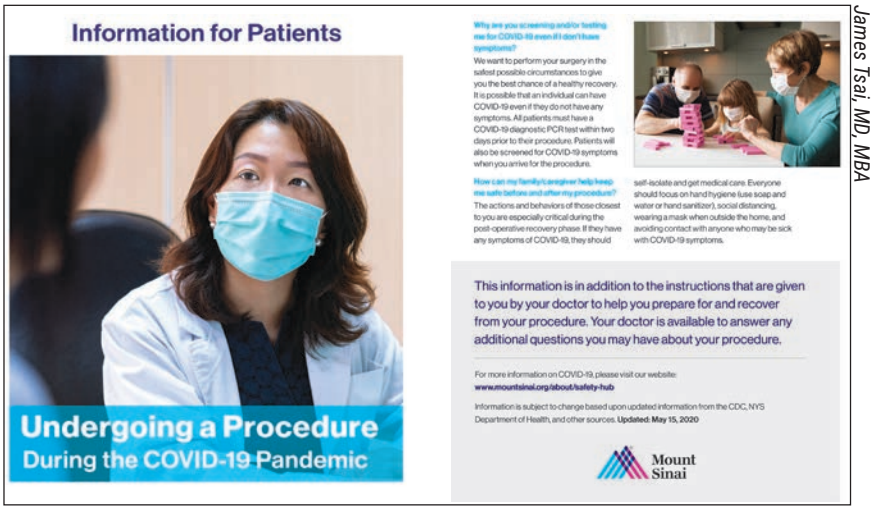
pandemic hit, we furloughed our staff at the cataract center and waited. We continued to pay their insurance. As soon as we could, in mid-May, we brought them back. The governor of North Carolina OK'd performing elective surgery, and we were operating within few days. So by late May we were performing surgery again in both my LVC and cataract practices.



To get nervous patients to return, practices have made videos and produced brochures like the one above that not only tell patients how to come in safely, but show many of the precautions being taken to protect them, to allay their fears.

"Initially, on the cataract side, we had numerous patients with second eyes that we hadn't done," he continues. "Some patients initially had canceled. As a result, we had a backload from April waiting for cataract surgery. But by June and July, our patients were pretty scared. People were dying; some were stuck in nursing homes and couldn't get out to have cataract surgery. At that point many people just said, 'Forget it.' As a result, I'd say our cataract volume dropped about 20 percent.

"Surprisingly, those people that did come in for cataract surgery were still getting premium lenses," he notes. "Those who came in tended to be the younger, more mobile population. And, ironically, we also had more new lenses to offer patients, such as Vivity and PanOptix, and I think that helped."

Changes Made

Dr. Stonecipher says he created a new model for managing patients during the pandemic, at both practices. "We focus on protecting the patient by having a safe environment," he says. "In our laser vision center, when a patient comes in, the waiting room is empty. We take the patient's temperature and ask the typical COVID questions; then the patient goes into an isolated room and stays there for the rest of their appointment, whether that be surgical or screening, except to go to diagnostics. We were cleaning everything constantly and made sure our patients were aware that we were doing that to protect them. We stopped cyclopleging patients, because we didn't want them sitting there for 45 minutes. All of these changes reduced the amount of time patients stayed in the office by about an hour and 15 minutes. Ultimately, we made videos with the staff to show our patients what we were doing.

"We also started using different diagnostic tools that were more COVID-friendly to get our information," he continues. "We now use manifest refraction, wavefront and the DRSplus, which is a nonmydriatic camera made by CenterVue. After evaluation, if the patient says 'I want surgery,' everything is done using telemedicine until the day of surgery. All consenting is done online; all payments are collected online using a new autopay system; all scheduling is done online; and all questions are answered via video meetings.

"On the day of surgery, the patient walks in, gets a temperature check,

James Tsai, MD, MBA

answers a few COVID-related questions and has surgery," he says. "With the new protocol we average about 48 minutes turnaround time. We're much more efficient on surgery day, because everything is already done. We also changed our postop protocol. We see the patient in person on day one, but postop week one and month one visits are done via telemedicine. The three-month visit is done in-office, because we want to collect that datapoint. After that, we see the patient at one year. If the patient has no problems, this becomes an annual event. Meanwhile, we're still giving the patient a lifetime commitment, which is business as usual."

Dr. Stonecipher says he implemented a lot of COVID restrictions in his cataract surgery practice as well. "You could come in for your surgery, but your significant other could not," he explains. "If you came in for cataract surgery, I'd see you one hour post-surgery, and that took the place of a day-one visit. The one-week and one-month visits were largely done using telemedicine. However, by August, we eased some of the restrictions; we were back to seeing patients routinely in the office. We're still doing the postop visit on the day of surgery, eliminating the day-one visit. We still do the one-week, three-month and one-year visits, but now we've largely eliminated the one-month visit.

"Of course, we have a hotline for patients who have a crisis," he adds. "We do a lot of telemedicine with these people. Some have simple issues such as dry eyes or wanting

drop refills. Others have specific concerns about their eyes; as much as possible we manage that over video as well.

If patients feel comfortable doing so, they can come in for an exam, but there's no waiting room any more. In the cataract practice, if you're not the patient, you can't come into the office at all unless you have power of attorney and the patient can't speak for him or herself."

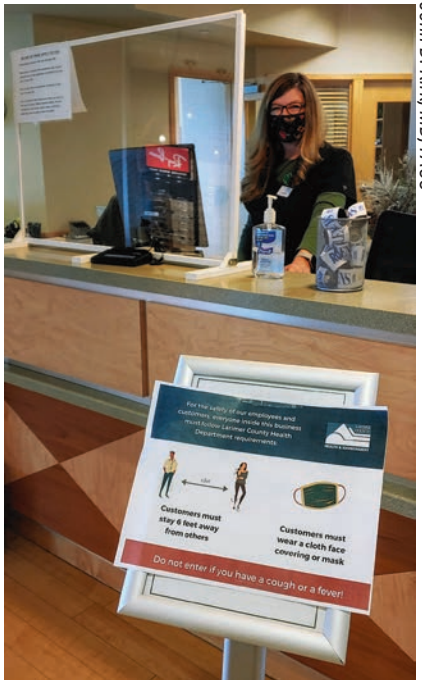
Farther from the Front Lines

Dr. Kirk's practice, in Loveland, Colorado, was not pummeled the way practices in New York were. He says his practice has weathered the pandemic pretty well. "Some practices here were closed for an extended period," he says. "We were closed for two weeks, then partially open for about four weeks after that, doing intravitreal injections and other things we really had to do. But since then, we've been completely open. We're nearly back up to pre-COVID patient volume. So we did better than a lot of practices.

"Of course, we took the COVID safety precautions you'd expect," he says. "However, we never did telemedicine. It's been difficult for us to get into that because of very low reimbursement, and we were busy enough seeing patients in-office that we didn't need to start doing that."

Dr. Kirk says he believes that in general, the ophthalmologists in his area weren't hit too hard by the pandemic. "I don't know of any practice that's struggling, although we certainly did take a financial hit last year," he says. "However, we got one of the PPP loans. That allowed us to keep all of our staff on the whole time; we didn't have to lay anybody off. In any case, we've gradually made our way back and built up our volume again."

One unfortunate reality of the pandemic is that doctors themselves aren't immune from getting sick. Dr. Kirk says he came down with COVID in October and was out for two and a half weeks, adding to the practice's financial losses. "It hit me hard," he says. "I've never experienced anything like it before. I wasn't in the hospital, but I've never been so sick. I cleared the virus after 10 or 12 days. Months later, I'm finally reaching my pre-COVID fitness level.



John D. Kirk, MD, FACS

How quickly practices return to crowded waiting rooms will depend in part on how much space is available in the practice to keep patients spread out at full volume.

"Ironically," he adds, "one member of our staff has tested positive multiple times and has never had symptoms."

Which Changes Will Linger?

To answer this question, John Pinto, president of J. Pinto & Associates, an ophthalmic practice management consulting firm, says it's worth looking at Singapore. "Singapore has suffered through multiple epidemics over the years," he explains. "Whenever they have to swing back into caution, out come the temperature guns and masks. They've gone through so many on-and-off cycles over the past 15 or 20 years that not only are medical offices well-practiced at this, so is the general society. They certainly don't think anything about wearing a mask if they have the sniffles, or wearing a mask when walking outside during flu season.

"I think many of the masking and temperature-reading precautions we've been taking to deal with COVID are going to stay with us," he continues. "I wouldn't be at all surprised to see that, at least during flu season, a lot of practices will have patients wait in the car; or take your temperature before you come in; or ask three screening questions about whether you've had a fever or been in contact with anyone who's had the flu."

Dr. Kirk points out that the virus could be with us for years. "We'll probably keep the plexiglass shields at the slit lamp and the reception desk," he says. "We're going to wear masks for some time to come, and we'll be less likely to shake hands with patients than prior to COVID." He does believe that many COVID safety measures will eventually be removed. "However," he says, "I think we have to take this in a stepwise fashion. We'll stop one thing at a time, and remain sensitive to what our patients are expecting."

Dr. Stonecipher believes many of the changes forced by COVID will remain in place once the pandemic subsides. "We're much more efficient now," he notes. "In addition, laws have been changed that have made a difference. Before COVID I wasn't allowed to contact patients by cellphone. Now, we can text you or your loved ones, and we do. When a patient comes in for LASIK, we call or text the family members to say 'He's going in for surgery;' then, 'He's back from surgery.' Finally we call to say we're bringing the loved one out. Patients and family members love it."

Corinne Z. Wohl, MHSA, COE, president of C. Wohl and Associates, a practice management consulting firm based in San Diego, notes that some changes wrought by COVID probably should have been in place

all along. "For example, we did a study that found that doctors pre-COVID only sanitized their hands half of the time between patients," she says. "That's certainly changed. Smart practices will embed this kind of safety protocol—and especially the visibility of safety protocols—into their routine going forward."

Ms. Wohl says she believes the COVID experience will also lead to lasting changes in most practices' attitudes regarding staff taking sick days. "In the past, people felt pressure to not call in sick," she notes. "Now, if someone isn't feeling well, they don't want you anywhere near the office. I suspect this change will remain for some time to come."

Planning for What's Next

After a tumultuous year—with plenty of uncertainty about the future remaining—many practices are unsure whether to resume planning for expansion or focus on staying the course. "Planning to expand still makes sense in most instances," says Mr. Pinto. "However, it's an individual question. Strategic planning and the growth and development of a business is as much about the personality of the doctor as it is about the opportunities in a particular marketplace.

"Because of COVID, some clients have had the personal epiphany that life is short and they don't want to work as hard or build as big as they did before the crisis," he notes. "Other clients—more aggressive ones—have said, 'Wow, there are lots of opportunities cropping up in the midst of all of this.' They say, 'Let's take all the energy we put into our pandemic response and put that back into our growth and development plans.' At the same time, small practices that may have been hit hard by the pandemic might be thinking about becoming part of a larger organization. In fact, we're seeing a lot of merger and acquisition activity right now."

"If I was planning to start a practice, I'd go ahead and do that," says Dr. Stonecipher. "However, these are not normal times. For example, right now we can't find an OD to hire. My colleagues are saying that there's a paucity of physician assistants as well."

"I'm advising clients to pivot from business planning—which focuses on day-to-day and week-to-week urgencies—to longer planning cycles," says Ms. Wohl. "We're updating long-range planning documents, helping practices dust them off and move on to better times. In most practices the trauma and fear triggered by facing the unknown with COVID-19 has calmed down. Most of them are going full-steam-ahead with plans to return to their historic norms, and beyond."

Mr. Pinto says practices should continue to communicate, create written plans and focus on managing projects effectively. "I recently pointed out to a client that he had a task force that was working hard to respond to the pandemic," says Mr. Pinto. "I told him, 'Don't disband the pandemic task force. Just change its name to "the operating committee." Meet every two weeks and make sure the practice is working as well as it can.' If you take that newfound energy and apply it to creating the best possible future practice, you'll emerge from this crisis with the greatest success.

"If a client asked whether they should hold off on growth and development because COVID might rear up again, my answer would probably be no," he concludes. "There are opportunities now that will sunset after the pandemic is over. So if your plan is to grow and build your practice, now is the time to get back to doing that."

The Long-lasting Impacts

So what will be the legacy of this crisis? Mr. Pinto believes the most fundamental change wrought by the pandemic has nothing to do with plexiglass shields or empty waiting rooms. "The most seminal component of this is a changed sense of what constitutes a big problem in a practice vs. a small problem, and how we respond to it briskly," he says. "In the past if you asked an ophthalmologist, 'What do you most fear?' the answer would be a comparatively small concern like: What if my favorite lens was no longer available?

"In the context of COVID, those sort of challenges are penny-ante," Mr. Pinto continues. "This experience has shown how strong and resilient we really are. And, it's given everyone a kind of vaccination preparing them for the next crisis—whether it's a tornado, or a building that burns down or a key staff member who leaves the practice. There'll be a kind of adroitness in responding that wasn't there before."

Mr. Pinto says another thing that's going to stick around is an increased appreciation for the concept of project management. "The response to COVID has been one giant, ongoing project," he points out. "I think everyone has taken their game up a notch in terms of project management. Clinicians and administrators have become better at collaborating with the appropriate people; writing in-depth plans; nominating leaders; and holding those leaders accountable for outcomes. These skills aren't going to disappear when the pandemic ends.

"I think the biggest meta-lesson to come from the pandemic is how profoundly resilient ophthalmology is as a profession," he concludes. "We've gotten through this better than almost any other type of service providers, except for people who are making masks and vaccines and PPE. No matter what happens, there are still 650 million eyeballs in America. That translates to an unrelenting market demand for better vision and preserving our sight." ◀

1. Saleem SM, Pasquale LR, Sidoti PA, Tsai JC. Virtual Ophthalmology: Telemedicine in a COVID-19 Era. Am J Ophthalmol 2020;216:237–242.

IOL REVIEW: 2021 NEWCOMERS

Three unique, non-diffractive/non-multifocal IOLs that strive for a greater range of vision.

BY CHRISTINE LEONARD
ASSOCIATE EDITOR

The Acrysof IQ Vivity (Alcon), Tecnis Eyhance (Johnson & Johnson Vision) and Rayner RayOne (a recent addition that was approved at press time) intraocular lenses were approved by the U.S. Food and Drug Administration this year. The lenses feature technologies not seen in the United States until now: Vivity is the first non-diffractive EDOF lens, and Eyhance and the RayOne are the first approved enhanced monofocals that extend depth of focus. These lenses may broaden the pool of potential candidates seeking greater range of vision, because they've each been shown to have low visual side-effect profiles and slightly increased tolerance of mild pathology. In this article, we take a look at the unique designs and features of these lenses.

The Vivity Extended-Vision IOL

Vivity is a novel, non-diffractive extended-depth-of-focus intraocular lens with a 6-mm biconvex, aspheric, wavefront-shaping optic that uses Alcon's proprietary X-Wave technology. The lens material is a hydrophobic acrylate/methacrylate copolymer with UV and blue light filtration. The lens is available in powers of +15 D to +25 D in 0.5 D increments. It's also available in a toric version.

Vivity is similar to a monofocal in that it's non-diffractive and has a comparable visual disturbance profile, but it's a true extended-depth-of-focus lens with a unique central optic, says Cathleen McCabe, MD, who was part of the FDA clinical trial. Alcon calls this lens a "disruptive" technology, indicated for patients who aren't suitable for diffractive lenses.[1] "We worry about implanting diffractive lenses in patients with pathology, since those lenses split light," she says. "We don't have that concern with Vivity."

Vivity's Novel Approach

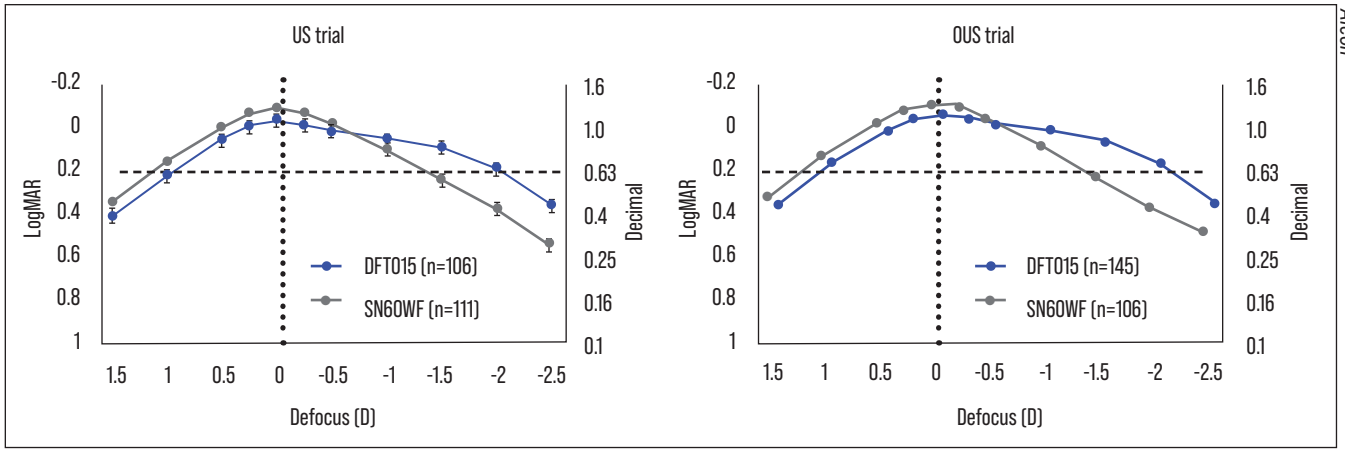
Vivity achieves an extended range of vision by reshaping the wavefront with its central optical element. This element has two features that affect the wavefront differently: elevation and a curvature change. Dr. McCabe explains that the elevation slows down the central wavefront, while peripheral light rays continue to enter the eye and proceed to the retina at the same speed, effectively stretching out the wavefront.

"The peripheral light rays, which focus for distance, reach the retina first, and the folding in of that wavefront, because of the delay in the central portion, extends the focused column of light from distance images outside the 2.2-mm zone all the way to the near-point, somewhere between -1.5 and -2 D," she says. "That stretched column of precisely focused light allows for a continuous range of vision from distance through intermediate and functional near range.

"The light rays in the middle are slowed down, so they come into focus in front of the retina, in the myopic range," she continues. "If the lens had only this elevation element, it would stretch the wavefront equally in front of and behind the retina. However, all of the light energy focused behind the retina, in the hyperopic range, is unusable. That's where the second element comes in. The small curvature change in the central 2.2-mm portion of the optic redis-

This article has no commercial sponsorship.

Dr. McCabe is a consultant for Alcon. **Dr. Berdahl** is a consultant for Alcon, Johnson & Johnson Vision, Bausch + Lomb and RxSight. **Dr. Chang** is a consultant for Johnson & Johnson Vision. **Dr. Findl** is a scientific advisor to Alcon, Carl Zeiss Meditec, Johnson & Johnson Vision, Croma and Merk. **Dr. Goes** has no relevant financial disclosures.



Alcon

Figure 1. At six months, Vivity provided continuous vision from distance to functional near in both trials. Vivity had a greater negative range of binocular defocus than the monofocal.

tributes the light energy that would have ended up behind the retina to the front of the retina. The summation of these two optical elements stretches the wavefront into a longer column of light and shifts the light energy to the functional near focus point instead of behind the retina."

One of the effects of not splitting light is good image quality. "When light is split, as in a diffractive optic, it's lost," Dr. McCabe notes. "For instance, a trifocal lens will use about 50 percent of the light to focus for distance, and 25 percent each for intermediate and near, so if you put a lens like that in a compromised eye, you may not have the image quality that you'd have in a healthy eye."

The Ideal Vivity Patient

Alcon says that Vivity is suitable for patients with imperfect or healthy eyes who are seeking an extended range of vision. "Vivity performs well in eyes that aren't pristine; it can provide some near vision, but not spectacle independence," says John Berdahl, MD, of Vance Thompson Vision in Sioux Falls, South Dakota, who was also involved in the clinical trial. "These lenses are also suitable for patients or surgeons who are intolerant of the potential for dysphotopsias. In my practice, I use Vivity primarily in non-pristine eyes. These are eyes that may have a little irregular astigmatism, some dryness or maybe mild pre-perimetric glaucoma, mild dry AMD or mild epiretinal membrane, but the patients still want some spectacle independence."

While Dr. Berdahl uses Vivity in less-than-pristine eyes, he says there isn't currently much data to support this. "You want to be cautious with this lens or any lens in eyes that are diseased," he says. "Our best data comes from the FDA clinical trial, but our experience so far has been pretty good. I wouldn't use this lens at first in significantly aberrated eyes or eyes with other significant pathology, however. Get a sense of how the lens performs and then you can consider moving into those more 'edge' cases."

Visual Outcomes with Vivity

Patients implanted with Vivity achieved significantly better intermediate and near vision compared to the SN60WF monofocal in both the US (n=220) and OUS (n=282) trials.

One of the clinical trial findings of particular interest was the amount of good distance vision the lens also provided, says Dr. Berdahl. "Distance vision was as good as the monofocal lens, and that was impressive," he says.

At six months postop, Vivity provided an improvement of a line or better in binocular distance-corrected, uncorrected intermediate and near vision versus the monofocal. Also at six months, 98 percent, 97 percent and 58 percent of Vivity patients reached 20/32 or better for binocular distance, intermediate and near (near point 40 cm), respectively. Mean MRSE was 0.049 D in the Vivity group (n=107) and 0.081 D in the monofocal group (n=113). Additionally, 91.6 percent of first eyes in the Vivity group were within 0.5 D of target versus 86.5 percent in the monofocal group.[2]

Overall, patients in the clinical study were satisfied with their quality of vision with Vivity. "The U.S. trial found that 94 percent and 88 percent of patients rated their vision as 'good/very good' without spectacles in bright and dim light, respectively, compared to 92 percent and 78 percent, respectively, with the monofocal," says Dr. McCabe. "I think this line of questioning is a good surrogate for how a lens is actually performing for them at different distances."

Vivity demonstrated no statistically significant difference from the monofocal in terms of visual disturbances. Two percent and 1 percent of Vivity patients reported that they were bothered "very much" by starbursts and halos, respectively. There were no complaints of glare. Dr. McCabe says complaints were elicited by showing patients pictures of mild, moderate and severe glare, halos and starbursts as reference points. "Because of this questionnaire method,

outcomes were reproducible in the OUS and US studies," she explains. "Numerically, it's interesting that the starbursts and glare were better in the Vivity than the monofocal lens for both sets of data points, and the halos were slightly more present in the Vivity. But again, none of those were statistically significant differences. Blur, however, was statistically significantly better with the Vivity lens."

Early Experiences

"One of the interesting things about Vivity is that it has a big plateau of 20/20 or better vision from +0.5 to -0.5 D on the binocular defocus curve," Dr. McCabe says (*Figure 1*). "It provides this 'flexible and forgiving' plateau of targeting for postoperative refractive error. Because of that forgiveness around plano, Vivity patients had slightly better uncorrected distance visual acuity than the monofocal patients.

"In the US trial we had to choose the target closest to plano, but in the OUS trial they could choose first minus, if they wanted to," she continues. "With that flexibility in targeting, there were a number of patients who had at least a half diopter of difference between the two eyes, and in that subset of patients they did have an improvement in one line at intermediate and near. Based on that, it seems like mini monovision would be a strategy that would allow for a little enhancement of intermediate and near vision.

"In my practice, I've been targeting the dominant eye for plano and the nondominant eye for -0.5 D," she says. "I've had a few patients who ended up slightly more myopic, but I think the sweet spot is around -0.5 D. We'll have data to back that up when the investigator-initiated trials conclude."

She adds that because of the plateau around plano, it's important to push plus in refractions postoperatively. "You can think they're a little more myopic than they actually are," she says.

Dr. McCabe points out that Vivity strongly resembles its monofocal cousin, so it's important to pay attention in the OR, especially when doing high-volume surgery. "It looks like the monofocal in every way until the light reflex from the microscope hits the surface of the lens exactly right—then you can see the central optical element," she says.

"The bench data for this technology showed that the point-spread function of light distribution is very tolerant of decentration and tilt, but you still want to look for the light reflex so you can center the lens and not mistake it for a monofocal," she adds. "Postoperatively, it's kind of the same thing—if the pupil isn't very dilated and you don't get the slit lamp exactly at the right angle, it's hard to see that this lens isn't just a monofocal. You have to look for that central element." To view a video of this light reflex, and additional photos, check out the online version of this article at reviewofophthalmology.com.

Eyhance

Eyhance is a one-piece monofocal with a 6-mm biconvex, aspheric anterior surface, made of a UV-blocking hydrophobic acrylic. It features a frosted, continuous 360-degree posterior square edge and C-haptics, offset from the optics. Johnson & Johnson Vision says that this lens provides a 30-percent improvement in contrast in low-light conditions at 5 mm compared to a standard monofocal and has a low dysphotopsia profile, comparable to that of the Tecnis one-piece monofocal. It's available in powers of +5 D to +34 D in 0.5-diopter increments, and also comes in a toric version.

The lens is one of a new breed of monofocals that offers increased depth of focus compared to standard monofocals. Others include the Xact Mono-EDOF (Santen), which isn't available in the United States (*see sidebar*) and RayOne EMV (Rayner), which was approved in late March.

"Eyhance is intended to provide 0.5 D better intermediate vision or 0.5 D better range [than a standard monofocal] at the 20/32 line," says Daniel Chang, MD, of Empire Eye and Laser in Bakersfield, California. "For reference, the Symfony provides more than 1 D of extended range of vision."

While not an EDOF lens, Johnson & Johnson says Eyhance does deliver true intermediate vision, and that its designation as a monofocal lens will benefit patients looking for more range of vision but who may not be able to afford an EDOF.

Eyhance's Unique Design

Eyhance's higher-order aspheric

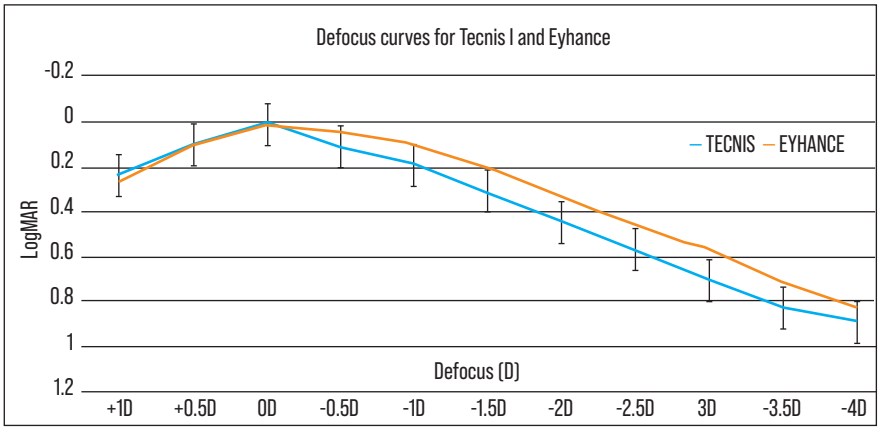
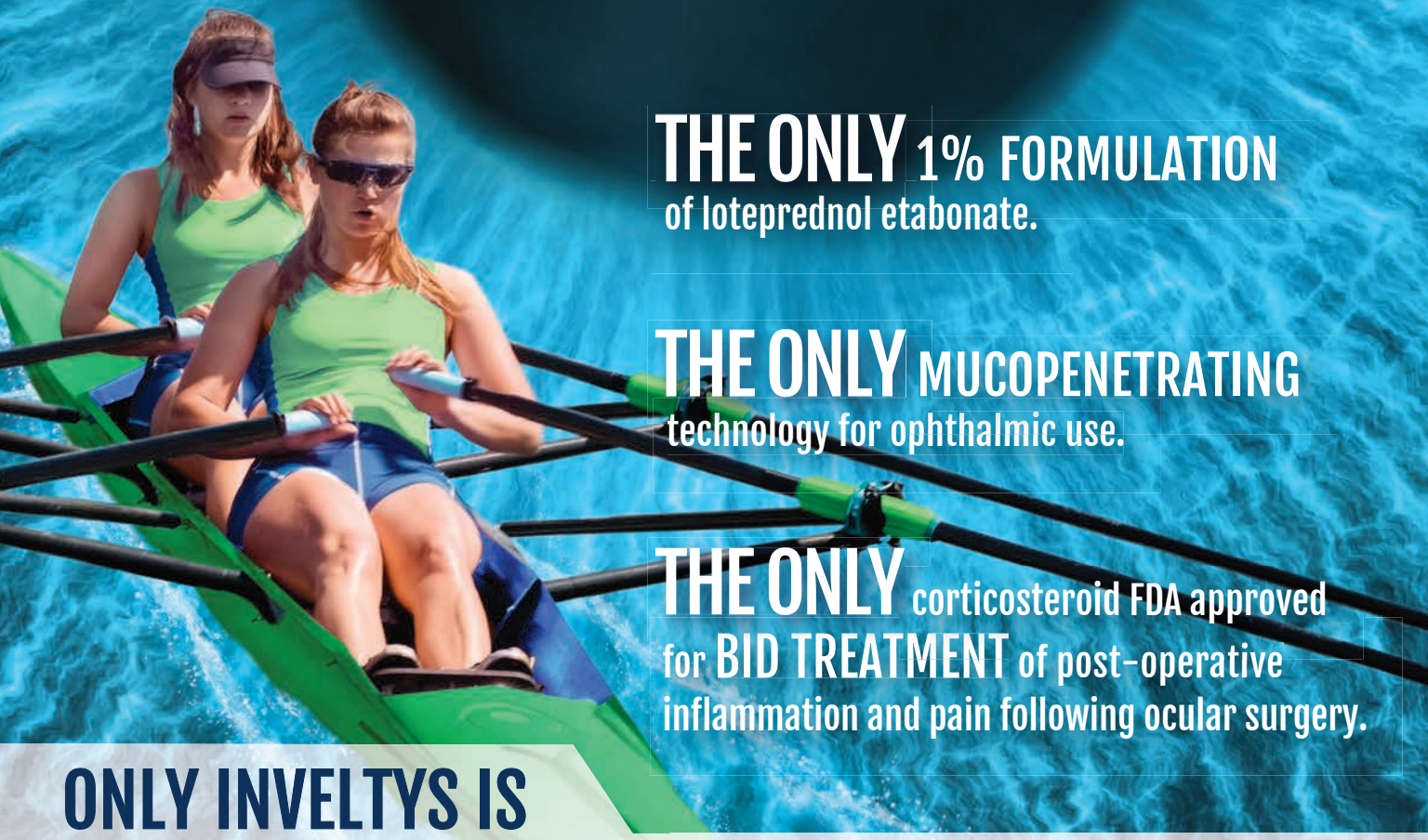


Figure 3. Mean monocular defocus curves for the Tecnis Eyhance (n=71) and Tecnis one-piece monofocal (n=45). Both were similar at 0 D, corresponding to distance (p=0.72). Eyhance had significantly better visual acuity from -0.5 to -4 D and also performed better at intermediate (defocus at -1.5 D) and near (defocus at -2.5 D) distances (p<0.01).[7]



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

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. If this product is used for 10 days or longer, IOP should be monitored.

Use of corticosteroids may result in posterior subcapsular cataract formation.

Use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

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

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

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

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

Please see Brief Summary of Prescribing Information for INVELTYS on the next page.

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INDICATIONS AND USAGE
INVELTYS is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.

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

WARNINGS AND PRECAUTIONS
Intraocular Pressure (IOP) Increase—Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, as well as defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. If this product is used for 10 days or longer, intraocular pressure should be monitored.

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

Delayed Healing—Use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

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

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

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

Risk of Infection—Do not to allow the dropper tip to touch any surface, as this may contaminate the suspension.

Contact Lens Wear—The preservative in INVELTYS may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of INVELTYS and may be reinserted 15 minutes following administration.

ADVERSE REACTIONS
Adverse reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with infrequent optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, delayed wound healing and secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

Clinical Trial Experience—Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The most common adverse drug reactions in the clinical trials with INVELTYS were eye pain and posterior capsular opacification, both reported in 1% of patients. These reactions may have been the consequence of the surgical procedure.

USE IN SPECIFIC POPULATIONS
Pregnancy—Risk Summary: INVELTYS is not absorbed systemically following topical ophthalmic administration and maternal use is not expected to result in fetal exposure to the drug.

Lactation—Risk Summary: INVELTYS is not absorbed systemically by the mother following topical ophthalmic administration, and breastfeeding is not expected to result in exposure of the child to INVELTYS.

Pediatric Use—Safety and effectiveness in pediatric patients have not been established.

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility—
Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma thymidine kinase (tk) assay, or in a chromosome aberration test in human lymphocytes, or *in vivo* in the single dose mouse micronucleus assay.

For a copy of the Full Prescribing Information, please visit www.INVELTYS.com.

Manufactured for:
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US-INV-2000053 August 2020

surface produces a change in power without using the diffractive rings commonly seen in many premium IOLs. "Standard aspheric designs predominantly change shape in the peripheral part of the lens, but the higher order asphere in Eyhance is designed to create a smooth and continuous increase in power from the periphery to the center of the lens, as well as continuously change shape in the central part of the lens," explains Frank Goes Jr., MD, of the Goes Eye Centre in Antwerp, Belgium.

"The higher-order apshere is rotationally symmetric and doesn't influence asymmetric higher-order aberrations such as coma," he says. "Eyhance's periphery is the same as the Tecnis one-piece IOL, and this feature enables both IOLs to reduce spherical aberration to near zero. The two lenses have the same base geometry, and the difference in shape is in the range of microns, which still means a lot for the lens power. Because the power change is continuous, it's not visible to the naked eye on the lens—i.e., Eyhance doesn't have any rings or disruptive changes in power. In terms of optical design, both lenses are refractive and reduce spherical aberration to near zero."

One study analyzing Eyhance's optical performance reported that the add power in the central 2-mm zone, coupled with the lens's greater negative spherical aberration values, induced a myopic shift of the maximum optical quality to improve intermediate vision.[6] With a 2-mm pupil, the maximum of the through-focus MTFa curve of Eyhance shifted to a myopic defocus of -0.5 D, they reported. For larger pupils of at least 3.5 mm, they found no differences between Eyhance and the ZCB00.[6]

Eyhance Patient Selection

Dr. Chang says that Eyhance offers a nice compromise for patients who may not be great candidates for presbyopia-correcting lenses, either because of concurrent pathology or some refractive uncertainty. "It doesn't compromise image quality, so even patients with some associated pathology will tolerate this lens well," he says. "I like that I can give them something more than a traditional monofocal or monofocal toric. "

Oliver Findl, MD, chief of the Institute and chief of the department of ophthalmology at Hanusch Hospital in Vienna, Austria, agrees, noting that his practice has been using Eyhance as its standard monofocal since the spring of 2019. "We're able to implant this lens in patients with comorbidities such as mild corneal pathology, glaucoma, AMD, DR and DME," he says. "I wouldn't expect more visual side effects from this lens, and in the two years I've been implanting it, I haven't encountered those effects."

Eyhance Studies

Several studies have found that the modified monofocal Eyhance delivers superior intermediate vision compared to standard monofocals.[3-5,7,9,11] Three studies found it offered better spectacle independence[3-5] and one study found it provided better tolerance of residual refractive error.[3]

The first study comparing Eyhance (n=80 eyes) to the ZCB00 reported significantly higher uncorrected intermediate visual acuity with Eyhance. Eyhance achieved 0.28 logMAR ±0.11 (Snellen equivalent: 20/38 ±20/25) versus the monofocal's 0.4 ±0.1 (20/50 ±20/25), $p<0.000$, for monocular UIVA. For binocular UIVA, Eyhance achieved 0.16 ±0.1 (20/28 ±20/25) versus 0.27 ±0.06 (20/37 ±20/22), $p<0.21$, with the monofocal.

Another independent study found that Eyhance provided better visual acuity than the ZCB00 across a greater range of defocus levels, including near vision.[7] Researchers assigned 116 consecutive eyes undergoing phacoemulsification for cataract to either Eyhance (n=71 eyes) or the monofocal (n=45 eyes). The visual acuity target was 0 D, or emmetropia, in both groups. Uncorrected intermediate and near visual acuity were significantly better with Eyhance, with both IOLs demonstrating comparable distance vision results (*Figure 2*).

A retrospective case-control study published in February comparing Eyhance to the Tecnis PCB00 monofocal found that Eyhance provided a significant improvement in intermediate visual acuity compared to the monofocal without compromising distance vision. The study included 120 eyes of 60 patients (30 in each group) who underwent bilateral cataract surgery. Average binocular UDVA was 20/22 and 20/20 in the Eyhance and PCB00 groups, respectively ($p=0.62$). Average binocular

OUS Non-multifocal Option for Extending Range of Vision

Santen's Xact Mono-EDOF is a CE-marked monofocal IOL that offers continuous focus from distance to intermediate with a minimal level of glare and halo, according to the company. The 12.5-mm lens is made from the same glistening-free hydrophobic acrylic material as the FDA-approved enVista, but with blue light filtration. It's available in powers of +10 to +30 D in 0.5-diopter increments.

A Phase IV clinical study of 39 eyes of 23 patients reported six-month follow-up data for monocular (n=7) and binocular (n=16) implantation with Xact. Binocular intermediate VA at 50 cm, 60 cm and 70 cm were 20/37, 20/29 and 20/27, respectively. DCIVA and UCIVA values were similar.[1]

1. New concept monofocal IOL with continuous focus. ESCRS Euro Times Supplement November 2019. Accessed 25 March 2020. https://www.eurotimes.org/wp-content/uploads/2019/11/Santen_Monofocal_Supplement_November2019-Press-Quality.pdf.

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UIVA was 20/30 in Eyhance and 20/40 in the control ($p<0.001$). According to the quality-of-life questionnaire administered, Eyhance patients reported less difficulty in performing activities requiring intermediate vision compared to the PCB00.

Eyhance Impressions

"In my experience, patients' distance visual acuity is similar or identical to that of a classic monofocal lens," Dr. Findl says. "The need for distance glasses tends to be a little less with Eyhance than with a monofocal lens as well. I believe the reason for this is because Eyhance has a larger landing zone for emmetropia, meaning that if the patient is slightly off-target postop, they'll still have pretty good unaided vision. This lens seems to have good tolerance to slight deviations in the postop refraction."

Dr. Goes says that his experience with Eyhance has been similar to the results reported by Professor Gerd Auffarth and his colleagues.[8] "I've found that Eyhance improves the monocular as well as the binocular DCIVA and UIVA by at least one line on the logMAR scale, while distance vision is comparable to the ZCB00," he says. "It also has contrast sensitivity comparable to the monofocal and doesn't have the side effects of multifocal intraocular lenses."

Eyhance's similarity to its monofocal cousin makes adapting to this lens easy for surgeons, according to Dr. Findl and Dr. Goes, who note that Eyhance also uses the same IOL constants as the monofocal. "You should treat this lens like a monocal," Dr. Goes advises. "It's very forgiving." He highly recommends using the max plus technique for refraction.

Because of the forgiving landing zone on the defocus curve, Dr. Chang says you can try two refractive strategies with Eyhance. "This lens has a single wide peak, as opposed to two peaks in its defocus curve, which presupposes some interesting options," he says. "You could use Eyhance to increase the range of intermediate vision and possibly some near vision, or you could left-shift the defocus curve so you can have some tolerance to refractive error. Eyhance has a smaller peak than the Symfony, so you'd only aim for about +0.25 D hyperopia with this lens. In essence, if you have more variability in the refractive target, you can still maintain good distance vision. The flip side of aiming hyperopic is that you won't gain intermediate or near vision."

Breaking News: The RayOne

At press time, the RayOne EMV (Rayner Global) received FDA approval from the United States Food and Drug Administration. Rayner says this monofocal offers up to 2.25 D (with 1-D offset) of extended depth of vision. The lens was created for patients desiring spectacle independence who aren't suitable candidates for diffractive trifocals. Additionally, the company says, "RayOne EMV is a cost-effective solution for patients when diffractive IOLs may be cost prohibitive or if there are concerns about dysphotopsias."

The 12.5-mm single-piece Rayacryl hydrophilic acrylic lens is available in powers of +10 to +30 D in 0.5-diopter increments in a preloaded intraocular lens injection system.

In a clinical study (n=20), the CE-marked lens demonstrated 20/20 vision in binocular UDVA and dominant eye UDVA, J1/J2 on the Jaeger chart (approximately equivalent to 20/24) for binocular UIVA and 20/32 vision for binocular UNVA.[12]

The newly-approved RayOne enhanced monofocal.

These newly approved IOLs are making strides toward what surgeons say is the future standard of IOL technology: lenses with the fewest visual side effects and the greatest range of vision. But as with any refractive procedure, experts say it's best to under-promise and over-deliver.

"Don't promise intermediate vision," says Dr. Goes, referring to the Eyhance, "but do tell the patients that their intermediate vision will be better than it would be with a normal monofocal lens, and that the landing zone of the lens is also better." ◀

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TREATING GLAUCOMA IN THE AGE OF MIGS AND LASER

Surgeons' protocols continue to evolve as new options appear and gradually prove their value.

BY CHRISTOPHER KENT
SENIOR EDITOR

Fifty years ago, only a handful of options existed for treating glaucoma. Today we have multiple medications, numerous surgeries, new laser options and new tools and devices. But as new treatment modalities appear, surgeons have to decide whether to incorporate them into their armamentariums—and perhaps more important, *how* to incorporate them.

"My treatment paradigm has definitely shifted in recent years," says Thomas W. Samuelson, MD, a founding partner and attending surgeon at Minnesota Eye Consultants in Minneapolis and an adjunct professor of ophthalmology at the University of Minnesota. "For the better part of my career, it was medications, then laser, then surgery. That's changed completely.

"One of the first things that triggered that change was the realization that cataract surgery helps lower eye pressure," he explains. "We have definitive, level-one evidence that demonstrates this. So today, one of the first metrics I look at when I see a new patient with glaucoma is the status of the native lens. Does the patient have a cataract, and is it ready to be removed? If so, then we go down one pathway: cataract surgery, plus or minus MIGS. If there's no cataract that's ready to be removed, then we go with medications or laser. And now we even have two different options with medications: eye drop therapy or the implantable, sustained delivery device, Durysta."

Joseph F. Panarelli, MD, an associate professor of ophthalmology and chief of the Glaucoma Service at NYU Langone Health in New York City, notes that new options rarely become the new first-line treatment right off the bat. "Whenever a new treatment option becomes available, many of us slowly work it into our treatment regimen," he says. "This often means not using it as a first-line treatment [in the beginning], because we want to gain more experience with it and see what the risks and benefits are in our patient population. Phase III results and other study data are very helpful in guiding us early on, but those results are not generalizable. Therefore, many of us will only resort to these treatment options when our usual topical medications don't get the job done. Meanwhile, the patient's preferences are still a key factor. For that reason, the decision-making process is shared with the patient."

Here, surgeons with extensive experience treating glaucoma share their thoughts on the current state of glaucoma treatment protocols.

New Topical Drops

Among the recent entries into the field of treatment options are several newly approved topical drugs, including rho kinase inhibitors and latanoprostene bunod.

Albert S. Khouri, MD, a professor of ophthalmology and director of resident education and the glaucoma service at Rutgers New Jersey Medical School, was involved in the clinical trials of the new rho kinase

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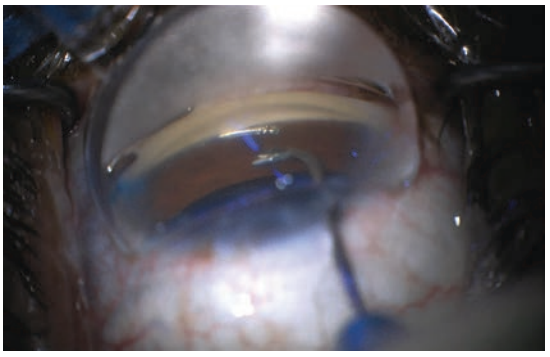
Dr. Samuelson is a consultant for Alcon Surgical, Abbott Medical Optics, AqueSys/Allergan, Equinox, Glaukos, Ivantis, Bausch + Lomb, Aerie, Advantix, SightScience, New World Medical and iScience. **Dr. Khouri** has received grant support from Allergan, is a consultant for Glaukos, and is on the speakers bureau for Allergan, Aerie and Bausch + Lomb. **Dr. Panarelli** is a consultant to Santen, Allergan, CorneaGen, New World Medical, Glaukos and Aerie. **Dr. Asrani** reports no financial ties to any product discussed.

inhibitors and latanoprostene bunod. "The last new class of drugs, the prostaglandins, appeared back in 1996," he points out. "Between then and 2018, when Rhopressa and Vyzulta appeared, we only got new fixed combinations of existing medications. Today, we have Rocklatan, the only FDA-approved fixed combination in the U.S. that includes a prostaglandin. Previous combinations incorporating prostaglandins didn't meet clinical trial endpoints, so they weren't approved by the FDA."



MIGS procedures such as the Hydrus make useful adjuncts to cataract surgery as a first-line treatment for a new glaucoma patient with a cataract, but other patients are likely to shy away from surgery as a first option.

Dr. Khouri believes these recent developments may shift the equation back toward favoring drug treatment options. "Among other things, we finally have medications that target the trabecular meshwork," he notes. "All of the previous medications we've had bypass the trabecular meshwork, either by reducing aqueous production or by diverting aqueous away from the trabecular meshwork into the uveoscleral outflow pathway. In contrast, rho kinase inhibitors enhance the trabecular meshwork, allowing more aqueous to flow through the traditional outflow channel. It's even possible that these new drugs will have an impact on the natural history of the disease if introduced early in the disease process. Time will tell."

Dr. Khouri notes that the *Preferred Practice Pattern* guidelines from the American Academy of Ophthalmology suggest that your first medication should deliver a 20- to 30-percent reduction in IOP from baseline. "To achieve that, most physicians typically start with a prostaglandin like latanoprost," he says. "It's effective; it's easy to use; it's well-tolerated. Also, it's used once a day, which is good for adherence—very important with a topical therapy. The prostaglandins have minimal systemic side effects, although there are some ocular side effects. Generally the discontinuation rate is pretty low, so they're well-tolerated. These brand new medications are well-positioned to become first-line options."

"There's an added potential for lowering IOP with the use of drugs like Rocklatan and Vyzulta, compared to a prostaglandin alone," says Sanjay Asrani, MD, a professor of ophthalmology at Duke University School of Medicine and director of the Duke Eye Center of Cary in Durham, North Carolina. "So, there's a possibility that one of these drugs used first-line could achieve the target pressure. That could change the game. The question is whether they'll work for everybody, and whether they'll be tolerated by everyone. That will have to be determined by trial and error."

"Netarsudil has a great mechanism of action; it's greatest limitation is tolerability," notes Dr. Samuelson. "Hyperemia is very common, and a significant number of patients haven't been able to tolerate it. But for patients with more advanced disease, or patients who have limited other options, I think it's a great drug for lowering pressure. Patients that already have physiological pressures tend to respond better to netarsudil than some other agents, based on its novel mechanism."

Perhaps more problematic, in terms of widespread acceptance into the glaucoma treatment regimen, are the issues of pricing and reimbursement. "Many of these drugs aren't covered by insurance unless you've tried another drug first," Dr. Asrani notes. "In the future, if a patient needed a significant pressure drop and could tolerate the new drugs and reimbursement wasn't an issue, they might be one-and-done—a single eye drop per day. But right now many insurances are still requiring that the patient try a prostaglandin first."

"We've had difficulty getting payors to price netarsudil so that patients can afford it," Dr. Samuelson adds. "Also, the tolerability is an issue. However, I do like to find out if a given patient is able to tolerate it, because it's a great option with a very favorable and novel mechanism of action if the patient can tolerate it and get it for an affordable price."

He notes that latanoprostene bunod seems to have better tolerability than netarsudil. "It's pretty uncommon that patients don't tolerate it," he notes. "It's basically latanoprost with a nitric-oxide-donating component; that gives it about a 1.3-mmHg advantage over standard latanoprost. But it tends to be very pricey, which can be a problem. But despite these concerns, I've found netarsudil and latanoprost bunod to be important options to have for patients with moderate or severe glaucoma."

Selective Laser Trabeculoplasty

SLT has been a treatment option for glaucoma for a number of years, but the recent data from the LIGHT (Laser for the Initial treatment of Glaucoma and ocular HyperTension) trial, conducted in the United Kingdom, has caused many ophthalmologists to rethink where this option belongs in their treatment protocol.

"Previous studies demonstrated that laser was about as effective as, say, a prostaglandin analogue," Dr. Samuelson says. "But that knowledge didn't change practice patterns as much as the data from the LIGHT trial did, because in the LIGHT trial, not only did the laser

group do as well as the drop group, they did *better* in many ways. They had fewer subsequent surgeries, including less need for subsequent cataract surgery. Patients did better both economically and medically. Their glaucoma was better controlled if they had laser first.

"That caused a paradigm shift for patients needing initial treatment," he continues. "We offer those patients first-line laser much more often now. And because we have more confidence in our story—that is, we have a prospective, randomized trial that showed laser is at least as good, and probably better than eye drop therapy—we can not only be confident in offering it, but confident in recommending it."

Nevertheless, it appears that SLT isn't yet displacing a prostaglandin as the most frequent first-line treatment, for a number of reasons ranging from patient perception to the difference between trial data and real-world clinical realities. "Most physicians are aware of the LIGHT study findings and support the idea of using SLT as an initial therapy, but in real-life practice, not that many of us actually do," confirms Dr. Khouri. "For one thing, in the U.K., where the LIGHT study was conducted, the health-care system is very different from here in the U.S. For another thing, it's easier for many patients to accept the use of an eye drop than the laser. I discuss SLT with patients upon diagnosis so they know it's an option, but for some, the word 'laser' triggers a negative response."

Dr. Asrani agrees. "The main reason most patients are still being treated with drops first is that not everyone is comfortable starting with a procedure," he says. "Recommending a procedure at your first meeting may be perceived as an aggressive stance. Furthermore if a drop doesn't work, the patient doesn't usually perceive that as being your fault. But if SLT doesn't work, the patient may assume that you didn't do a good job. And of course, some doctors may not be very conversant with doing SLT, making them inclined to go straight to drops."

Dr. Samuelson points out two caveats about the LIGHT trial data. "It's important to realize that in the LIGHT trial, about a third of the patients that received laser were ocular hypertensives," he says. "They weren't even categorized as glaucoma patients. So, this was a patient population with pretty mild glaucoma. This means that the results of the LIGHT trial can't be extrapolated to patients with more severe glaucoma. Many of us looked at the results of the LIGHT trial and thought, 'I don't see response rates as good as those reported in this trial.' The reason may be that we're not used to doing laser on such early glaucoma cases. If your patient has much more severe glaucoma, you can't necessarily expect to see the same response."

So what's the current reality regarding SLT? "What I think has really changed because of the LIGHT study is that we're now typically offering SLT after the first medication," Dr. Khouri says. "Many years ago we'd discuss SLT with patients when they weren't reaching their target on the second or third medication. Now, if the pressure isn't on target after a prostaglandin, for example, we quickly discuss SLT."

Dr. Samuelson notes that he rarely tries to persuade the patient to do SLT. "I offer it and maybe give a gentle recommendation, but if the patient is resistant to having laser as their initial treatment, I don't push it," he says. "I'd say about half of these patients choose to start with the laser treatment. When patients are indecisive or hesitant, I just take out my business card and write down 'the LIGHT trial (Laser for the Initial treatment of Glaucoma and ocular Hypertension Trial)' and hand it to the patient. I say, 'We'll start with this drop. If you're interested, go online and take a look at this trial that was conducted in

A STANDALONE MIGS FOR FIRST-LINE TREATMENT?

Although many MIGS procedures have only been approved for use in conjunction with cataract surgery, a few can be done as standalone procedures. Would they make sense as first-line glaucoma treatment options?

"I don't think patients will be inclined to undergo MIGS without first trying drops," says Sanjay Asrani, MD, a professor of ophthalmology at Duke University School of Medicine. "Even if it's a MIGS procedure, there's some risk associated with it, and some cost, and it requires a trip to the OR. You need to enter the anterior chamber, and there's always the risk of endophthalmitis or hyphema. Those risks are small, but real. In contrast, SLT and medications don't have those risks."

However, he notes that a noncompliant patient might be an exception. "The patient may have demonstrated noncompliance in other areas of medical care," he says, "or you know that the patient is at risk of losing their insurance and not being able to afford long-term medical therapy. In that situation it may be appropriate to consider proceeding with MIGS as a first choice."

"I find it hard to justify a standalone MIGS procedure as a first-line choice," says Albert S. Khouri, MD, a professor of ophthalmology and director of the glaucoma service at Rutgers New Jersey Medical School. "However, if you have patients who aren't on target, they've already had their cataract done and they want to avoid a trabeculectomy or subconjunctival procedure like a Xen or tube shunt, then you could discuss this option with them. Of course, there are some patients, such as those with juvenile glaucoma, younger patients, and those with pigment dispersion or exfoliation glaucoma, for whom goniotomies tend to be more effective. In those cases it might make more sense to attempt a goniotomy."

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INDICATIONS AND USAGE

ZERVIATE® (cetirizine ophthalmic solution) 0.24% is a histamine-1 (H1) receptor antagonist indicated for treatment of ocular itching associated with allergic conjunctivitis.

IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

The most commonly reported adverse reactions occurred in approximately 1%-7% of patients treated with either ZERVIATE or vehicle. These reactions were ocular hyperemia, instillation site pain, and visual acuity reduced.

Please see brief summary of Full Prescribing Information on the adjacent page.

References: 1. ZERVIATE [package insert]. Fort Worth, TX: Eyevance Pharmaceuticals LLC; 2018. **2.** Malhotra RP, Meier E, Torkildsen G, et al. Safety of cetirizine ophthalmic solution 0.24% for the treatment of allergic conjunctivitis in adult and pediatric subjects. *Clin Ophthalmol.* 2019;13:403-413. **3.** Meier EJ, Torkildsen GL, Gomes PJ, et al. Phase III trials examining the efficacy of cetirizine ophthalmic solution 0.24% compared to vehicle for the treatment of allergic conjunctivitis in the conjunctival allergen challenge model. *Clin Ophthalmol.* 2018;12:2617-2628.

eyevance pharmaceuticals

ZERVIATE™ (cetirizine ophthalmic solution) 0.24%

Brief Summary

INDICATIONS AND USAGE

ZERVIATE (cetirizine ophthalmic solution) 0.24% is a histamine-1 (H1) receptor antagonist indicated for treatment of ocular itching associated with allergic conjunctivitis.

DOSAGE AND ADMINISTRATION

Recommended Dosing: Instill one drop of ZERVIATE in each affected eye twice daily (approximately 8 hours apart). The single-use containers are to be used immediately after opening and can be used to dose both eyes. Discard the single-use container and any remaining contents after administration. The single-use containers should be stored in the original foil pouch until ready to use.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Contamination of Tip and Solution: As with any eye drop, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle or tip of the single-use container to avoid injury to the eye and to prevent contaminating the tip and solution. Keep the multi-dose bottle closed when not in use. Discard the single-use container after using in each eye.

Contact Lens Wear: Patients should be advised not to wear a contact lens if their eye is red.

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

ADVERSE REACTIONS

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

In 7 clinical trials, patients with allergic conjunctivitis or those at risk of developing allergic conjunctivitis received one drop of either cetirizine (N=511) or vehicle (N=329) in one or both eyes. The most commonly reported adverse reactions occurred in approximately 1%–7% of patients treated with either ZERVIATE or vehicle. These reactions were ocular hyperemia, instillation site pain, and visual acuity reduced.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There were no adequate or well-controlled studies with ZERVIATE in pregnant women. Cetirizine should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Data

Animal Data

Cetirizine was not teratogenic in mice, rats, or rabbits at oral doses up to 96, 225, and 135 mg/kg, respectively (approximately 1300, 4930, and 7400 times the maximum recommended human ophthalmic dose (MRHOD), on a mg/m^2 basis).

Lactation

Risk Summary

Cetirizine has been reported to be excreted in human breast milk following oral administration. Multiple doses of oral dose cetirizine (10 mg tablets once daily for 10 days) resulted in systemic levels (Mean C_{max} = 311 ng/mL) that were 100 times higher than the observed human exposure (Mean C_{max} = 3.1 ng/mL) following twice daily administration of cetirizine ophthalmic solution 0.24% to both eyes for 1 week. Comparable bioavailability has been found between the tablet and syrup dosage forms. However, it is not known whether the systemic absorption resulting from topical ocular administration of ZERVIATE could produce detectable quantities in human breast milk.

There is no adequate information regarding the effects of cetirizine on breastfed infants, or the effects on milk production to inform risk of ZERVIATE to an infant during lactation. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZERVIATE and any potential adverse effects on the breastfed child from ZERVIATE.

Pediatric Use: The safety and effectiveness of ZERVIATE has been established in pediatric patients two years of age and older. Use of ZERVIATE in these pediatric patients is supported by evidence from adequate and well-controlled studies of ZERVIATE in pediatric and adult patients.

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

In a 2-year carcinogenicity study in rats, orally administered cetirizine was not carcinogenic at dietary doses up to 20 mg/kg (approximately 550 times the MRHOD, on a mg/m^2 basis). In a 2-year carcinogenicity study in mice, cetirizine caused an increased incidence of benign liver tumors in males at a dietary dose of 16 mg/kg (approximately 220 times the MRHOD, on a mg/m^2 basis). No increase in the incidence of liver tumors was observed in mice at a dietary dose of 4 mg/kg (approximately 55 times the MRHOD, on a mg/m^2 basis). The clinical significance of these findings during long-term use of cetirizine is not known.

Mutagenesis

Cetirizine was not mutagenic in the Ames test or in an *in vivo* micronucleus test in rats. Cetirizine was not clastogenic in the human lymphocyte assay or the mouse lymphoma assay.

Impairment of Fertility

In a fertility and general reproductive performance study in mice, cetirizine did not impair fertility at an oral dose of 64 mg/kg (approximately 875 times the MRHOD, on a mg/m^2 basis).

PATIENT COUNSELING INFORMATION

Risk of Contamination: Advise patients not to touch dropper tip to eyelids or surrounding areas, as this may contaminate the dropper tip and ophthalmic solution. Advise patients to keep the bottle closed when not in use. Advise patients to discard single-use containers after each use.

Concomitant Use of Contact Lenses: Advise patients not to wear contact lenses if their eyes are red. Advise patients that ZERVIATE should not be used to treat contact lens–related irritation. Advise patients to remove contact lenses prior to instillation of ZERVIATE. The preservative in ZERVIATE solution, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted 10 minutes following administration of ZERVIATE.

Administration: Advise patients that the solution from one single-use container is to be used immediately after opening. Advise patients that the single-use container can be used to dose both eyes. Discard the single-use container and remaining contents immediately after administration.

Storage of Single-use Containers:
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the U.K. If you change your mind and you want to go with laser as an alternative to the drop, just give me a call.' "

Where Do MIGS Fit In?

Choices regarding when to offer minimally invasive glaucoma surgeries to a glaucoma patient have been largely influenced by the FDA labeling. "Several of the MIGS options are only approved for use in combination with cataract extraction, although a few can be done as standalone procedures," Dr. Khouri says. "The way I approach it is, any patient in need of cataract extraction who is being treated for glaucoma is a candidate for a MIGS procedure.

"In the past, once medications and laser failed to meet the target pressure, your discussion with the patient would be a trabeculectomy or a tube," he continues. "Those are more effective than phaco plus MIGS, but they're also more risky. Their complication rates are higher, and some of the complications can be grave. The phaco-MIGS procedure can keep the pressure in check for some period of time, and hopefully prevent or delay the need for a riskier procedure.

"The uncertainty with MIGS—particularly with the procedures that help get aqueous past the trabecular meshwork—centers around the condition of the traditional distal outflow from the eye," he notes. "If the distal pathway beyond the trabecular meshwork is still preserved, then you'll get a nice response from your MIGS procedure. But if the distal pathway is dysfunctional, you may not get a response beyond what the phaco would have provided by itself. Unfortunately, you're only going to find out how good the response is after the procedure. So I think it's key to discuss this reality with patients when you talk about MIGS."

What about recommending clear lens extraction to a glaucoma patient without a problematic cataract?

Dr. Samuelson says he almost never recommends a clear lens replacement to address slightly elevated pressure. "I don't take someone who has no visual complaints and offer them cataract surgery plus MIGS," he says. "I generally require a vision complaint, and the vision loss needs to be directly attributable to the cataract in most cases.

"That's not to say they have to have severe symptoms," he continues. "If they have a vision complaint and a cataract, and I think the complaint is related to the cataract, and they also need better control of their glaucoma, I'll present cataract surgery plus MIGS as an option, especially if they have an unfavorable refractive error. I explain that the procedure can improve clarity of vision, improve pressure control, reduce medications and give them a more favorable refractive error. And it's a procedure they'll need at some point in their life anyway.

"If the benefits are substantial, proceeding with phaco-MIGS is simply moving something a little forward in the treatment scheme, and the idea is generally well-received," he notes. "Of course, to take this approach, you have to mandate very low complication rates and high-quality surgery, but cataract surgery is so good these days that most of the time we can expect that."

What about just offering cataract surgery without MIGS? "The only time I might offer cataract surgery without MIGS to a glaucoma patient is when the patient has compromised angles," says Dr. Samuelson. "In that situation, just removing the cataract might be beneficial for their outflow. But most glaucoma patients can benefit from cataract surgery plus MIGS."

Continuous Drug Delivery

Another recent addition to the glaucoma armamentarium is the sustained-release device Durysta that's implanted inside the eye and releases a steady dose of bimatoprost. Using a prostaglandin as a first-line treatment is hardly a new idea, but this new format comes with several benefits and drawbacks—at least for now.

"I'm convinced that slow, sustained release is the future of glaucoma medical management," says Dr. Khouri. "We're all familiar with the obstacles to successful topical therapy: poor adherence; hand-eye coordination issues; arthritis; tremors; and poor aim, among others. These medications only work if they actually make it to the surface of the eye, and even when they do, they can cause ocular surface disease. I think a lot of the variability in IOP that we witness in glaucoma patients—which is definitely associated with progression—is due to patients not using their topical medications correctly. Slow-release drug delivery options could avoid all of these obstacles."

"Typically, these devices provide six months of pressure-lowering," notes Dr. Asrani. "Sometimes it's nine months. But we're talking about months, not years, and the sustained-delivery choice that we have at present is, unfortunately, not repeatable, per the FDA. Clearly more doctors would choose this option if it could be repeated. If a patient is controlled solely on a prostaglandin—and that's a lot of patients—but doesn't want the hassle of using drops every day, they could be better off with the prostaglandin released inside the eye rather than on the surface. These devices would not only remove the compliance concern, they'd reduce the amount of preservative getting onto the eye, and potential side effects associated with prostaglandins.

"Everyone anticipates that there will be even longer-lasting sustained-release delivery systems, or that the FDA might approve a repeat injection," Dr. Asrani adds. "That could change the way we practice. But so far, we're not there."

"I think the sustained-release implant does have a role, but there

WILL DRUGS EVER BECOME OBSOLETE?

One thing most surgeons seem to agree on: Topical drops will always need to be an option, no matter what the future holds.

"I don't see a future for glaucoma treatment in which drugs won't be around," says Sanjay Asrani, MD, director of the Duke Eye Center of Cary in Durham, North Carolina. "Everyone knows they work, and they're the least risky tool we have in our armamentarium. You can try different combinations, and you can stop them if there's a problem. The biggest issue is delivering them. If a drug-delivery platform could reliably control the pressure for a year, that could be a game-changer."

Albert S. Khouri, MD, a professor of ophthalmology and director of the glaucoma service at Rutgers New Jersey Medical School, also believes that drops will never disappear. "SLT and MIGS, for the most part, target the traditional outflow pathway," he notes. "If the outflow system has collapsed, or is dysfunctional, they won't reduce the pressure to levels that some patients with glaucoma need. Also, every surgery is associated with risk, no matter how micro-incisional or minimally invasive it is, and the outcomes are determined in part by the healing response, which is variable. That means that doing away with medical therapy would be difficult—at least with our current procedures."

Joseph F. Panarelli, MD, an associate professor of ophthalmology and chief of the Glaucoma Service at NYU Langone Health in New York City, agrees. "Topical medications are a safe, effective, and reliable way to slow disease progression," he points out. "They've worked for us for decades. They may not be the answer for every patient, but they are the answer for a large number of patients."

Dr. Asrani says he thinks it's possible that some procedure will be invented that can lower IOP significantly without much risk. "If that happens, then it's possible that many people won't need drugs anymore," he admits. "However, not everyone has access to an operating room, and not everyone is willing to take the risks associated with a procedure."

"Drugs will always be necessary," agrees Thomas W. Samuelson, MD, a founding partner and attending surgeon at Minnesota Eye Consultants in Minneapolis. "We don't have any one treatment modality that's good enough to be the only treatment modality. Even with surgery, drugs and laser, some patients still lose vision from glaucoma.

"Whatever the future holds," he adds, "the options we have now are much better than when I started practice. It's been a great privilege to watch it all play out."

—CK

are two significant limitations to offering it right now," says Dr. Samuelson. "First, it's been difficult to get payors to buy into the concept, so there's an insurance barrier. Second, patients are receptive to the idea, but it's a bit of a challenge to explain how it's going to be beneficial in a chronic disease if it's only approved for one-time use. Naturally, Allergan is working with the FDA to try to figure out how best to move toward being able to implant it more than once.

"We've been using it in patients with significant ocular surface disease who just don't tolerate medical therapy, and those with compliance issues," he continues. "However, some of those matters would also push us toward doing laser first, because that's very well established in terms of payor reimbursement coverage. If your options come down to Durysta or SLT, it's far more straightforward to do SLT than to go through all of the prior authorization gymnastics you have to do to get approval to use the bimatoprost implant."

SR Options in the Pipeline

Dr. Asrani points out that other new variations on the sustained-release idea may hold promise as well. "Some that are in the works are intracameral, such as a drug-releasing iStent," he says. "That would require surgery. It would be great if something similar to the bimatoprost-containing ring that sits on the eye underneath the eyelids gets approved; that's something we can remove if it doesn't work. We know some polymers can be formulated with medications and last longer than a month; we currently have a punctal plug for dry eye that takes six months to dissolve, called FormFit. Couldn't a glaucoma drug be mixed with that polymer?"

Nevertheless, Dr. Panarelli says that he believes that for continuous drug delivery, an intracameral device makes the most sense. "That would seem to be the best option in terms of eliminating compliance and tolerability issues," he notes. "Other platforms, such as punctal plugs that elute medications or ring inserts that do the same, have great potential benefit from a compliance standpoint. However, there are issues with retention and dislodgement of those devices."

"An advantage of Durysta is that you can do the procedure right at the slit lamp," Dr. Samuelson adds. "Some of the others—for example, the iDose from Glaukos—require a much more sterile OR-type setting. On the other hand, early reports suggest that the duration of response with the iDose might be long enough that this is palatable because you won't have to go to the OR very often."

Dr. Khouri notes that Durysta is just the first chapter in this book, and Dr. Panarelli agrees. "If a single implant could replace multiple medications and have a long-lasting effect—and maybe even help permanently enhance outflow facility—I think many ophthalmologists would implement that option early in their treatment algorithm. In the meantime, physicians and patients will continue to become more comfortable with the currently available options and, as this happens, we'll get a better sense of how effective and safe these options are." ◀

THE CURRENT STATE OF SMILE VS. LASIK

Postop results and safety profiles are similar, but there are key differences between the procedures.

BY MICHELLE STEPHENSON
CONTRIBUTING EDITOR

LASIK has been performed for more than 30 years with impressive results, but surgeons and patients are always on the lookout for something new and—possibly—improved. It's with this mindset that eyes were turned toward the relative newcomer in the refractive surgery marketplace, small-incision lenticule extraction, performed with the VisuMax femtosecond laser (Carl Zeiss Meditec; Jena, Germany). Even though SMILE is in its relative infancy as a go-to refractive procedure, it's producing results similar to advanced LASIK—but it's not without its issues. Here, experts discuss the relative merits of the two procedures, and we also look at the results of well-performed studies of the surgeries.

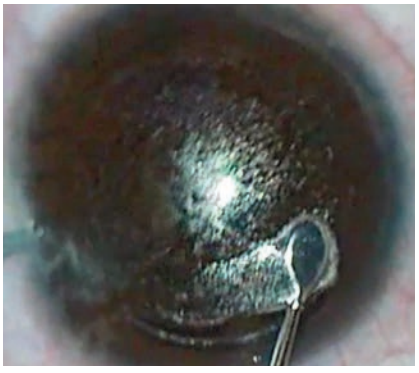
A Look at the Results

Because the results are so similar, it can be difficult for surgeons and patients to choose between the two procedures.

For example, a retrospective case series from Turkey found that SMILE and FS-LASIK were safe and similar in terms of efficacy and predictability at five-year follow-up for the correction of myopia and myopic astigmatism.[1] The study included 44 eyes from 22 patients who received SMILE in one eye and FS-LASIK in the contralateral eye. Patients were examined at one, three and five years.

At the five-year follow-up, all eyes in both groups were within 1 D of attempted spherical equivalent refraction, and no statistically significant difference was found between the intended and achieved correction comparing the groups at any time points.

Edward Manche, MD, director of the Cornea and Refractive Surgery Service at Stanford University School of Medicine, has been performing SMILE surgery since it was approved in 2016, so he's familiar with the trade-offs of each. "Both LASIK and SMILE work very well," he says. "Both provide excellent outcomes and safety, and both can be used in about 85 percent of all patients that come into a typical practice. However, SMILE isn't yet approved for hyperopia or mixed astigmatism. In addition, in the United States, we're limited to 3 D of astigmatism or less with SMILE. So, within those parameters, SMILE and LASIK have a pretty wide approval, and a lot of the choice in procedure comes down to patient preference."



All images: Edward Manche, MD

Separating the lenticule from the stroma can be technically difficult, surgeons say.

John Vukich, MD, who is in practice in Wauwatosa, Wisconsin, was one of the primary investigators for SMILE and VisuMax and has a long history of performing LASIK. "In my previous refractive surgery practice, we were considering SMILE to be a premium procedure, so we were charging slightly more for it," he says.

This article has no commercial sponsorship.

Pertinent to the article's topic, **Dr. Manche** performs sponsored research for Alcon, Carl Zeiss Meditec and Johnson & Johnson Vision. He is a consultant for Johnson & Johnson Vision. **Dr. Vukich** has no financial interest in any of the products discussed.

"We believe that SMILE and LASIK aren't completely equivalent and, physiologically, SMILE may have some advantage over LASIK, the more traditional option. SMILE is the newer technology, has a very good safety profile, and preserves a greater amount of integrity of the structure of the cornea."

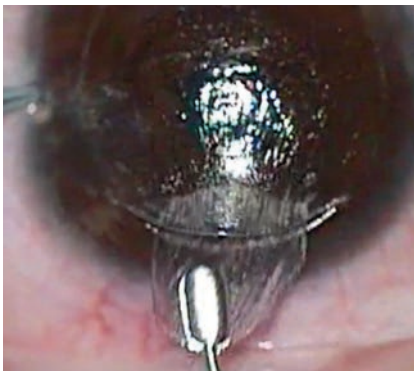
Dr. Vukich says he's encountered patients who have done research and have come to the conclusion that SMILE was a better procedure for them. "You try to be even-handed," he says. "The majority of our cases remained LASIK, however. When given the choice, some of the decision was driven by the price differential, some of it was driven by familiarity and some of it was driven by just the potential longevity of exposure to LASIK.

"The quality of vision is very high for both procedures," he adds. "Sometimes, there's a day or two of additional recovery time for SMILE. However, there's also always the possibility of delayed healing with LASIK, whether it be from striae or epithelial issues related to drops or other things. So, I would say the procedures are roughly equivalent in terms of acuity and patient satisfaction."

The Advantages of LASIK

According to Dr. Manche, one of the advantages of LASIK is that it's been around a long time, with tens of millions of procedures having been performed. "It's a very well-known and mature technology," he says. "SMILE was approved in the United States in 2016, and about 3 million cases have been performed worldwide."

Additionally, LASIK has faster visual recovery. "When SMILE was initially approved in the United States, we were using relatively high energy levels," Dr. Manche says. " The use of higher energy levels in SMILE surgery has been associated with significantly slower visual recovery. So, when SMILE was first released,



Physicians say that, once the SMILE lenticule is removed, it pays to check it for tears that could mean tissue is left behind.

many patients experienced slower recovery of vision. It was common to have patients seeing 20/40 or 20/30 on postoperative day one. This is in contrast to what you see with LASIK, after which the majority of patients see 20/20 or 20/15 on day one."

SMILE was first approved in the United States for spherical myopia. A second approval for the treatment of compound myopic astigmatism came in 2018. With the second approval, surgeons were finally allowed to make adjustments to the energy levels. "The Zeiss clinical care specialist, in concert with the surgeon, carefully adjusts the energy levels to the point where the surgeon can still achieve easy lenticule dissection, but where they're not seeing much of the opaque bubble layer," explains Dr. Manche. "Lower energy levels can provide significantly better uncorrected visual acuity from postop day one. With the lower energy settings, we're now seeing patients who are 20/20 or 20/25 on day one. We even see an occasional patient at 20/15 or better. The postoperative day one vision is still not quite as good as with LASIK, but it's significantly better than what we saw in the early approval with our standard, fixed, higher treatment energy levels."

Another advantage of LASIK is that it's easy to do a touch-up. Surgeons can lift the flap and perform a retreatment. "In comparison, surgeons cannot perform a repeat SMILE surgery on an eye that's already had SMILE," notes Dr. Manche. "If an eye that has previously had SMILE requires an enhancement procedure, you are left with a couple of options. You can perform LASIK surgery by cutting a flap in the SMILE cap. In the United States, the SMILE cap thickness is defaulted at 120 µm, so you then have to cut a LASIK flap at either 90 µm or 95 µm, which only gives you about 25 to 30 µm of play between the cap cut and the flap cut. Some surgeons aren't comfortable with that. Another choice is to perform a side cut and open up the original 120-µm SMILE cap and convert that into a LASIK flap. A final choice is to perform PRK surgery on top of the SMILE cap. I don't like to cut a LASIK flap 25 to 30 µm away from the SMILE cap interface, so I perform PRK touch-ups for all of my SMILE enhancements."

The Advantages of SMILE

One of the advantages of SMILE is the smaller incision. "We're defaulted to a 4-mm incision in the United States," Dr. Manche explains. "In other countries, it's even smaller. This small incision provides less transection of the nerves in the cornea, and that's directly correlated to how denervated the cornea becomes, and also how much dry eye the patient experiences, especially in the early postoperative period. Typically, there's less induced dry eye with SMILE compared with LASIK because LASIK requires a 270-degree circumference flap. With LASIK surgery, you're severing all of the nerves in that area, which leads to relative denervation of the cornea. Typically, corneal reinnervation takes place over the course of six to 12 months. Another advantage to SMILE is that there are no flap complications."

Additionally, studies have shown that, compared to LASIK, SMILE provides potentially better biomechanical stability of the cornea. "Some very good work has shown that the anterior lamellar tissue in the cornea is the strongest," Dr. Manche says.

"SMILE spares the anterior corneal lamellar tissue. The side incision with SMILE is only 4 mm compared to the 20-mm incision with LASIK. There's significantly more transection of the corneal lamellae with LASIK compared to SMILE. Preservation of the anterior stromal tissue results in a reduced biomechanical insult to the cornea with SMILE, and that could have implications with regard to lowering the risk of ectasia."

Head-to-Head Studies

As mentioned above, outcomes of the two procedures are quite comparable. Dr. Manche just completed a randomized clinical trial of 40 patients who underwent wavefront-guided LASIK in one eye and SMILE in the fellow eye. He assessed patients at one, three, six and 12 months. "We did find slightly better outcomes with wavefront-guided LASIK compared to the SMILE surgery," he says. "We had slightly more LASIK eyes achieve an uncorrected visual acuity of 20/20, as well as higher levels of visual acuity of 20/16 and 20/12.5. Additionally, we had greater gains of lines of best-corrected visual acuity in the wavefront-guided LASIK group compared to the SMILE group. So, on the whole, the outcomes were very similar, but there were small but measurable benefits to wavefront-guided LASIK compared to SMILE." Dr. Manche will be presenting the results of this study at this year's meeting of the American Society of Cataract and Refractive Surgery.

For another perspective, a recent study conducted in China found that, when compared to LASIK, SMILE may offer better safety and objective visual quality, comparable stability and efficacy, but slightly inferior predictability when correcting myopia exceeding 10 D.[2] This prospective, randomized, comparative study included 60 eyes in 60 patients. Thirty eyes were corrected using SMILE, and 30 were corrected using FS-LASIK. Patients received preoperative and six-month postoperative examinations.

At six months postoperatively, the uncorrected distance visual acuity was -0.01 ±0.06 logMAR (a little better than 20/20) in the SMILE eyes and -0.05 ± 0.10 (a little better still) in the LASIK eyes, while the corrected visual acuity was -0.07 ± 0.07 logMAR in the SMILE eyes and -0.08 ± 0.08 (a shade off of 20/16) in the LASIK eyes.

Postoperative spherical equivalent refraction was -0.20 ±0.25 D in the SMILE eyes and -0.03 ± 0.20 D in the LASIK eyes, and the posterior corneal curvature was unchanged after both procedures. The measured corneal thickness was reduced by 137.40 ±15.01 µm in the SMILE eyes and by 155.06 ±17.43 µm in the LASIK eyes. The change in the SE was -0.01 ±0.26 D in the SMILE eyes and -0.13 ± 0.30 D in the LASIK eyes after one week. Only the peak distance (the distance between the highest points of the nondeformed corneal parts) differed between the groups; the distance was 1.06 ±1.44 mm in the SMILE eyes and -0.26 ±1.16 mm in the LASIK eyes. The SMILE eyes had smaller changes in higher-order aberrations and spherical aberration than the LASIK eyes.

Interestingly, another Chinese study found that, while SMILE is as effective as FS-LASIK in correcting high myopia, attention should be paid to the induction of vertical coma in highly myopic patients following SMILE.[3]

This prospective, comparative study included 52 eyes of 34 consecutive highly myopic patients with spherical equivalent between -8 and -10 D. Twenty-three eyes of 16 patients underwent FS-LASIK, while 29 eyes of 18 patients underwent SMILE. Visual outcomes and wavefront aberrations were analyzed preoperatively and six months postoperatively.

At the six-month visit, 96.6 percent of eyes in the SMILE group and 91.3 percent in the FS-LASIK group achieved unchanged or better best-corrected distance visual acuity. Additionally, 96.6 percent of eyes in the SMILE group and 95.7 percent in the FS-LASIK group achieved uncorrected distance visual acuity of 20/20 or better. As for wavefront aberrations, high-order aberrations and spherical aberrations increased significantly after surgery in both groups relative to preoperative values, and vertical coma increased after SMILE. Other than the difference in vertical coma, there were no statistically significant differences in the changes in higher-order aberrations, spherical aberrations, horizontal coma, coma, horizontal trefoil, vertical trefoil or trefoil between the two groups.

The Future

According to Dr. Vukich, SMILE is another step in the evolution of corneal recontouring as it relates to a refractive outcome. "We have data to support that the intrastromal removal of tissue versus the creation of a cap leaves intact a greater percentage of the corneal strength and integrity, and we believe that to be an advantage in the long run," he says. "Many patients seeking refractive surgery are in their 20s and 30s, and they're making decisions with the understanding that they will need to have healthy eyes and good vision for maybe another 70 years. All things being equal, a greater percentage of retained corneal structural integrity is a tiebreaker for many people."

Dr. Manche agrees. "In all fairness, SMILE is relatively new, and it's really quite impressive how good the data are this early in the evolution of the procedure," he says. "I think it'll just get better with time." ◀

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IS COVID FORCING PRIVATE EQUITY INTO THE SUNSET?

The truth may surprise you. Find out the ups and downs and future outlook.

BY SEAN MCKINNEY
SENIOR EDITOR

March 17, 2020 will be remembered as the date that private equity's expansion into ophthalmology screeched to a halt. It was one day after former President Donald J. Trump introduced initial emergency guidelines that would eventually shut down large parts of America and two days before a suspension of elective and non-essential surgery, as well as non-essential medical care everywhere.

"On March 16, 2020, we were representing 16 or 17 clients interested in closing private equity deals," says Bruce Maller, founder and CEO of BSM Consulting, a firm in Incline Village, Nevada, that brokers the sale of ophthalmology practices to investor-financed private equity companies. "On March 17, that number went down to zero. The private equity side of this market disappeared."

Like all effects of the pandemic, this one wasn't permanent, however. What has followed since has been a return of private equity sales, although fewer of them, and a changed and still-evolving private equity environment that can still benefit doctors. Deals are more complicated now, experts like Mr. Maller say, and yet doctors in solo or smaller practices are also more eager to at least explore the potential opportunities these transactions might represent, including protection against near-calamitous shutdowns, shrinking reimbursements and a sweeping merger-mania that's eating away at the turf of traditional, independent private practitioners.

In this report, consultants and ophthalmologists with deep experience in this field advise you on whether private equity is the right fit for you, signs of strong and supportive corporate platforms, financial risks and benefits and how to increase your leverage. They'll also explain new ways to keep younger, employed doctors from deserting a practice before a sale.

Why Private Equity?

Private equity companies, capitalized by investors, have been increasingly purchasing private practices in ophthalmology for the past four to five years, continuing a trend that also swept through radiology, anes-

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None of the sources for this article had any relationships with relevant commercial interests to disclose.

thesiology, dermatology, orthopedics and other specialties during the past 15 years, according to Steven I. Rosenfeld, MD, FACS, President of Delray Eye Associates in Delray Beach, Florida.

Dr. Rosenfeld, whose five-partner practice sold Delray Eye Associates to a private equity firm two years ago, is recognized for offering expert advice on private equity in the era of COVID-19 during panel discussions at the most recent meeting of the American Academy of Ophthalmology. Although virtually all ophthalmology practices lost a fiscal quarter's worth of revenue because of virus-related shutdowns in 2020, he says private equity companies continue to be attracted to post-pandemic practices that are recovering financially, especially when the doctors—both partners and non-partners—represent a range of career stages and plan to stay at the practice after the sale, reflecting a commitment to continuity. The companies also look for the potential to increase profits by adding doctors, merging with or acquiring additional practices and introducing or increasing noncovered services, such as offering facial rejuvenation, premium intraocular lenses, refractive surgery, use of the femtosecond laser for cataract surgery and even, in some settings, optical dispensaries.

"The way the model works, the private equity firm is one step away from the practice," Dr. Rosenfeld says. "A private equity firm that buys several practices usually creates a platform, called a medical services organization, or MSO, which hires a talented and experienced CEO who assembles a corporate team with the knowledge and business acumen to run the platform and acquire additional practices."

He says his practice's private equity partner manages business matters better than the doctors, freeing up time for the practice to concentrate on patient care, and also leverages pooled national resources

Chief operating officer Christopher J. Quinn, OD, and Douglas K. Grayson, MD, a cataract and glaucoma surgeon, are bullish on the post-COVID future of their private equity organization, Omni Ophthalmic Management Consultants, one of four major private equity platforms in the New York and New Jersey metropolitan area.

to negotiate better prices on everything from employee health-care insurance to ophthalmic equipment. He and his colleagues believe their corporate partner will help them survive reimbursement cuts and thrive competitively as health care consolidates around them, controlling access to tens of millions of patients through accountable care organizations, hospital networks and corporate entities.

To secure Delray Eye Associates' position as an island of semi-independent practice, Dr. Rosenfeld says private equity provides the "deep pockets" to add a surgery center or other assets to benefit the doctors and their patients. The expanding bandwidth of the practice through acquired practices spawns increased referrals to their tertiary care practice, which offers glaucoma, cornea, retinal, neuo-ophthalmology and oculoplastic services.

The downside of selling to private equity is that you lose autonomy. "It's a paradigm shift," admits Dr. Rosenfeld. "Most ophthalmologists who run their own practices are used to having total independence. In this model, the private equity firm makes the final decisions." At the same time, he notes, a carefully selected private equity company that's the right fit for you won't want to overhaul your practice. "They're buying you because you're profitable and your practice has its own 'secret sauce.' And, you know how to meet the needs of your local community," he says.

What About Non-Partners?

One challenge you may face if you're a private practice owner thinking of selling to private equity, or if you're an employed doctor in a private practice, is that these deals have discouraged employed doctors from participating. Employeed doctors typically stand to lose in two ways:

- never becoming a partner once a practice is owned by a corporation; and
- having to settle for a lower salary once the corporation takes over the

CLOSE-UP ON A PRIVATE-EQUITY SALE

Attorney Mark E. Kropiewnicki, Esq, LLM, says too many doctors he consults with don't fully grasp how much they'll earn if they sell their practices to a private equity company. Here's what to consider about these transactions, which are based on Earnings Before Interest, Depreciation Taxes and Amortization (EBIDTA).

"Let's say you're a solo doctor grossing $1 million per year and your overhead is 60 percent, resulting in $400,000 in net income that goes into your pocket," says Mr. Kropiewnicki, an attorney with Health Care Law Associates and a consultant with the Health Care Group, both in Plymouth Meeting, Pennsylvania. "That 60 percent is what I call real overhead, including all of the expenses of running the practice, except the doctor's salary. So how much EBIDTA is there?

Well, in reality, there's no EBIDTA—if you pay yourself $400,000 a year. So, one of the ways private equity can enter into a deal with you, the selling doctor, is to tell you that you'll be paid at 30 cents on every dollar you earn, instead of 40 cents, after the transaction. That frees up $100,000 per year. If you negotiate a multiple of seven on your cash payment, you're looking at a $700,000 payment for your practice."

(Mr. Kropiewnicki's example excludes ancillary and other revenue you would surrender to the private equity company after you sell the practice.)

"So after the sale, you'll receive 30 percent of the revenue you earn—nothing more. But you do get that $700,000 upfront payment in cash, minus the amount of equity (20 to 40 percent of $700,000) that you agree to invest into that practice that you've just sold to help it expand, as a condition of the sale. You'll be entitled to collect that equity and growth on that equity, when you leave the practice."

If you plan to leave practice in four or five years, Mr. Kropiewnick says the deal probably makes sense. "If you sold the practice to another doctor, you'd probably get $300,000 to $400,000. This is because the value of the practice to a buying private doctor isn't the same as it is to a private equity firm. The private equity firm wants to buy the practice, grow it and sell it to earn a multiple of 15 or 20 times their initial investment later on. That's the way private equity thinks: 'We'll buy this is at a multiple of seven, set up our platform practice here, expand with some add-on practices, increase volume and private pay services, drive up the EBIDTA, and then take the platform to market in five years, selling it at a multiple of 15.

"The doctor who is five years away from retirement says, 'I'll take the $700,000, plus growth on my equity investment. That's better than I would get from selling the practice to another doctor for $300,000 or $400,000. I can also still earn $300,000 dollars a year working for private equity.' But in essence, you're also losing out on $100,000 a year that used to be included in your earnings. So, you'd need to do the math to see if the private equity deal is worth it to you. It may depend on how many more years you plan to stay in practice."

practice.

Some former owners who have sold their practices to private equity say increased payments associated with more referrals in their expanding, networked settings have filled a gap by increasing younger, employed doctors' opportunities to perform procedures and care for more patients. The centralized management and financial security of a private equity company that enables practices to purchase coveted equipment and negotiate better contracts with commercial payers can also satisfy younger doctors. Another factor is that many younger doctors, seeking a healthy work-life balance, may not feel deprived because they've never been interested in becoming practice partners, declining to take on the rigors of ownership, with all of its management headaches.

Nonetheless, productive salaried, younger doctors who account for high patient volume are highly desired by private equity, experts say. If they leave to pursue other opportunities, it could kill a deal.

New solutions to this challenge have emerged. Sometimes, Dr. Rosenfeld notes, you can now create incentives for younger doctors who aren't partners when you join private equity.

"You can give bonuses to younger employees who are on a partnership track," he says. "You might want to expedite a physicians' entry into partnership at the time of the private equity sale, or you can offer these younger doctors equity in the new platform to provide an incentive for them to come along. Someday, they'll be rewarded by growth on their investment when the practice is sold to a second private equity organization."

Douglas K. Grayson, MD, a cataract and glaucoma surgeon at Omni Eye Services, owned by Omni Ophthalmic Management Consultants, one of four major private equity practices in the New Jersey-New York City area, agrees with the need to respect the leverage of employed doctors in advance of today's equity deals. The need to share "some type of financial interest in the practice" with the employed doctor may be paramount. He recommends that practice owners and employed doctors communicate in advance of potential private equity opportunities—or missed opportunities—to avoid misunderstandings and hard feelings among all parties.

What's Changed Post-COVID-19

The structure of private equity deals remains the same despite the pandemic's squeezing down of 2020 practice revenue. However, the payments you can expect to receive if you sell your practice are lower. Below is a summary of pre-COVID-19 and post-COVID-19 terms, according to Drs. Rosenfeld and Grayson and Mr. Maller.

• ***Pre-COVID-19 practice sales.*** Ophthalmologists with an owner-

ship stake in practices were paid a multiple of the strategic value of their practices, ranging from five to 10 or higher. (The strategic value is the practice's Earnings Before Interest, Depreciation, Taxes and Amortization, or EBIDTA.) As part of the sale pre-or-post-pandemic, the selling doctors have been obligated to invest 20 to 40 percent of the cash payment they receive back into the newly formed private equity practice, an investment that can pay them back handsomely if the firm achieves its goal of later selling off the practice at multiples of 15 to 20, typically in five to seven years. As always in private equity arrangements, the selling doctors have remained as employees in the practices they've sold, earning a reduced percentage of their billings.

• ***Post-COVID-19 practice sales.*** Although the structure of these deals remains the same, the upfront multiples paid on a practice's EBIDTA are "a bit softer," according to Mr. Maller. Dr. Grayson concurs, adding that an offer to an ophthalmologist in a successful but small private practice might be the practice's EBIDTA at a multiple of four or five instead of 10 or higher. "Some acquisition contracts will be worded differently than they were previously," says Dr. Grayson. "Everybody's more cautious now. In some cases, for private equity companies, the EBIDTAs of the practices after they were purchased weren't as high as expected in recent years, because the private equity companies may not have been rigid enough in terms of the performance criteria they'd put in place."

Meanwhile, if you sell to private equity now, your EBIDTA will be based on 2019 revenue, but your upfront payment will be reduced, at least temporarily. For example, Mr. Maller says, private equity might pay 80 percent of the usual initial payment. Dr. Rosenfeld adds: "If your practice achieves agreed-upon goals in one or two years, the withheld funds, called an earnout, will be turned over to you. But if the practice doesn't fully recover or achieve the desired goals, then a certain percentage of this earnout will be withheld. This approach represents the most significant change in how these deals have been done since COVID."

In addition, because of the paralyzing effect the pandemic temporarily imposed on ophthalmology practices for at least the second quarter of 2020, Mark E. Kropiewnicki, Esq, LLM, an attorney with Health Care Law Associates and a consultant with the Health Care Group, both in Plymouth Meeting, Pennsylvania, says he's introduced *force majeure* clauses to contracts related to private equity sales, spelling out conditional terms that will apply unless unforeseeable circumstances ("acts of God or nature") prevent a party from meeting the terms of the agreement. "I have only used such clauses in real estate contracts until recently," says the attorney. "Now I put them in every agreement."

Risks, Hard Work and Rewards

Dr. Grayson says he knows of private practice doctors who as recently as early 2020 were sitting on significant chunks of potential revenue they could've earned on sales of their practices to private equity. They were waiting for their practice values to increase even more, but now the pandemic has left them waiting in line for the return of interested private equity companies. "Now they're being told, 'Well, let's see how well you recover,'" says Dr. Grayson. "Of course, as the owner of a private practice, you want the highest number you can get. If you have to get out of private practice now, you have to get out now. It's like Vegas, because essentially you're gambling when you wait and then have to make a move."

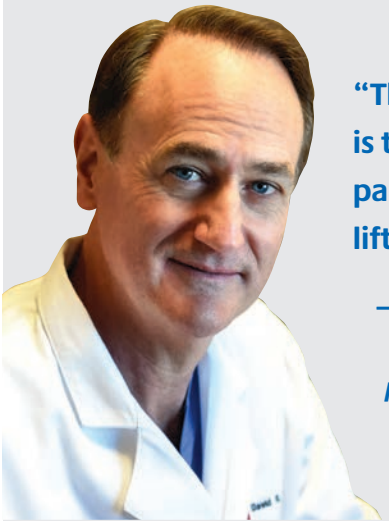
Besides accepting risks, you'll need to invest a lot time and proceed carefully to enter a private equity deal securely.

"Private equity companies tend to get into transactions that are relationship-based," says Dr. Rosenfeld. "If you have a consultant or someone helping you who is well-known and connected, he or she may be able to assist you in getting the kind of deal you're seeking." He says getting involved in private equity can be a year-long process, from the time that a private equity company evaluates your practice as a potential acquisition until the sale is consummated. "A lot goes into it," he says. "Even the accounting is different. Private equity looks at revenues differently than we do, on an accrual instead of cash basis." After interviewing a number of private equity companies, Dr. Rosenfeld says you may ask them to submit letters of intent.

"Once you decide which company you want to work with, you sign one of the letters of intent, and then you work with the suitor over the next several months to find out if you can consummate a deal. This process involves a lot of learning, number-crunching, negotiating and compromising before you can arrive at the final deal."

Mr. Maller speaks to the risks of not exercising appropriate degrees of caution, especially in today's post-COVID environment. "The experience of COVID has varied among doctors and it's shined a bright light on the quality and integrity of existing private equity platforms," he says. "When you're managing through a crisis, which is what we're still in, it ordinarily reveals key indicators of stability and lack of stability." Those indicators, he continues, include:

- the quality, integrity and strength of the leadership of the organization;
- the financial strength of the organization, including cash reserves, good credit and ability to borrow money; and
- the quality of the practice cul-



"The premise of private equity is that you're going to have a partner who will do the heavy lifting in practice management."

—Minnesota surgeon David R. Hardten, MD, FACS, who's partnering with a private equity firm 1,000 miles away to get through the pandemic.

ture and brand.

"In other words," Mr. Maller continues, "you want to see if the company has been able to weather the storm. If I were to objectively survey all of these companies, the outcome of that assessment, I suspect, would be variable. And variability can affect the satisfaction of the doctors who have joined these groups."

Mr. Maller says some doctors are relieved that they've joined private equity at such a challenging time. "And then we'll hear other doctors saying, 'Oh my God, they laid off this person and they took this and that away,'" he says. "The worry and concern are palpable among some of these doctors."

Meanwhile, if you're a practice owner who's getting ready to sell, Mr. Kropiewnicki urges you to understand all aspects of your new reality.

"For example, you may have invested in horizontal expansion, offering a lot of ancillary services that have driven up the value of your practice and attracted a private equity buyer," he says. "You need to realize that you'll lose all revenue from those ancillary services," he says. "The one thing I think a lot of doctors exploring private equity don't realize is that they're only going to earn 30 cents on each dollar of their personal billing, or whatever salary they've negotiated. The other sources of revenue go away." (*See "Close-up on a Private-Equity Sale" on page 58.*)

Keeping Your Options Open

So why, you may ask, would now be a good time to join a private equity company, if the opportunity presented itself?

"Having survived the pandemic, some practitioners are asking themselves, 'Do I really want to be alone, either by myself or with 10 or 20 other doctors? Or should the results of the pandemic make me think that my interests would be better served by being part of some larger group or platform?'" muses Mr. Maller. "That's a fundamental shift in one's mindset that I've witnessed. I would call that a trend that's developed in this so-called post-COVID landscape: A lot of doctors start re-evaluating their situations."

David R. Hardten, MD, FACS, an anterior segment surgeon at Minnesota Eye Consultants, which has five locations in the greater Minneapolis-Saint Paul area, says he and his colleagues have benefited from their partnership with private equity from the time they sold their practice to Dallas-based Unifeye Vision Partners four and a half years ago right on through the challenges of the pandemic. Besides Minnesota Eye Consultants, UVP owns Northwestern Eye, also in the Twin Cities, as well two large practices in California, Pacific Eye Institute and Inland Eye Institute.

"The premise of private equity is that you're going to have a partner who will do the heavy lifting in practice management," Dr. Hardten says. "Although you're still going to have input, and suggestions, and you're going help direct the culture and the flavor of the practice, it will be managed by your private equity company. I suspect that, for someone who isn't part of a private equity group, the number of hours they've spent on practice management during this past year has been higher than the number of hours they've spent on practice management during several previous years combined.

"This effort required the doctor in private practice to confront, alone, all of the challenges, twists and turns that we had to overcome during the pandemic," he continues. "I'm sure that a lot of these doctors are now thinking that it was way too much work. They may envision the advantages in the go-forward environment of a practice with more depth as well as access to increased resources, with the ability to pool those resources across multiple markets. For these doctors, private equity is certainly worth looking at."

Dr. Grayson is also confident that private equity can ultimately provide a secure landing for many of today's practices. "The banks are now more inclined to lend money as we get past some of the worst aspects of COVID," says Dr. Grayson. "Ophthalmology is still a good business. There are many, many people to care for, especially with the patient population aging, so it's not like it's going anywhere. There's still plenty of activity and interest."

He says COVID-19 seems to have decreased revenues only in the short term. "Patients are happy to come in, and volume is up in most places," he says. "By the end of the summer, I think most ophthalmology practices are probably going to be the way they were before COVID." ◀

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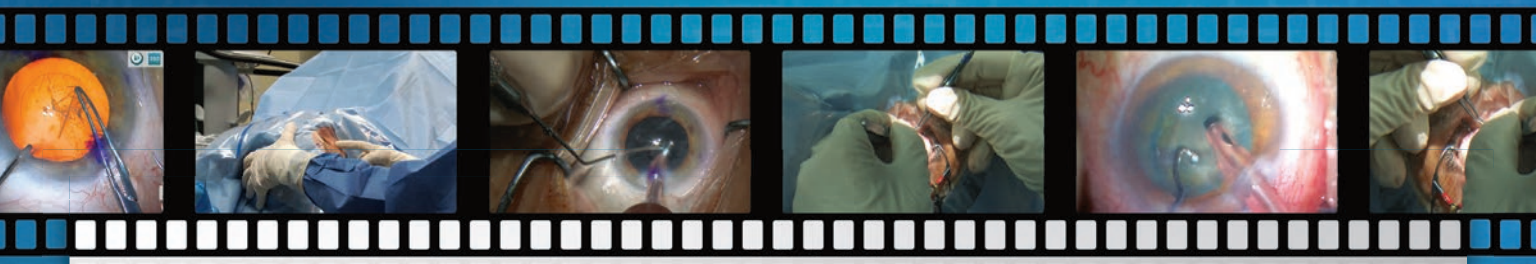

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A Peek into the Diabetic Retinopathy Pipeline

Though anti-VEGF injections dominate today's treatment landscape, novel therapies are in the works.

PREM PATEL DALLAS
CHIRAG P. SHAH, MD, MPH BOSTON

Intravitreal anti-vascular endothelial growth factor agents are the standard of care for diabetic macular edema, and perhaps even diabetic retinopathy in general. However, despite their proven efficacy, anti-VEGF injections aren't curative, and many patients require long-term therapy with regular injections. Since DR primarily affects working-age individuals; for a 21-year-old college student or a working mother, regular injections might not be tenable and could reduce compliance.[1] These patients already face a heavy burden from managing their diabetes in general. Help appears to be on the way, however. In this review, we discuss the current efforts to improve the longevity and durability of existing anti-VEGF agents, while keeping an eye on alternative agents in the pipeline that might eventually join the clinician's armamentarium.

High-dose Aflibercept (Eylea)

There is excellent Phase III data supporting the use of aflibercept for both DME and DR. Aflibercept binds all isomers of VEGF-A, but also binds VEGF-B and placental growth factor. The VIVID and VISTA trials reported improvement in visual acuity and macular thickness in eyes with DME.[2] In DRCR.net's Protocol T, aflibercept was compared to ranibizumab and bevacizumab for DME.[3] All drugs improved vision at one year: aflibercept (+13 letters); ranibizumab (+11 letters); and bevacizumab (+10 letters). However, patients with more significant disease at baseline (worse than 20/50 vision or >400 µm macular thickness), fared better with aflibercept.

Post-hoc analyses of VIVID and VISTA data suggest stabilization or even improvement of retinal nonperfusion and diabetic retinopathy, prompting further study.[4] The Phase III PANORAMA trial found eyes with moderately-severe to severe non-proliferative diabetic retinopathy had significant improvement in the degree of retinopathy following aflibercept treatment, either q8 weeks or q16 weeks.[5] The DRCR.net Protocol W is a similar Phase III trial, with results expected in 2022.

If the standard 2-mg aflibercept dose is effective for DME, could an 8-mg dose have increased efficacy and durability? To answer this question, researchers have started the PHOTON study (NCT04429503), a Phase II/III, randomized, double-masked study comparing the efficacy and safety of 8 mg high-dose aflibercept with the current FDA-approved dose of 2 mg aflibercept.[5] The primary objective of the study, which is currently recruiting patients, is to determine if treatment with high-dose aflibercept at intervals of 12 or 16 weeks provides non-inferior best corrected visual acuity (BCVA) compared to aflibercept dosed every eight weeks. The study aims to enroll 640 patients with a slated end date of April 2022. Depending on the results of PHOTON, high-dose aflibercept could build a bridge from the current anti-VEGF monotherapy regimens to more durable treatments in the future.

Brolucizumab (Novartis)

At a size of ~26 kDa, the humanized single-chain antibody fragment brolucizumab may provide enhanced tissue penetration, clearance and drug delivery characteristics compared to more traditional "bulky" anti-VEGF agents. By comparison, ranibizumab and aflibercept have molecular weights of 48 kDa and 115 kDa respectively.[6] The molar dose of brolucizumab is 11.2 to 13.3 times higher than that of aflibercept, permitting greater drug concentrations and therefore longer duration. Brolucizumab achieved positive results in two Phase III trials for wet AMD, HARRIER (NCT02434328) and HAWK (NCT02307682), leading to its FDA approval in October 2019 for that disease.[7]

As with ranibizumab and aflibercept, drugs demonstrating efficacy for wet AMD are often evaluated for DR/DMR. Three current Phase III studies evaluating brolucizumab for DR/DME are KITE, KESTREL

This article has no commercial sponsorship.

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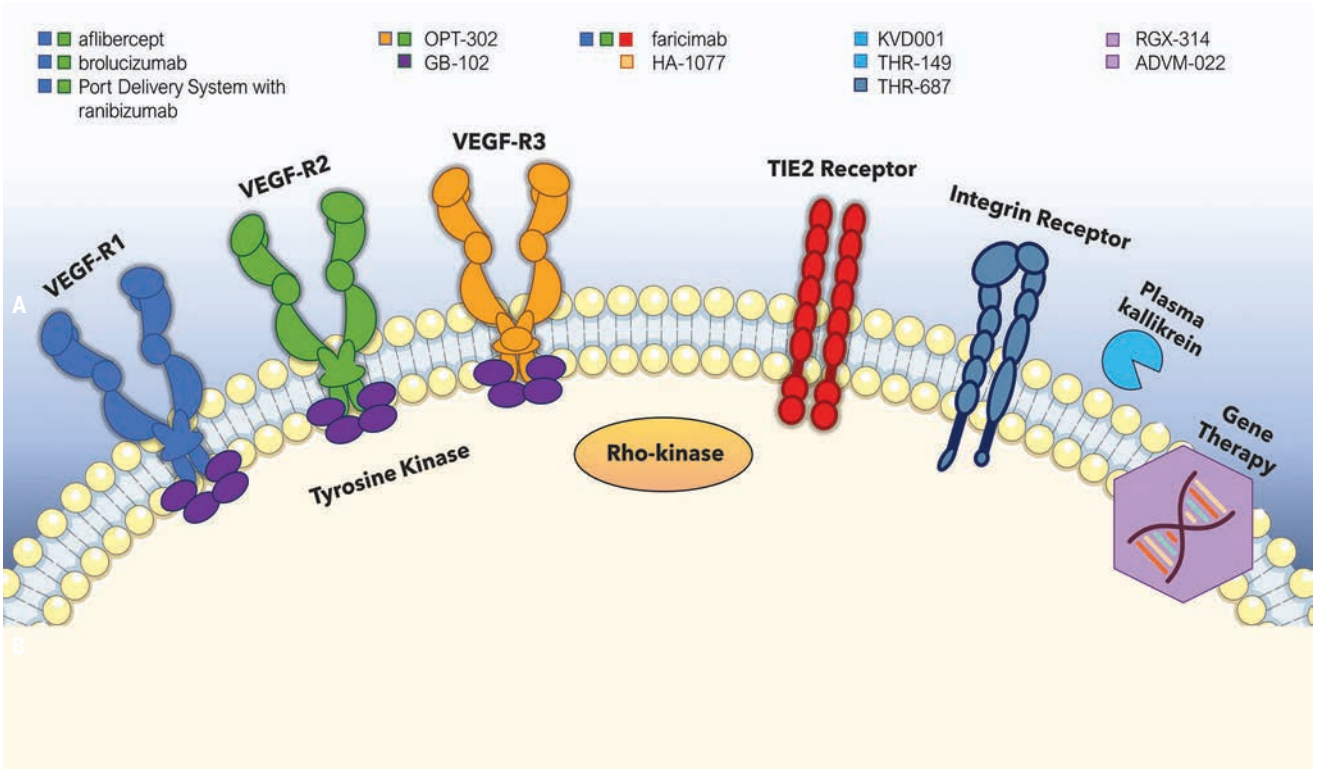
Dr. Yonekawa is an assistant professor of ophthalmology at Sidney Kimmel Medical College at Thomas Jefferson University. He serves on the Education Committee of the American Society of Retina Specialists and on the Executive Committee for the Vit Buckle Society, where he is also the vice president for academic programming.



Several current therapeutic agents and their specific cellular targets.

and KINGFISHER.

The first Phase III trial, KITE, achieved positive topline results comparing brolucizumab 6 mg to aflibercept in DME.[8] According to the company, the trial met its primary and key secondary endpoints, demonstrating non-inferiority for brolucizumab versus aflibercept 2 mg in mean change in best-corrected visual acuity at week 52.

Similarly, the KESTREL study was started as another randomized, double-masked, noninferiority study in DME patients.[9] The experimental arms compare 3 mg and 6 mg doses of brolucizumab given every six weeks for five injections, followed by maintenance injections every eight or 12 weeks until the end of the study. The comparator arm is 2-mg aflibercept dosed every four weeks for five injections and then every eight weeks as maintenance until completion of the study. KESTREL reached full enrollment with 571 patients in March 2020. Study completion is expected in 2021.

KINGFISHER is randomly assigning participants with DME to receive 6 mg of brolucizumab every four weeks or 2 mg of aflibercept every four weeks.[10] The primary outcome is change in BCVA from baseline to 12 months. Data from the full enrollment of 521 patients in KINGFISHER are expected in 2021.

Despite the efficacy of brolucizumab for wet AMD, and its superior pharmacokinetics, many retina specialists are concerned about the risk of occlusive vasculitis and blindness with the drug. In June 2020, the FDA approved an updated brolucizumab label that includes additional safety information specifically including the characterization of adverse events, retinal vasculitis and retinal vascular occlusion. These effects were noted as part of the spectrum of intraocular inflammation observed in HAWK and HARRIER for AMD.[11,12] Entering 2021, pending the results of KESTREL and KINGFISHER, it's unclear whether these adverse events will outweigh the potential benefits for brolucizumab.

Faricimab (Genentech/Roche)

Faricimab is the first bispecific monoclonal antibody designed for intraocular use. With two arms, the antibody independently binds and neutralizes both VEGF-A and angiopoietin-2 (Ang-2); this synergistically promotes vascular stability.[13] Inhibition of the VEGF pathway has long been exploited in DR, but targeting the Ang-2/Tie pathway is of recent therapeutic interest. Ang-1 and Ang-2 are key cytokines in the angiopoietin pathway that interact with transmembrane receptor tyrosine kinase (Tie-2). In healthy states, Tie-2 is bound by angiopoietin-1, which is a protective factor, promoting vascular stability, pericyte recruitment and the inhibition of vascular permeability factors. However, in angiogenic states, the competitive inhibitor angiopoietin-2 is upregulated, displacing Ang-1, and causing endothelial destabilization, inflammation and breakdown of the

blood-retina barrier. The hope is that Ang-2 blockade may further stabilize vasculature structures in patients with DME.

The Phase II BOULEVARD study[14] evaluated the efficacy and durability of faricimab in patients with DME compared to monthly ranibizumab. In the study, 229 anti-VEGF treatment-naïve patients with center-involving DME were randomized into one of three arms. Participants received 1.5-mg faricimab, 6-mg faricimab or 0.3-mg ranibizumab every fourth week up to week 20, after which all subjects underwent an observational period until week 36. At week 24, the patients in the faricimab 6-mg arm had a mean improvement in visual acuity of 13.9 letters compared with 10.3 letters for the ranibizumab arm. Faricimab-treated patients also showed anatomic improvements at week 24 compared with ranibizumab-treated patients, namely a reduction in central subfoveal thickness and improvements in DR severity. These data from BOULEVARD suggested a benefit of combined Ang-2/VEGF-A blockade compared to anti-VEGF monotherapy.

Based on these promising Phase II results, two identical Phase III trials, YOSEMITE (NCT03622580) and RHINE (NCT03622593) were initiated to further evaluate the safety and efficacy of faricimab.[15,16] In each study, more than 900 patients worldwide were randomized to one of three arms. One arm received faricimab 6 mg every eight weeks. The second arm was a personalized treatment interval arm in which faricimab 6 mg was spread to every 16 weeks as long as the patient's central subfoveal thickness didn't increase and require more frequent treatment. The comparison arm was 2-mg aflibercept dosed every four weeks for 16 weeks, then every eight weeks thereafter.

In December 2020, the study met the primary endpoint of non-inferiority to aflibercept. The long-term safety and tolerability of faricimab is being evaluated in the Phase III Rhone-X study (NCT04432831), with an estimated completion date of August 2023.

Phase III data from YOSEMITE and RHINE were presented in February 2021 at the Angiogenesis, Exudation, and Degeneration 2021 conference.[18] In YOSEMITE, the average vision gains from baseline were 11.6 and 10.7 eye-chart letters in the faricimab personalized-treatment arm and two-month arms, respectively. The aflibercept arm reported vision gains of 10.9 letters. In the identical RHINE trial, the average vision gains

THE ANTI-VEGF REVOLUTION

Diabetes is a growing public health problem that affects 463 million individuals worldwide, with a projected increase in prevalence to 700 million by 2045.[1] Diabetic retinopathy (DR) is observed in an estimated one-third of the diabetic population.[2] At any stage of DR, diabetic macular edema (DME) can develop, which accounts for the majority of diabetes-associated blindness.[3] The alarming epidemiologic trends surrounding diabetes highlight the ongoing need to appropriately manage and prevent the onset of DR.

The discovery of vascular endothelial growth factor (VEGF) has ushered a new era in the fight against DR. From its humble 1948 origin as diffusible neovascular "Factor X," VEGF has been identified as one of many key angiogenic factors in blinding eye diseases, such as DR.[4] VEGF leads to increased vascular permeability and leakage, and interplays with other cellular (PKC, Polyol, AGEs), oxidative, and inflammatory changes in sustained hyperglycemia.[5] These powerful discoveries guided the swift translation to therapy; several FDA-backed clinical trials (RISE, RIDE, VIVID, VISTA, DRCR, etc.), showed superior clinical outcomes of anti-VEGF agents compared with the traditional use of laser therapy alone for DR.[6-10] This diabetic retinopathy research has led to the useful agents we have today: ranibizumab (Lucentis, Genentech); bevacizumab (Avastin, Genentech); and aflibercept (Eylea, Regeneron).

Multiple pharmaceutical companies have enthusiastically dived into the search for longer acting and more durable agents beyond anti-VEGF therapy. With several promising agents in the pipeline, and several in Phase III trials *(see Figure, p. 63)*, it appears another paradigm shift is imminent. One approach has been to target related pathogenic pathways (Ang-2/Tie2), or other receptors (tyrosine kinase inhibitors). Another strategy has been to "piggyback" on other VEGF receptors (VEGF-C and D) that synergize with traditional anti-VEGF agents. Lastly, sustained delivery strategies and gene therapies have generated excitement due to their potential to minimize the need for frequent injections.

– PP, CS

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from baseline were 10.8 and 11.8 letters in the faricimab personalized-treatment interval arm and two-month arms, respectively, and 10.3 letters in the aflibercept arm. As with other monoclonal antibodies, some patients developed inflammation after faricimab treatment.

PDS with Ranibizumab (Genentech/Roche)

Ranibizumab was the first FDA approved anti-VEGF agent for both DME and DR. There's strong data from the RIDE and RISE studies demonstrating the efficacy of ranibizumab for DME. Post-hoc analyses of RIDE and RIDE[19] recognized the benefit of anti-VEGF blockage in improving the degree of DR and retinal nonperfusion. This led to the DRCR.net protocol S, which found ranibizumab to be non-inferior to PRP for proliferative diabetic retinopathy, with reduced risk of center-involving DME in ranibizumab-treated eyes.[20]

Could a longer-acting ranibizumab, delivered via a surgically implanted depot, allow for long-term treatment of DR and DME while reducing the need for regular injections? The Port Delivery System with Ranibizumab allows continuous release of ranibizumab into the vitreous via passive diffusion, and is intended to reduce the frequency of intravitreal injections, potentially allowing patients with DME to go several months before needing a refill of the implant.[21] The device is self-sealing and requires surgical implantation; it can be refilled in the office via injection through the conjunctiva. At the moment, the PDS holds 20 µl of a customized formulation of ranibizumab (100 mg/ml). This dosage was found to be the most effective dose in the Phase II LADDER trial in wet AMD, looking at visual and anatomic success.[22]

For DME, the Phase III noninferiority study PAGODA has been started.[23] In total, 550 patients with DME were randomized to receive the PDS 100 mg/ml, refilled at fixed six-month intervals, or monthly intravitreal injections of ranibizumab 0.5 mg. The primary endpoint is change in BCVA from baseline to week 64. Genentech is expected to release primary outcome data in 2021.

By contrast, PAVILION (NCT04503551) was started to evaluate the efficacy, safety and pharmacokinetics of PDS for the treatment of DR in patients without DME.[24] The exclusion of DME could provide interesting data to compare with PAGODA. Patients with moderately severe or severe nonproliferative DR are randomized to receive PDS with ranibizumab 100 mg/ml or 0.5-mg ranibizumab injections. The primary endpoint is the percentage of participants with an improvement of more than two steps from baseline on the ETDRS Diabetic Retinopathy Severity Scale at one year. Participants will receive two intravitreal 0.5-mg ranibizumab injections before PDS insertion, and then the PDS will be refilled with 100 mg/ml ranibizumab every 36 weeks. A comparator arm will undergo regular examinations every four weeks until crossing over to receive the PDS implant. PAVILION is actively recruiting, aiming for 160 patients.

The concept of a surgically implanted drug depot is intriguing but does carry potential risks. The LADDER study found that 10.6 percent of patients developed vitreous hemorrhage, 2.8 percent developed retinal detachment, 1.7 percent developed endophthalmitis and 15.1 percent developed cataract.[25] Retinal surgeons and patients must weigh these potential risks against the potential benefits.

RGX-314 Gene Therapy

Gene therapy has shown promise for the treatment of inherited retinal diseases, and recently there's been a push to find gene therapy solutions for AMD and DR. RegenxBio has been at the forefront of this development with its novel gene therapy, RGX-314, a vector designed to bind

and neutralize VEGF in a manner similar to ranibizumab.[26] RGX-314 utilizes adeno-associated virus serotype 8 (AAV8) as its vector, with research suggesting that AAV vectors provide long-term transgene expression.[27] The gene therapy vector is preferentially taken up by retinal cells, leading to high levels of production of the monoclonal antibody fragment. Interestingly, the company is advancing two separate routes of ocular administration of RGX-314: a one-time subretinal administration during vitrectomy; and in-office suprachoroidal delivery. The hope is that the long-standing and stable production of the anti-VEGF therapeutic protein will reduce the need for frequent intravitreal injections.

In December 2020, RegenxBio announced that the first patient had been dosed in ALTITUDE, a Phase II trial designed to evaluate the suprachoroidal space (SCS) delivery approach with RGX-314 using the SCS Microinjector, for the treatment of DR without DME.[28] The trial is expected to enroll 40 patients with DR across two cohorts. Patients will be randomized to receive RGX-314 versus observational control at a 3:1 ratio; two dose levels of RGX-314 will be evaluated. Patients won't receive prophylactic immune-suppressive corticosteroid therapy before or after administration of RGX-314. The primary study endpoint is the proportion of patients with improved DR severity at 48 weeks. Safety and development of DR-related ocular complications are other endpoints that will be evaluated. Initial data from ALTITUDE are expected in 2021.

ALTITUDE comes on the heels of positive one-year data for RGX-314 for wet AMD. In these Phase I and IIa trials, the company reported stable-to-improved visual acuity and retinal thickness, as well as a meaningful reduction in anti-VEGF injection burden, with higher dose levels of RGX-314 at one year.[29] With these interim results, and pending the data from ALTITUDE, one-time treatment with anti-VEGF gene therapy may have a meaningful impact on DR patients requiring frequent anti-VEGF, and may allow physicians to treat patients with DR earlier in the disease course.

> **There's much excitement for the possibility of a one-time treatment with sustained intraocular VEGF suppression that could slow the course of diabetic eye disease.**

ADVM-022 Gene Therapy

Developed by Adverum Biotechnologies, ADVM-022 is another intriguing gene therapy that targets the VEGF pathway. Similar to RGX-314, ADVM-022 uses an adeno-associated vector capsid, AAV.7m8; however, this gene therapy carries an aflibercept coding sequence under the control of a strong, ubiquitous expression cassette.[30] With one-time intravitreal injection, ADVM-022 is designed to deliver long-term efficacy and reduce the burden of frequent anti-VEGF injections, optimize patient compliance and improve vision outcomes for patients with wet AMD and DME.

INFINITY, a Phase II trial evaluating the safety and efficacy of ADVM-022 in patients with DME, completed patient enrollment in January 2021. In INFINITY, 33 subjects will be randomized to receive a single intravitreal injection of one of the two doses of ADVM-022, or to a comparator arm of a single injection of aflibercept. The study is designed to demonstrate superior control of disease activity with ADVM-022, as shown by time to worsening of DME. All subjects will be assessed regularly and will receive additional aflibercept injections should DME disease activity progress. The primary objective is to assess the durability of a single intravitreal injection of ADVM-022. All subjects will be followed for 48 weeks after randomization. The company aims to present clinical data from the INFINITY Phase II trial in the second half of 2021.

With gene therapy, no hardware is implanted in the eye, which may circumvent potential complications such as conjunctival erosion. Moreover, there's tremendous value in the potential role of gene therapy in preventing chronic exudative eye conditions such as DR and DME, since many researchers believe that early intervention is valuable in diabetic eye disease. While one or two intravitreal injections are generally tolerable, ongoing treatment with no definite cessation for patients who are asymptomatic can often be untenable for them. So, there's much excitement about the possibility of a one-time treatment with sustained intraocular VEGF suppression that could slow the course of diabetic eye disease.

One potential disadvantage to gene therapy, though, is the inability to turn it off. The consequences of long-term VEGF blockade in diabetic eyes are unclear.

OPT-302

This "trap" molecule binds and neutralizes the activity of VEGF-C and VEGF-D, with the thought that combining OPT-302 with currently available anti-VEGF-A may address mechanisms of resistance associated with existing therapies.[31] A Phase Ib/IIa clinical study in patients with treatment-refractory DME found a mean improvement in BCVA of 6.6 letters (n=22) from baseline to week 12 following OPT-302 + aflibercept combination treatment, compared to a gain of 3.4 letters (n=13) for patients continuing on aflibercept monotherapy.[32] This visual acuity improvement accompanied a reduction in macular edema of 42.3 µm in the OPT-302 combination therapy group and 15.5 µm in the aflibercept mono-

therapy group. Lastly, 13.6 percent of patients in the OPT-302 combination therapy, and 7.7 percent in the aflibercept monotherapy group saw an improvement of two or more steps in their underlying diabetic retinopathy.

GB-102

GB-102 is an injectable formulation of sunitinib, a multi-targeted, receptor tyrosine kinase inhibitor that reportedly inhibits all VEGF receptor types.[33] The Phase IIa trial of GB-102 in patients with DME was initiated in September 2019; it enrolled 21 patients at six clinical sites in the United States. Patients received a single intravitreal injection of either 1 or 2 mg GB-102 and are being followed for six months. The primary objective is to evaluate the safety, tolerability and pharmacodynamic response of both doses. The trial was expected to conclude in the second quarter of 2020.[34]

Rho Kinase Inhibitors

The Rho/Rho Kinase (ROCK) pathway promotes leukocyte adhesion to microvascular structures via increased levels of activated Intercellular Adhesion Molecule-1 (ICAM-1) and expression of other downstream proteins.[35] Most clinical research has emphasized the effects of these ROCK inhibitors on lowering intraocular pressure, but a few studies have explored their potential benefits in diabetic eye disease.

Increased activity of the ROCK pathway is thought to be intertwined with the pathogenesis of DR and DME.[36] One randomized clinical trial in patients with center-involving DME investigated the use of ROCK inhibitor, HA-1077 (Fasudil) from the Japanese pharmaceutical company, Asahi Kasei.[37] Results demonstrated significant improvement in BCVA at three and six months in the HA-1077+bevacizumab combination group versus bevacizumab alone. Additionally, there was statistically significant improvement in central macular thickness.

Plasma Kallikrein Inhibitors

Independent from VEGF, the plasma kallikrein-kinin system pathway is activated during vascular injury; it functions by mediating factors in innate inflammation, blood flow and coagulation. This pathway offers a therapeutic target in nonresponding anti-VEGF patients. Following are some attempts to make use of this new target.

• ***KVD001.*** Patients with advanced DR were recently found to have elevated levels of components of the plasma KKS pathway.[38,39] The first Phase Ib study of a plasma kallikrein inhibitor in patients with DME and suboptimal response to anti-VEGF showed that plasma kallikrein inhibition in the vitreous is generally safe and well-tolerated. Plasma kallikrein inhibitor KVD001 (Kalvista Pharmaceuticals) was intravitreally-administered in 14 patients with center-involved DME. Although not designed as an efficacy study, a trend in improved visual acuity was observed for patients receiving KVD001. However, a larger, sham-controlled, Phase II study of four monthly injections of KVD001 in 123 patients didn't meet its primary endpoint.[40]

• ***THR-149***. Another plasma KKS inhibitor in development is THR-149 by Oxurion, which functions by inhibiting the release of bradykinin in the plasma and vitreous.[41-46] In September 2020, the first patient was dosed in a two-part Phase II study (KALAHARI) evaluating THR-149 for the treatment of center-involved DME. Part A (n=18) is a single-masked, dose-finding part of the study assessing three dose levels of THR-149 to select the optimal dose for Part B. Part B (n=104) is the double-masked, active-controlled part of the study with a single dose level of THR-149, and aflibercept as the comparator. Part A data is expected by mid-2021, and topline results from Part B are expected in the first half of 2023. In a previous Phase I study reported in mid-2019, THR-149 was shown to be well-tolerated and safe, with no reported dose-limiting toxicities or drug-related serious adverse events.[47]

Integrin inhibitors

The inhibition of integrins targets multiple processes involved in pathological angiogenesis and vascular leakage, unlike anti-VEGF treatment.

The highest-profile integrin inhibitor currently being studied is THR-687 (Oxurion), which is expected to enter Phase II testing in 2021. This pan-arginine-glycine-aspartic acid (RGD) integrin antagonist targets a broader spectrum of DR hallmarks. Preclinical models show that it is a potent inhibitor of angiogenesis-induced vascular leakage.

Oxurion has reported positive topline data from a Phase I clinical trial evaluating THR-687 for treatment of DME.[48] In 2021, the company's Phase II study of the drug will evaluate THR-687 as a VEGF-independent treatment option for treatment-naïve DME patients.

In conclusion, while anti-VEGF agents have revolutionized our treatment of both DME and DR, the field continues to evolve in the hope of providing better options for our patients. As discussed, numerous novel molecular targets may allow us to go beyond the clinical outcomes achieved by VEGF blockade, and various longer-acting pharmaceuticals might yield good results with fewer treatments, helping to improve compliance and possibly allowing us to treat more patients. ◀

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Recognizing Artifacts in Visual Field Testing

During a busy clinic day, it's easy to mistake an artifact for progression. See how many artifacts you can identify.

BY JO ANN GIACONI, MD
LOS ANGELES

Like any test, visual field tests can contain artifacts. The test subject is a human being, prone to being imperfect and influenced by external factors, and the same is true of the person administering the test. So, when we're reviewing field results in an attempt to determine a patient's condition, and whether or not progression has occurred, we have to expect variability and artifacts.

Most of us are aware of the issue of artifacts, and we know the patterns of many of them. However, that can make it easier for us to misinterpret a field; we feel comfortable that if there's an issue, we'll notice it. But in the clinic, seeing a host of patients on a busy day, we may be looking through visual fields quickly while simultaneously fielding patient questions, and not always looking carefully at the indices and other details—details that might alert us that something isn't what it appears to be.

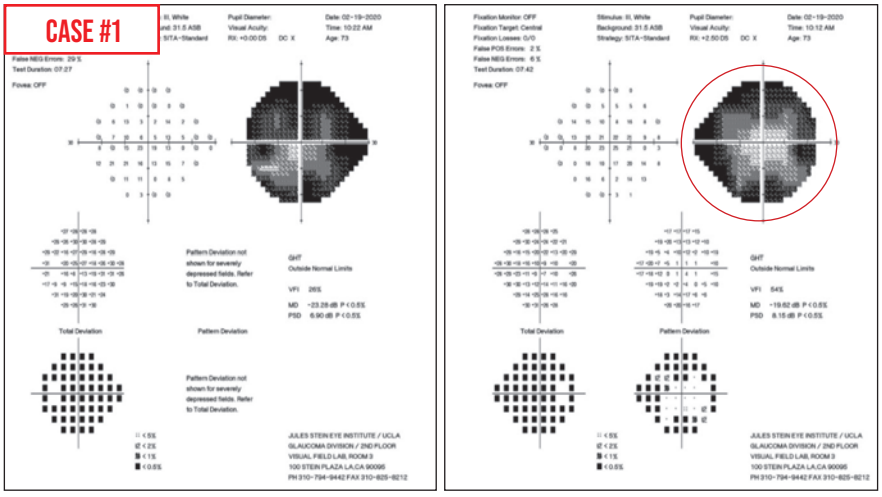
It's true that some nonglaucomatous problems produce a pattern that's recognizable as something other than glaucoma. On the other hand, some diseases—as well as some types of human error—can produce test results that do resemble glaucoma, giving the appearance of a glaucomatous scotoma. It's important that we remain vigilant for artifacts and errors.

Here, I'll present a number of visual fields in which something is amiss, and then explain what produced the artifact. See if you can identify the nature of the artifact and its cause before reading the explanation.

Case 1. At first glance, the visual field defects look like dense arcuate scotomas. However, the central points in each quadrant are much lighter than the surrounding points. This is a classic "cloverleaf" pattern (see circled area)—a type of false negative result. The reason this occurs is that the testing algorithm always starts in the center of each quadrant; that's where it does a threshold test, even if you're using the SITA standard strategy. Test points spiral out from those central quadrant testing points.

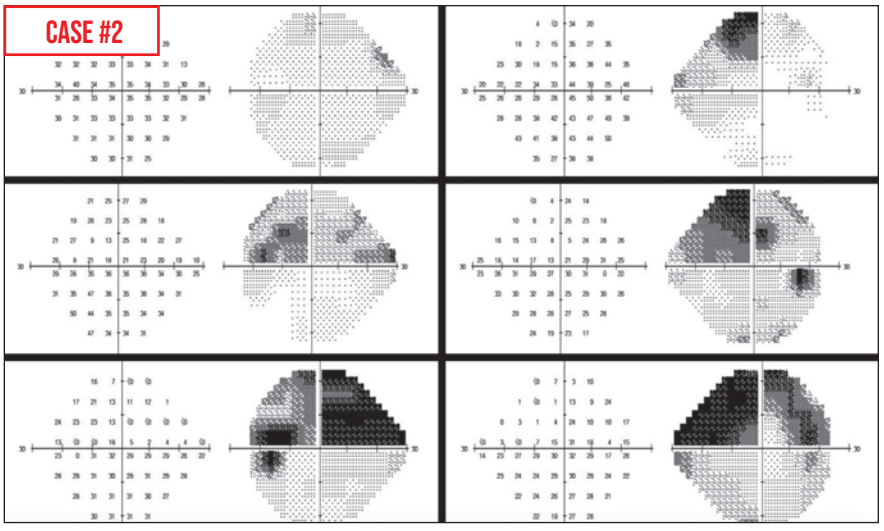
Why would this lead to false-negative responses? Usually, while the first four spots are tested, the technician is hovering over the patient and the patient does a good job. Once the technician walks away, perhaps to start another patient on a visual field test, the patient can lose interest in the test and stop responding. That's why you get this four-leaf-clover pattern.

This type of artifact is fairly common; in a busy clinic I expect you'll see it at least a couple of times a month. Some patients may repeat this pattern over and over again, either because they don't understand the test, they're lulled to sleep during the test, they have early dementia or they simply don't like taking the test. This pattern can be seen in patients with advanced glaucoma, in which case it can be difficult to know the true status of the peripheral vision. It can also be seen in those with milder glaucoma,



This article has no commercial sponsorship.

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



in which case an examination of the optic nerve will help one realize that the test was faulty, because the optic nerve would look much healthier than a nerve consistent with such a poor visual field.

Case 2. Here, the total deviation plot is normal but the pattern deviation plot shows an inferior depression. This should jump out at you as unusual, because normally the total deviation plot shows some depression if the pattern deviation plot is abnormal (except in some rare circumstances among younger patients). If the total deviation plot is normal and the pattern deviation plot isn't, something is likely amiss.

Another clue that something is unusual is that the mean deviation in a normal patient is usually no higher than +2 dB. Here, it's reading +2.31 dB. Other signs include that the false-positive index is a little high, and the blind spot isn't as dark as you'd expect it to be. Furthermore, the glaucoma hemifield test is flagging that there's abnormally high sensitivity.

All of these factors point to a high rate of false positives, meaning that the patient is trigger-happy. The patient is responding to every test point—even if he or she can't see it. The absolute sensitivities at many points will be much higher than expected for the patient's age (normal sensitivity would be around 30 to 32 dB). In addition, if there are test points that the patient actually did see at the expected decibel level and responded to accurately, those normal points will end up looking abnormally low because all of the surrounding test point sensitivities are so abnormally high.

The reason the pattern deviation isn't normal while the total deviation is, is that pattern deviation is usually calculated based on the total deviation plot values. The software finds the seventh most sensitive non-edge point on the total deviation plot, and then resets that value to zero. Then, it adds or subtracts that amount of change from all the other spots. For example, if the seventh most sensitive spot was +7 dB, and you convert that to zero, then all the other test points get 7 subtracted from them. Mathematically, points with the expected normal sensitivities will look depressed in comparison to all the other superhumanly sensitive test points because of the patient's high rate of false positives.

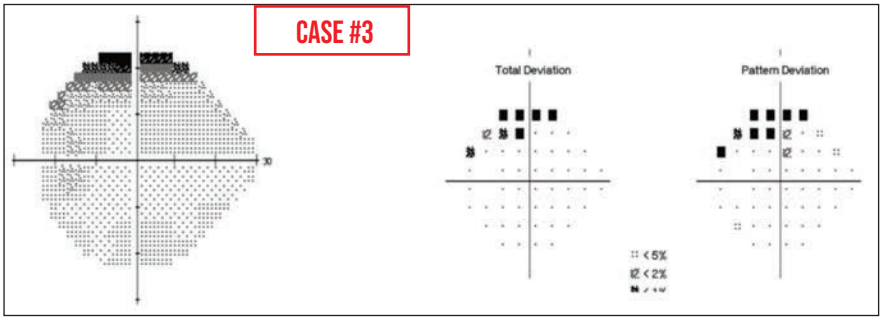
Why might a patient produce this kind of test result? This happened with one of my patients who had severe glaucoma and obvious arcuate scotomas on her first visual field; she later became a "bad" test taker. Subsequent visual field tests looked a lot better, with less dense or no scotomas (*see Figure*). I believe she was nervous about losing her vision and knew how much weight I placed on visual field results, and she wanted her results to look better than they were to avoid further surgery.

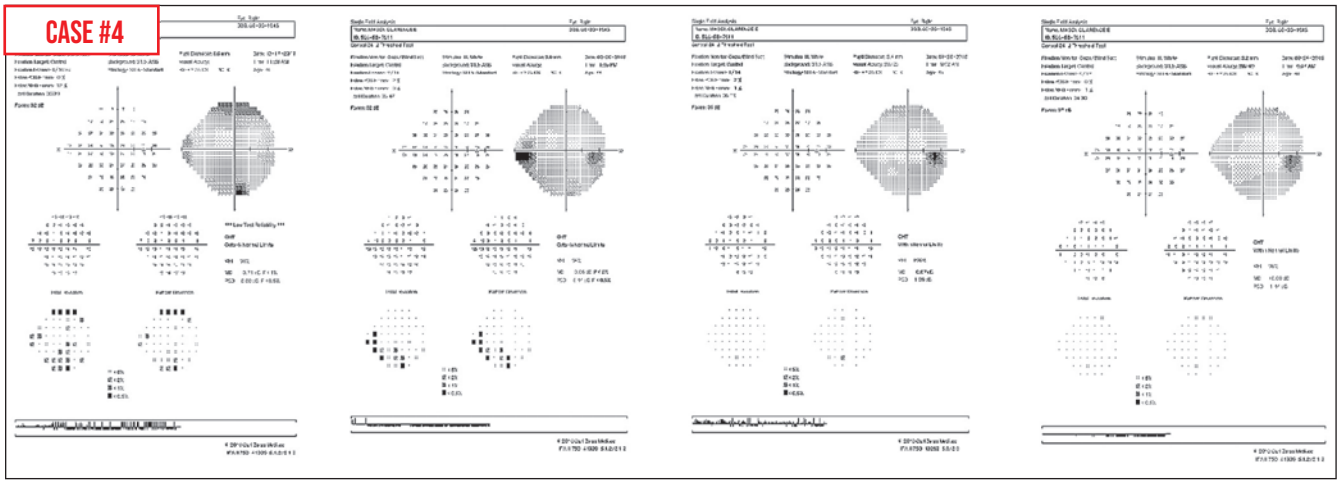
Certainly, if visual fields start looking better in a patient that you know has severe glaucoma and defects, you should suspect that the cause is a high rate of false positives. (These tests should be ignored when you're looking at progression. They're very unreliable.)

Case 3. This field is from a patient's left eye. There's a superior defect, particularly prominent on the total deviation and pattern deviation plots, that look arcuate.

In this case, the defect was caused by severe dermatochalasis obstructing peripheral vision. However, it could also have been the result of a trial lens rim blocking vision. The patient's chin can slip off-center in the chinrest; the head becomes tilted a bit and the patient is looking upwards with a chin-down position. Then, the superior test point lights could be blocked by the trial lens.

One of the clues that the pro-





jected lights are being blocked from view is an absolute sensitivity score less than zero. Zero means that the machine is projecting a light to the patient with no filter dimming the intensity, so it's the brightest light the machine can project. If the sensitivity is <0, that means the patient couldn't see that brightest light. If test points adjacent to those <0 points are close to normal sensitivity, the <0 dB probably indicates that something was blocking the light, preventing the patient from seeing it.

Case 4. Here's a series of visual fields from a glaucoma suspect I've been following. The first field in 2017 showed some defects around the periphery. We repeated the visual field about four months later; that field showed an inferior nasal step that looks glaucomatous. However, when tested again six months later, the inferior nasal step had disappeared. Furthermore, a year later the visual field looked normal again. Meanwhile, the nerve consistently looked normal on examination, as did the retinal nerve fiber layer on OCT.

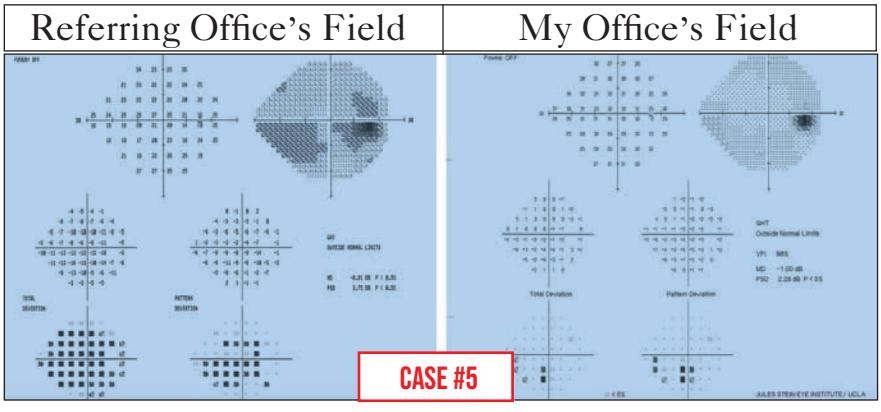
This is an example of a patient with a significant learning curve. For some patients, it takes a few visual field tests to figure out what's required of them. This is why whenever there's an abnormality—especially the first time patients are tested—you want to repeat it to confirm the result.

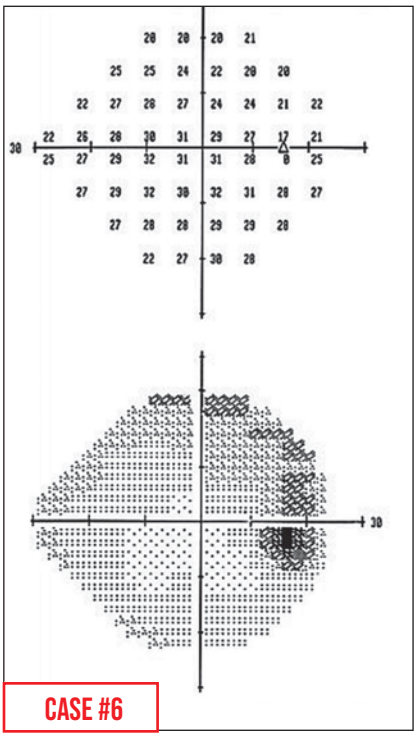
Learning-curve errors can last through seven or eight visual fields for some patients. Many patients are anxious when they're first doing these tests, and they may not fully hear the instructions; they're worried about going blind. They may also be physically uncomfortable after the first few minutes and shift in the seat or in the chinrest. All kinds of issues can result in an abnormal test, especially when the patient is new to the experience.

Case 5. This patient was sent to me for a possible trabeculectomy because of progression seen on her visual fields. While the patient and I were talking about visual field testing in general, she expressed to me how difficult it had been to see the test lights during her last test. She didn't believe the changes shown by the test were real.

Because she didn't believe the results, we decided to do another visual field in my office, and there was a big difference in the result. In the visual field done at the referring office, the total deviation plot was very depressed generally, and there was an inferior arc, as well as possible superior changes. In my office the total deviation plot was much better, and the mean deviation went from -8.91 dB to -1 dB. That's a huge improvement. In fact, it was clear that her inferior arc scotoma, seen in earlier testing, hadn't progressed.

As the patient and I talked, it became clear that the technician in the referring office didn't use a trial frame with the patient's refractive correction. Since she wasn't wearing her contact lenses, she took the test blurred. For each diopter of blur, one expects a depression of 1 dB in the visual field. If the lights aren't in sharp focus, the patient isn't going to do very well on the test.





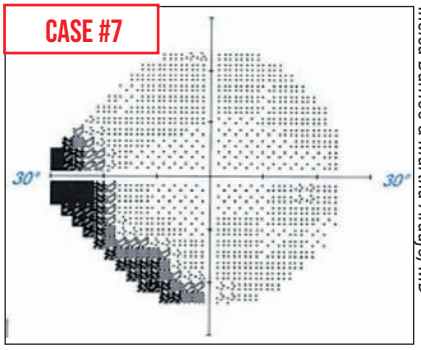
Case 6. This patient is a high myope, with what looks like a superior arcuate scotoma. However, the physical exam suggested another explanation: The optic disc was a little bit tilted.

This artifact is called a refraction scotoma, or tilted-disc-syndrome scotoma. Because the disc is tilted, even when the eye is refracted correctly the tilt causes a part of the retina to be farther away from the point of best focus. As a result, the trial frame brings light into focus anterior to the retina that tilts posteriorly with the nerve, and the test lights in those locations are blurred on the retina. This can cause the appearance of a shallow scotoma in that area.

Typically this area will be superior, because most nerves are tilted inferiorly; however, some myopic nerves are tilted in other directions, causing the scotoma to appear elsewhere. This example is a typical one—the apparent defect is superior and comes off of the nerve.

As noted, this explanation for the apparent scotoma can be confirmed by your physical examination of the nerve. If you have time, you could retest, providing more minus correction, which should make the relative scotoma disappear. (Of course, most busy offices don't have time for this repeat testing.)

This artifact is relatively common. In a busy clinic, a doctor could encounter this weekly.



Inelsa Barrios & Martha Araujo, MD

Case 7. In this patient the visual field revealed what appeared to be a superior nasal step scotoma. However, a few minutes later the test was repeated, and the defect disappeared. This is a defect many ophthalmologists began noticing in 2020, when patients started wearing masks because of COVID-19. The scotoma went away when the mask was taped down. A related defect observed in the past year was an illusion of worsening scotomas caused when trial frame lenses fogged up with mask use. Again, taping down the superior edge of the mask to prevent the patient's breath moving upwards solves the problem.

A similar defect may be caused by a prominent nasal bridge that blocks the patient's view of nasal test points. Sometimes just turning the patient's head a few degrees towards the nose can get the nose out of the field of view and eliminate the defect.

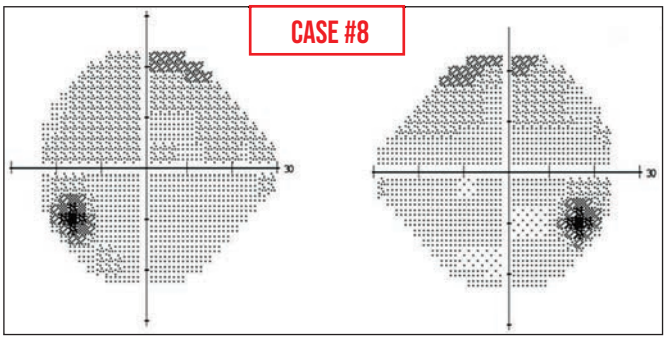
Case 8. In this visual field the blind spot is much lower than we'd expect it to be. Normally the blind spot is right at the horizontal meridian; here, it's a number of degrees below that.

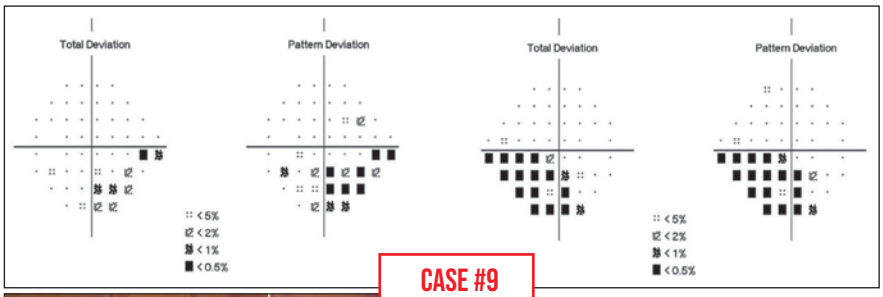
This can happen because the patient fixates on the marks for foveal threshold testing, which are on the perimeter bowl below the central fixation light, or because they aren't told to change fixation after foveal threshold testing. If their fixation is below the central target, then their entire visual field will be lower than expected, including the blind spots.

Case 9 *(See next page)*. In this patient's field, the defect looks glaucomatous. However, a quick look at the nerve reveals that the defect is being caused by drusen.

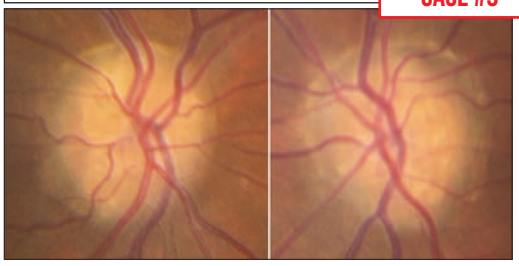
What's interesting is that in some eyes, the drusen are buried under the surface where you can't see them on a physical exam; in these patients the optic nerve tends to look normal, with no cupping, but there will still be nerve fiber bundle defects resembling glaucoma on OCT imaging. You can check this further by performing an OCT of the optic nerve head, where drusen will appear as hypoechoic black areas, or by using ultrasound. The drusen are usually calcified, so on ultrasound you'll see bright spots at the optic nerve head.

Unfortunately, we don't have any treatment for removing optic nerve head drusen. Visual field defects from drusen are treated the same way scotomas due to glaucoma are treated; the rationale is, if you reduce the IOP you're taking pressure





CASE #9



off the nerve that's getting squeezed from the other side by these drusen. So, if the hidden drusen lead to a misdiagnosis of glaucoma, the patient may get the same treatment.

Case 10 *(below)*. This is the visual field of a woman sent to me for a second opinion. She was 34 years old, and had been prescribed glaucoma medications because she had an inferior defect on her field. She wanted a second opinion.

Looking carefully at the printout, the pattern deviation map does resemble glaucoma, but there's something odd when you look at the grayscale map. Often, glaucoma starts in the nasal step area and then spreads back to the nerve, but here, it looks like the defect is coming off of the blind spot.

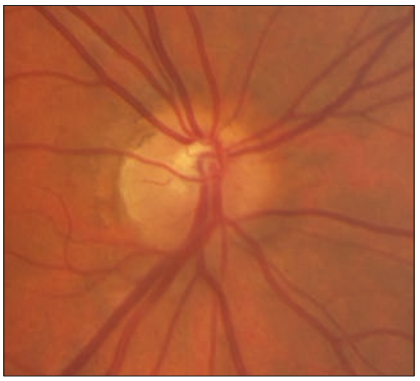
As always, it's important to correlate field defects to the physical exam. In fact, her optic nerve looked a little strange *(below, right)*. The person who started her on drops noticed that the superior blood vessels were very close to the rim of the nerve and thought that was glaucomatous thinning. However, if you make a line through the avascular trunk, you can see that the lower half of the nerve has a different radius than the upper half; it actually looks like the upper half is smaller. Furthermore, when you look at this patient's OCT, on the deviation map *(below)* there's thinning of the entire upper half of the nerve.

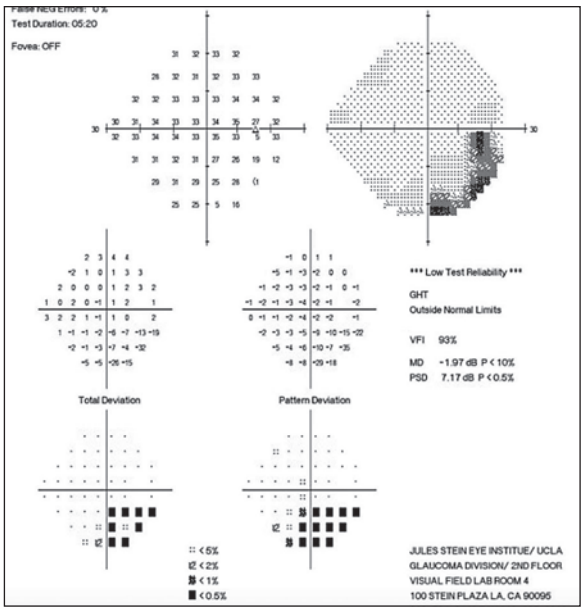
This is an example of superior segmental optic nerve hypoplasia, which isn't common. Reports in the literature show a correlation between superior segmental hypoplasia and gestational diabetes. In my patient's case, her mother never had diabetes; this may just have been an unfortunate developmental coincidence.

The important thing is that this problem doesn't progress, so we stopped her eye drops. We're just following her.

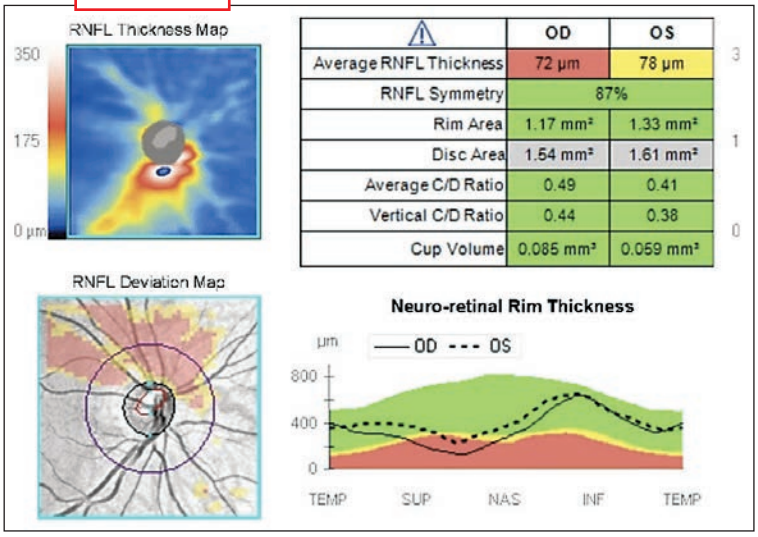
Case 11 *(facing page)*. This patient has impressive superior arcuate and inferior nasal step defects. However, looking at the grayscale map, the defects don't appear to be typically glaucomatous. For such an advanced arcuate scotoma, one would expect more paracentral involvement, and there's a lot of temporal depression.

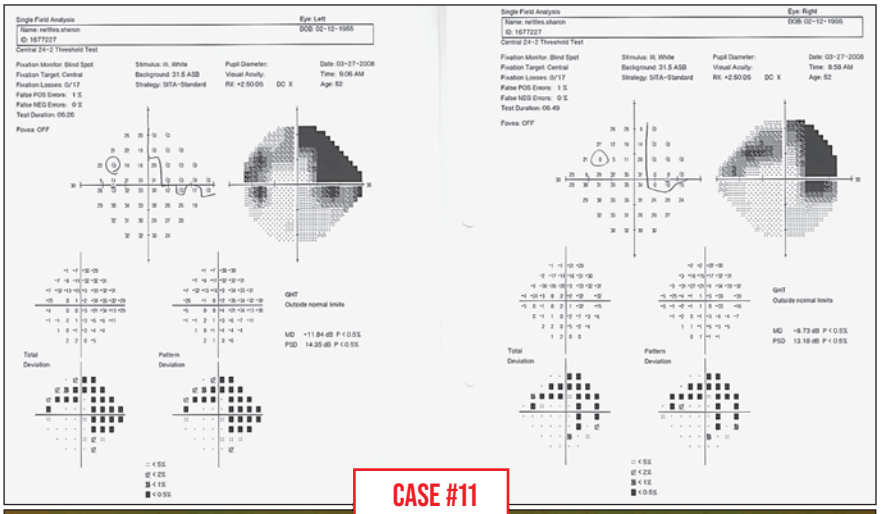
Again, the physical exam is incredibly important. The nerves look normal, but on the retina there's a pigment epithelium abnormality in





CASE #10





CASE #11

a circular shape, mimicking retinal nerve fiber layer defects.

This isn't glaucoma; it's a retinal problem. Again, this demonstrates the importance of looking carefully at the patient. One can't base a diagnosis on only one or two tests without examining the patient.

Case 12 *(below).* This patient has pseudoexfoliation and high pressures, and his visual fields appear to show considerable progression over a six-year period. However, it turned out that because of the pseudoexfoliation, his IOL was sinking inferiorly over time and his superior opacified capsule came to lie in the visual axis, making it very likely that the visual field "progression" was caused by the capsule opacity, rather than increased optic nerve damage.

Case 13 *(See next page).* This is a 72-year-old woman seeking a second opinion after she was told to start glaucoma drops. She reported that she suddenly noticed peripheral vision problems. If you only look at the total deviation and pattern deviation plots, you might conclude that the patient has a superior arcuate scotoma and inferior nasal step.

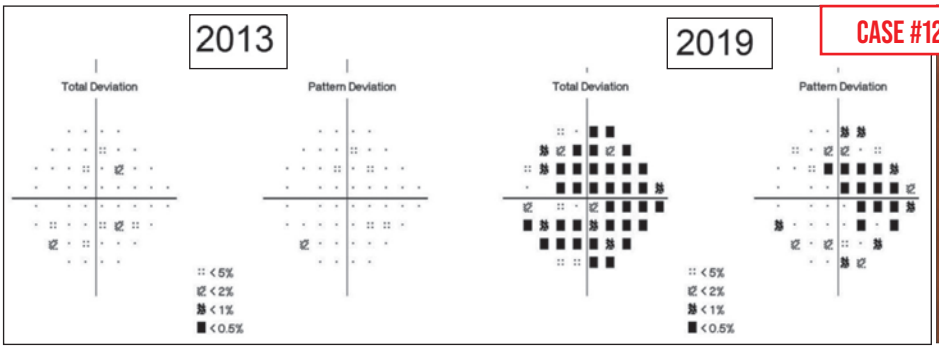
However, if you look at the gray-scale map, it doesn't look typically glaucomatous. In the right eye, I'd expect that the nasal step area would be a lot denser than the rest of the arc if glaucoma was the cause. It's also important to look at the left and right eye visual fields together, because here the left and right sides of both images look very similar.

The other clue here is that the patient stated that she suddenly noticed peripheral vision problems. With glaucoma, people don't usually suddenly notice defects; they come on gradually. Often, patients are unaware of their scotomas until they start to affect central vision. So that history, combined with the way her visual fields looked, and the fact that her nerves looked normal, led us to request an MRI scan, which showed bilateral occipital stroke. (MRI shown is same condition from a different patient.) It happened to result in what looks like a superior arcuate scotoma.

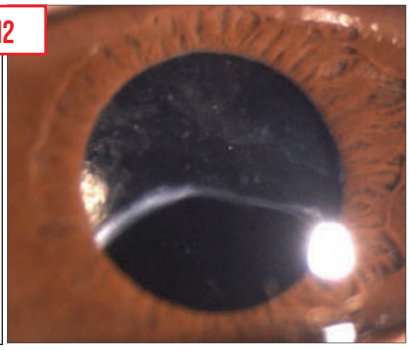
This is not glaucoma; these are two incomplete homonymous hemianopsias that form arcs in each eye.

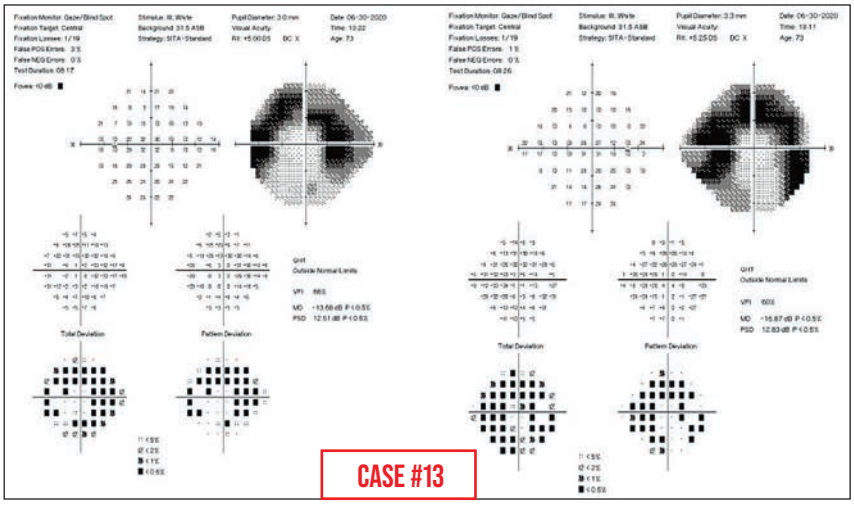
Case 14 *(Not shown).* Occasionally the latest visual field in a series may look very different from previous fields, with no apparent explanation. What might account for this?

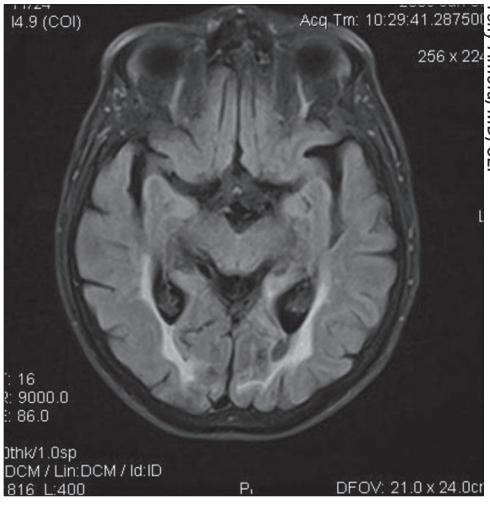
One possible explanation is that the patient received slightly different instructions from different technicians; different instruction can profoundly affect how the patient does on the test. That's because one of the things the test is doing is trying to find the threshold of



CASE #12







Tony Arnold, MD, SEI

light dimness that patients can see 50 percent of the time. It's showing patients some pretty dim lights, and patients can have a hard time being sure if they really saw them. When they're unsure, the technician's instructions can make them more inclined to choose one way or the other, affecting the outcome. This is called "response bias."

If the patient is told: "Press the button the moment you think you see a light," the test may come out looking really good, close to normal, even if the patient has field defects. But if the patient is told: "Don't press the button unless you're 100-percent certain you've seen a light," the test results can make it appear that the patient's vision is much worse than it actually is. On the other hand, more neutral instructions, such as: "Press the button whenever you see a bright or dim light. You're not expected to see all of them," tend to produce more representative results. (An excellent example can be found in Kutzko et al, 2000.[1])

So, if you've been following a patient for some time and suddenly the visual field looks a lot better or worse—and you know there are no false positive or negatives and everything else seems to be OK—you may want to check to see if your technician decided to change their patient instructions.

Strategies for Success

Here are some pearls that will help ensure accurate interpretations of questionable visual fields:

• ***If the test shows something you weren't expecting, look for correlations in the physical exam and OCT scans.*** This can prevent a visual field artifact from leading you to a misdiagnosis and inappropriate treatment.

• ***Don't overlook the grayscale plot.*** When we teach residents to interpret a visual field, we always say, "Don't look at the gray scale—look at the pattern deviation plot." But some artifacts, such as the classic cloverleaf pattern indicating false negative responses, are much more readily appreciated in the grayscale plot. So the grayscale map is always worth looking at.

• ***Some tests with artifacts can be used to judge whether progression has occurred—but others can't.*** A test with a higher number of fixation losses may still be used for judging progression, but a test with a high rate of false positives should not be.

• ***If the 24-2 strategy you're using has stopped being useful, switch to an alternate version of the test.*** I've seen cases in which patients continued to be administered the 24-2 visual field, even though the pattern deviation plot returns with the message "pattern deviation not shown for severely depressed fields." At some point you need to switch to a test strategy that's more useful for following progression. For some patients, that may be a 10-2 field, because all they have left is their central field; for others, the visual acuity may not be good enough to see the size-III stimuli (4 mm^2) that the machine projects, so you have to switch over to a size V stimuli (64 mm^2).

Don't let yourself (or your techs) get in a rut. You need to individualize the test for some patients.

• ***Make sure the 10-2 test administered isn't using the red stimulus light.*** These machines are capable of testing the 10-2 field test using a red stimulus light, which, for a while, was recommended for Plaquenil screening. I've seen technicians assume that all 10-2 testing should be done using the red stimulus. Others simply don't notice that the stimulus light has been set to red.

Unfortunately, test results always look worse when a red stimulus is used. It's simply harder for most people to see the red stimulus. ◀

1. Kutzko KE, Brito CF, Wall M. Effect of instructions on conventional automated perimetry. IOVS 2000;41:2006-2013.

ABOUT THE AUTHOR

Dr. Giaconi is health sciences professor of ophthalmology at the Jules Stein Eye Institute, David Geffen School of Medicine, UCLA, Los Angeles. She is a consultant to Allergan.

A 34-year-old presents with blurred vision after refractive surgery.

CHARLES BRODOWSKI, MD, BEERAN MEGHPARA, MD
PHILADELPHIA

Presentation

A 34-year-old Caucasian female presented for evaluation of blurry vision in both eyes for approximately one month in duration, with her left eye being more symptomatic than her right. In addition to her blurry vision, she also reported intermittent burning, irritation, and foreign body sensation in both eyes. There was no history of ocular trauma or contact lens wear. The review of systems was within normal limits. At the time of presentation, the patient was intermittently using artificial tears in both eyes, but without symptomatic improvement.

Medical History

The patient's past medical history was significant for dry-eye syndrome, diagnosed 10 years prior to presentation. Her past surgical history was significant for a bilateral small-incision lenticule extraction procedure performed in February 2019. Her family history was positive for Sjögren's syndrome, lupus and diabetes mellitus on the maternal side. The patient was a non-smoker, consumed alcohol socially and denied illicit drug use. She denied allergies to medications. The patient's medication list included topical tretinoin.

Exam

Visual acuity without correction was 20/20 in the right eye and 20/30+1, 20/25 pinhole in the left eye. Pupils were equal, round and reactive bilaterally with no relative afferent pupillary defect. Intraocular pressure was 12 mm Hg in both eyes. Visual fields were full to confrontation bilaterally. Extraocular motility was full bilaterally. Adnexa and eyelid examination was within normal limits bilaterally.

Slit lamp examination demonstrated diffuse 3+ punctate epithelial erosions (PEE) with decreased tear breakup time in both eyes. Additionally, the left eye demonstrated a superonasal paracentral opacity measuring 1.5 (h) x 1 (v) mm (*Figure 1*). Circumferential haze surrounding the opacity was noted. There were no associated infiltrates, edema or epithelial defects. The lesion appeared to be subepithelial and located at the SMILE interface. The remainder of the anterior segment and funduscopic examination in both eyes were unremarkable.

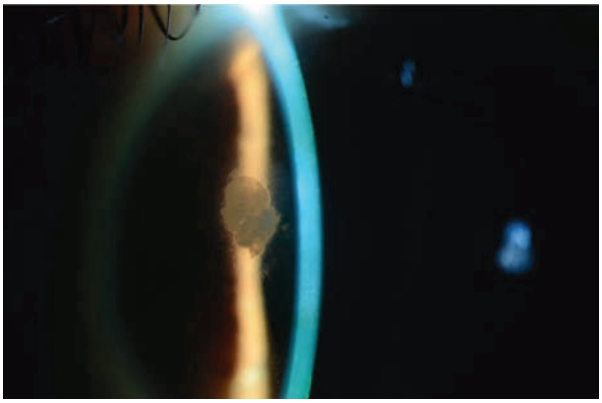


Figure 1. Slit lamp photograph demonstrating a superonasal, subepithelial infiltrate with surrounding haze.

What is your diagnosis? What further workup would you pursue? The diagnosis appears on p.78.

Work-up, Diagnosis, and Treatment

The differential diagnosis for opacification within the SMILE interface includes diffuse lamellar keratitis, infectious keratitis and epithelial ingrowth. Given the length of the patient's blurry vision, lack of pain, and history (albeit several years prior) of a SMILE procedure, epithelial ingrowth was highest on the differential with diffuse lamellar and infectious keratitis being less likely.

Optical coherence tomography of the left eye demonstrated a hyper-reflective lesion at the SMILE interface (*Figure 2*). Corneal topography was subsequently obtained, which documented flattening at the location of the opacity with surrounding elevation (*Figure 3*); the left eye was also noted to have increased astigmatism compared to the right eye.

Given the constellation of slit lamp, OCT, and corneal topography findings it was determined that the corneal opacity was likely secondary to epithelial ingrowth following the patient's SMILE procedure. Treatment options were discussed with the patient, including observation, surgical intervention, and laser treatment. Given the chronicity and relative mildness of the patient's symptoms, she was given the option to think about her treatment options and follow-up in two months.

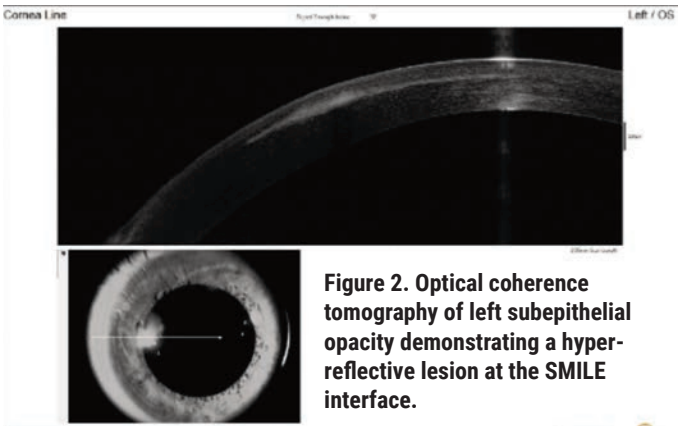


Figure 2. Optical coherence tomography of left subepithelial opacity demonstrating a hyper-reflective lesion at the SMILE interface.

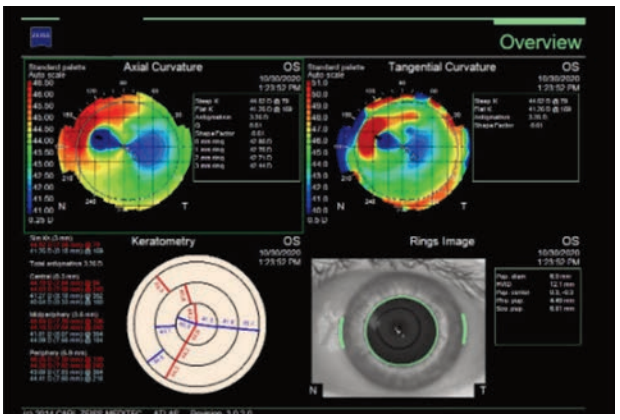


Figure 3. Corneal topography of left eye demonstrating corneal flattening at the site of the subepithelial opacity with surrounding corneal elevation.

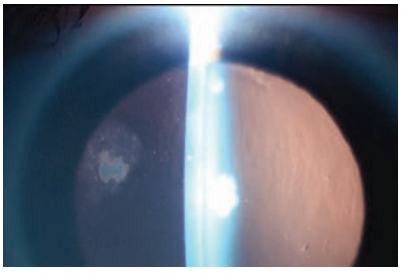


Figure 4. Slit lamp photograph demonstrating a superonasal, subepithelial infiltrate of decreased size and surrounding haze.

The patient followed up two months later and continued to complain of persistent dryness and irritation in both eyes. She also reported blurry vision which was worse in her left eye than her right, though she noted that it had slightly improved. Visual acuity without correction was 20/25 in both eyes. Slit lamp exam was notable for 3+ PEE and decreased tear breakup time in both eyes; once again, a subepithelial opacity at the SMILE interface was noted in the left eye. On close observation, a reduction in both the size of the opacity and the surrounding haze was noted compared to the initial visit (*Figure 4*).

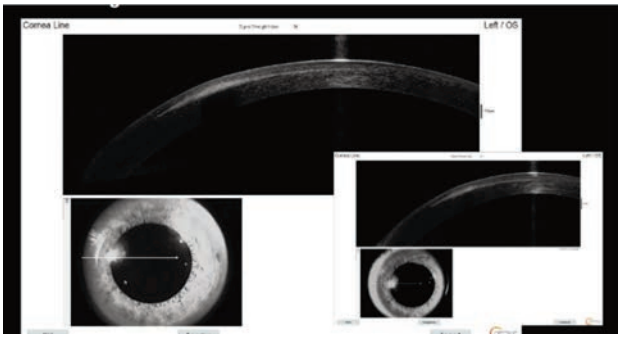


Figure 5. Optical coherence tomography of the left subepithelial opacity demonstrating reduction in size of the hyper-reflective lesion at the SMILE interface (inset of OCT from initial visit).

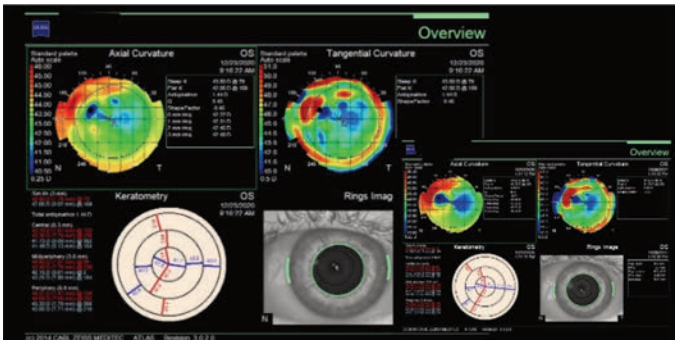


Figure 6. Corneal topography of the left eye demonstrating reduction of corneal flattening and surrounding corneal elevation at the site of the subepithelial opacity (inset of corneal topography from initial visit).

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Repeat OCT demonstrated a hyper-reflective lesion at the SMILE interface of the left eye which had slightly decreased in size compared to the initial OCT (*Figure 5*). Corneal topography was repeated, showing less flattening at the site of the opacity (*Figure 6*). Astigmatism was still greater in the left eye, however the difference between the left and right eyes had decreased from the initial visit.

With all three exam modalities showing recession of the presumed epithelial ingrowth, it was decided to further observe the opacity and see if it continued to self-resolve with a plan for surgical removal if no significant reduction was noted. The patient was agreeable and consented for surgery with a tentative date shortly after a scheduled two-month follow up.

Discussion

First introduced in 2008 and gaining FDA approval for myopic correction in 2016, the small-incision lenticule extraction procedure is a recently developed refractive surgery procedure that's an alternative to LASIK and PRK. The SMILE approach focuses on the creation and removal of a refractive lenticule without epithelial removal or flap creation. The intrastromal lenticule is created with a femtosecond laser, and is composed of an upper (known as the cap) and lower interface. A 2 to 3 mm side incision, for removal of the lenticule, is also made.[1] The side incision also serves to connect the cap to the corneal surface (*Figure 7*). Currently, in the United States SMILE is approved for correction of up to 10 D of myopia and 3 D of astigmatism.

Multiple studies have demonstrated the efficacy of SMILE. The prospective multicenter study which led to FDA approval studied 357 eyes treated with SMILE and followed patients for up to 12 months. The study found 95.3 percent (n=289) of treated patients to be within 0.5 D of emmetropia; 89 percent (n=270) of patients had UDVA of 20/20 or better at the 12-month follow-up.[3]

A study performed at the Singapore National Eye Institute compared refractive predictability in patients who underwent SMILE in one eye and LASIK in the fellow eye. At the three-month follow-up, 99 percent of SMILE eyes and 97 percent of LASIK eyes were within 1 D of emmetropia; these results stayed statistically unchanged at the 12-month follow-up, with 99 percent of SMILE and 99 percent of LASIK eyes being within 1 D of emmetropia. Additionally, this study also found that both SMILE and LASIK achieved an uncorrected distance visual acuity of 20/20 or better at a similar rate after a year (SMILE: 84 percent; LASIK: 87 percent).[4]

It's been surmised that because SMILE doesn't violate the anterior stroma in the manner that LASIK and PRK do, it offers patients enhanced postop corneal biomechanical properties. A non-linear regression analysis using depth-dependent tensile corneal strength found that postoperative tensile strength would be greatest in SMILE compared to PRK and LASIK, although a formal study has yet to use this regression to prove superior postop tensile strength.[2,5] SMILE's minimal violation of the anterior cornea has led to the hypothesis that it provides faster postop corneal nerve innervation allowing for enhanced corneal sensation and reduction in ocular surface disease. A study comparing eyes treated with SMILE and LASIK found that at one week, one month, three months and six months postop central corneal sensation was decreased from baseline in both groups, however the reduction was greater in eyes treated with LASIK.[6] Using confocal microscopy, a study demonstrated that LASIK produced a greater decrease in corneal nerves compared to SMILE;[7] an additional study describes increased subbasal nerve fiber density in eyes treated with SMILE vs LASIK at three months postop.[8] A report comparing dry-eye parameters between SMILE and LASIK found that the Schirmer's test and tear break-up time were greater in SMILE patients than LASIK patients.[9] (It should be noted that other studies comparing dry-eye parameters found no statistically significant difference between the two procedures.)

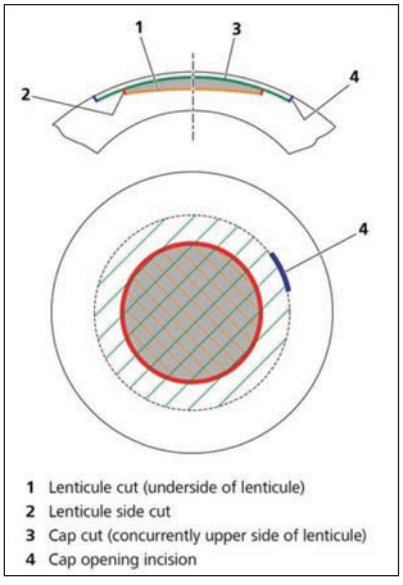

Figure 7. Schematic demonstrating the geometry of the SMILE procedure.

In addition to its efficacy and enhanced biomechanical/corneal innervation properties, SMILE has also been proven to be safe. In the FDA clinical trial, 2.2 percent of eyes (n=8) experienced postoperative adverse events, none of which negatively impacted the patients' long-term visual acuity.[3] A clinical control cohort study at the Department of Ophthalmology at Aarhus University in Aarhus, Denmark, followed 1,800 post-SMILE eyes and found 1.5 percent of them (n=24) had reduced best-corrected distance visual acuity from baseline at

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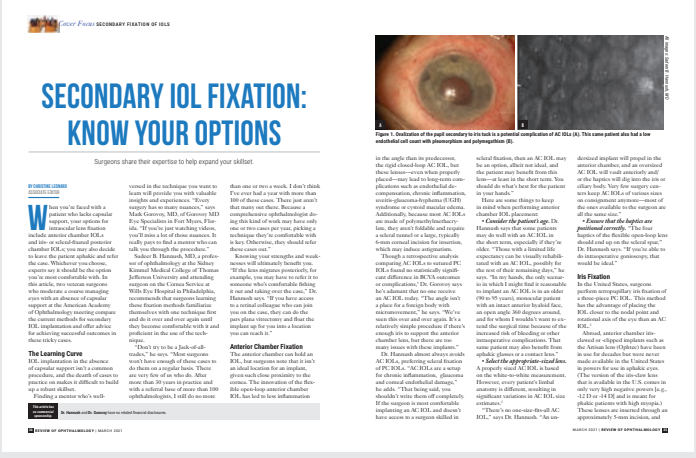
Cover Focus SECONDARY FIXATION OF IOLS

SECONDARY IOL FIXATION: KNOW YOUR OPTIONS

Surgeons share their expertise to help expand your skillset.

BY CHRISTINE LEONARD
ASSOCIATE EDITOR

When you're faced with a patient who lacks capsular support, your options for intraocular lens fixation include anterior chamber IOLs and iris- or scleral-fixated posterior chamber IOLs; you may also decide to leave the patient aphakic and refer the case. Whichever you choose, experts say it should be the option you're most comfortable with. In this article, two veteran surgeons who moderate a course managing eyes with an absence of capsular support at the American Academy of Ophthalmology meeting compare the current methods for secondary IOL implantation and offer advice for achieving successful outcomes in these tricky cases.

The Learning Curve

IOL implantation in the absence of capsular support isn't a common procedure, and the dearth of cases to practice on makes it difficult to build up a robust skillset.

Finding a mentor who's well-versed in the technique you want to learn can help you avoid common insights and experiences. "Every surgeon has so many nuances," says Mark Gorovoy, MD, of Gorovoy MD Eye Specialists in Fort Myers, Florida. "If you're just watching videos, you'll miss a lot of those nuances. It really pays to find a mentor who can talk you through the procedure."

Sadeer B. Hannush, MD, a professor of ophthalmology at the Sidney Kimmel Medical College of Thomas Jefferson University and attending surgeon on the Cornea Service at Wills Eye Hospital in Philadelphia, recommends that surgeons learning these fixation methods familiarize themselves with one technique first and do it over and over again until they become comfortable with it and proficient in the use of the technique.

"Don't try to be a Jack-of-all-trades," he says. "Most surgeons won't have enough of these cases to do them on a regular basis. There are very few of us who do. After more than 30 years in practice and with a referral base of more than 100 ophthalmologists, I still do no more than one or two a week. I don't think I've had a year with more than 100 of these cases. Three just aren't there out there. Because a comprehensive ophthalmologist doing this kind of work may have only one or two cases per year, picking a technique they're comfortable with is key. Otherwise, they should refer these cases out."

Knowing your strengths and weaknesses will ultimately benefit you. "If the lens migrates posteriorly, for example, you may have to refer it to someone who's comfortable fishing it out and taking over the case," Dr. Hannush says. "If you have access to a retinal colleague who can join you on the case, they can do the pars plana vitrectomy and float the implant up for you into a location you can reach it."

Anterior Chamber Fixation

The anterior chamber can hold an IOL, but surgeons note that it isn't an ideal location for an implant, given such close proximity to the cornea. The innovation of the flexible open-loop anterior chamber IOL has led to low inflammation

Figure 1. Dislocation of the pupil secondary to iris tuck is a potential complication of AC IOLs (A). This same patient also had a low endothelial cell count with pleomorphism and polymegathism (B).

in the angle than its predecessor, the rigid closed-loop AC IOL, but these lenses—even when properly placed—may lead to long-term complications such as endothelial decompensation, chronic inflammation, uveitis-glaucoma-hyphema (UGH) syndrome or cystoid macular edema. Additionally, because most AC IOLs are made of polymethylmethacrylate, they aren't foldable and require a scleral tunnel or a large, typically 6-mm corneal incision for insertion, which may induce astigmatism.

Though a retrospective analysis comparing AC IOLs to sutured PC IOLs found no statistically significant differences in BCVA outcomes or complications,[1] Dr. Gorovoy says he's adamant that no one receive an AC IOL today. "The angle isn't a place for a foreign body with micromovement," he says. "We've seen this over and over again. It's a relatively simple procedure if there's enough iris to support the anterior chamber lens, but there are too many issues with these implants."

Dr. Hannush almost always avoids AC IOLs, preferring scleral fixation of PC IOLs. "AC IOLs are a setup for chronic inflammation, glaucoma and corneal endothelial damage," he adds. "That being said, you shouldn't retire them off completely. If the surgeon is most comfortable implanting an AC IOL and doesn't have access to a surgeon skilled in scleral fixation, then an AC IOL may be an option, albeit not ideal, and the patient may benefit from this lens—at least in the short term. You should do what's best for the patient in your hands."

Here are some things to keep in mind when performing anterior chamber IOL placement:

• ***Consider the patient's age.*** Dr. Hannush says that some patients may do well with an AC IOL in the short term, especially if they're older. "Those with a limited life expectancy can be visually rehabilitated with an AC IOL, possibly for the rest of their remaining days," he says. "In my hands, the only scenario in which I might find it reasonable to implant an AC IOL is in an older (90 to 95 years), monocular patient with an intact anterior hyaloid face, an open angle 360 degrees around, and for whom I wouldn't want to extend the surgical time because of the increased risk of bleeding or other intraoperative complications. That same patient may also benefit from aphakic glasses or a contact lens."

• ***Select the appropriate-sized lens.*** A properly sized AC IOL is based on the white-to-white measurement. However, every patient's limbal anatomy is different, resulting in significant variations in AC IOL size estimates.[2]

"There's no one-size-fits-all AC IOL," says Dr. Hannush. "An undersized implant will propel in the anterior chamber, and an oversized AC IOL will vault anteriorly and/or the haptics will dig into the iris or ciliary body. Very few surgery centers keep AC IOLs of various sizes on consignment anymore—most of the ones available to the surgeon are all the same size."

• ***Ensure that the haptics are positioned correctly.*** "The four haptics of the flexible open-loop lens should end up on the scleral spur," Dr. Hannush says. "If you're able to do intraoperative gonioscopy, that would be ideal."

Iris Fixation

In the United States, surgeons perform retropupillary iris fixation of a three-piece PC IOL. This method has the advantage of placing the IOL closer to the nodal point and rotational axis of the eye than an AC IOL.[3]

Abroad, anterior chamber iris-claw or -clipped implants such as the Artisan lens (Ophtec) have been in use for decades but were never made available in the United States in powers for use in aphakic eyes. (The version of the iris-claw lens that is available in the U.S. comes in only very high negative powers [e.g., -12 D or -14 D] and is meant for phakic patients with high myopia.) These lenses are inserted through an approximately 5-mm incision, and

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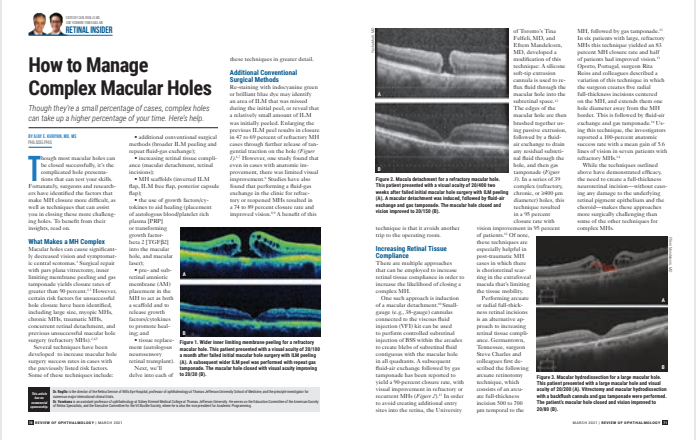
RETINAL INSIDER

How to Manage Complex Macular Holes

Though they're a small percentage of cases, complex holes can take up a higher percentage of your time. Here's help.

BY GARY C. BROWN, MD, MD
PHILADELPHIA

Though most macular holes can be closed successfully, it's the complicated hole presentations that can test your skills. Fortunately, surgeons and researchers have identified the factors that make MH closure more difficult, as well as techniques that can assist you in closing these more challenging holes. To benefit from their insights, read on.

What Makes a MH Complex

Macular holes can cause significantly decreased vision and symptomatic central scotomas.[1] Surgical repair with pars plana vitrectomy, inner limiting membrane peeling and gas tamponade yields closure rates of greater than 90 percent.[2,3] However, certain risk factors for unsuccessful hole closure have been identified, including large size, myopic MHs, chronic MHs, traumatic MHs, concurrent retinal detachment, and previous unsuccessful macular hole surgery (refractory MHs).[4,5]

Several techniques have been developed to increase macular hole surgery success rates in cases with the previously listed risk factors. Some of these techniques include:

• additional conventional surgical methods (broader ILM peeling and repeat fluid-gas exchange);

• increasing retinal tissue compliance (macular detachment, retinal incisions);

• MH scaffolds (inverted ILM flap, ILM free flap, posterior capsule flap);

• the use of growth factors/cytokines to aid healing (placement of autologous blood/platelet rich plasma [PRP] or transforming growth factor-beta 2 [TGFβ2] into the macular hole, and macular lysis);

• pro- and sub-retinal amniotic membrane (AM) placement in the MH to act as both a scaffold and to release growth factors/cytokines to promote healing; and

• tissue replacement (autologous neurosensory retinal transplant).

Next, we'll delve into each of these techniques in greater detail.

Additional Conventional Surgical Methods

Re-staining with indocyanine green or brilliant blue dye may identify an area of ILM that was missed during the initial peel, or reveal that a relatively small amount of ILM was initially peeled. Enlarging the previous ILM peel results in closure in 47 to 69 percent of refractory MH cases through further release of tangential traction on the hole (*Figure 1*).[6] However, one study found that even in cases with anatomic improvement, there was limited visual improvement.[7] Studies have also found that performing a fluid-gas exchange in the clinic for refractory or reopened MHs resulted in a 74 to 89 percent closure rate and improved vision.[8,9] A benefit of this technique is that it avoids another trip to the operating room.

Figure 1. Wider inner limiting membrane peeling for a refractory macular hole. This patient presented with a visual acuity of 20/160 a month after failed initial macular hole surgery with ILM peeling (A). A subsequent wider ILM peel was performed with repeat gas tamponade. The macular hole closed with visual acuity improving to 20/30 (B).

Increasing Retinal Tissue Compliance

There are multiple approaches that can be employed to increase retinal tissue compliance in order to increase the likelihood of closing a complex MH.

One such approach is induction of a macular detachment.[10] Small-gauge (e.g., 38-gauge) cannulae connected to the viscous fluid injection (VFI) kit can be used to perform controlled subretinal injection of BSS within the arcades to create blebs of subretinal fluid contiguous with the macular hole in all quadrants. A subsequent fluid-air exchange followed by gas tamponade has been reported to yield a 96-percent closure rate, with visual improvement in refractory or recurrent MHs (*Figure 2*).[11] In order to avoid creating additional entry sites into the retina, the University of Toronto's Tina Felfeli, MD, and Ethem Mandelcorn, MD, developed a modification of this technique: A silicone soft-tip extension cannula is used to re-flux fluid through the macular hole into the subretinal space.[12]

The edges of the macular hole are then brushed together using pneumatic retinopexy, followed by a third-air exchange to displace any residual subretinal fluid through the hole, and then gas tamponade (*Figure 3*). In a series of 39 complex (refractory, chronic, or >400 µm diameter) holes, this technique resulted in a 95 percent closure rate with vision improvement in 95 percent of patients.[12] Of note, these techniques are especially helpful in pseudophakic eyes, as cases in which there is chorioretinal scarring in the extrafoveal macula diminish the tissue mobility.

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Performing accurate or radial full-thickness retinal incisions is an alternative approach to increasing retinal tissue compliance. Gemmatorres, Tennessee, surgeon Steve Charles and colleagues first described the following accurate retinotomy technique, which consists of an accurate full-thickness incision 500 to 700 µm temporal to the MH, followed by gas tamponade.[13] In six patients with large, refractory MHs this technique yielded an 83 percent MH closure rate and half of patients had improved vision.[13] Oporto, Portugal, surgeon Rita Baixo and colleagues described a variation of this technique in which the surgeon creates five radial full-thickness incisions centered on the MH, and extends them one hole diameter away from the MH borders. This is followed by fluid-air exchange and gas tamponade.[14] Using this technique, the investigators reported a 100-percent anatomic success rate with a mean gain of 5.6 lines of vision in seven patients with refractory MHs.[14]

While the techniques outlined above have demonstrated efficacy, the need to create a full-thickness retinal incision—without causing any damage to the underlying retinal pigment epithelium and the choroid—makes these approaches more surgically challenging than some of the other techniques for complex MHs.

Figure 2. Macula detachment for a refractory macular hole. This patient presented with a visual acuity of 20/400 two weeks after failed initial macular hole surgery with ILM peeling (A). A macular detachment was induced, followed by fluid-air exchange and gas tamponade. The macular hole closed and vision improved to 20/150 (B).

Figure 3. Macular hydrodissection for a large macular hole. This patient presented with a large macular hole and visual acuity of 20/200 (A). Vitrectomy and macular hydrodissection with a backflush cannula and gas tamponade were performed. The patient's macular hole closed and vision improved to 20/60 (B).

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the three-month follow-up visit. By 12 months, however, all 24 eyes were within one line of their preop BCDVA. The study also found that 9.78 percent of eyes (n=154) experienced postoperative complications, with the most common adverse events being trace haze and corneal surface dryness. In both the FDA clinical trial and Danish study, epithelial ingrowth was found to be a rare complication. The FDA and Danish studies found that 0.6 percent (n=2) and 0.64 percent (n=10) of eyes experienced epithelial ingrowth, respectively. Of the 12 eyes found to have ingrowth between the two studies, 11 had spontaneous resolution with no effect on BCDVA. One eye required surgical intervention at the 12-month follow-up, with a resultant UDVA of 20/20.[10]

One potential drawback with SMILE is the case in which a patient needs an enhancement. SMILE enhancements aren't FDA-approved, and surgeons usually have to either cut a LASIK flap or perform surface ablation to enhance a SMILE patient, potentially negating some of SMILE's purported benefits compared to these other procedures in the process.[11]

The exact cause for epithelial ingrowth following SMILE procedure isn't known, however there are two prevailing hypotheses. The first is that when making the small side incision for the lenticule extraction a tract is formed which allows corneal epithelial cells to migrate and form a nest at the surgical interface. The other hypothesis states that, during the procedure, epithelial cells are spread and ultimately planted at the interface during lenticule extraction.

Given the rarity of epithelial ingrowth following SMILE, no studies exist providing the appropriate approach to handling the complication. There are few case reports that describe both progressively increasing and visually significant epithelial ingrowth, and they describe varying approaches to correct it.

One case study described two patients who presented with subjective blurry vision following SMILE, with the slit lamp exam demonstrating a corneal opacity at the SMILE interface site in both patients. Subsequent OCT imaging found both patients to have an incisional tear and nest of epithelial ingrowth at the interface. Given the combination of subjective blurry vision and presence of ingrowth, it was decided to pursue surgical removal of the epithelial cells. The procedure consisted of using basic saline solution to separate the epithelial cells from the interface, followed by scraping of the cells with a blunt spatula, ensuring their complete removal. Once the cells were separated from the interface, 27-ga. vitreoretinal forceps were used to completely remove them. The interface was subsequently closed with 10-0 nylon sutures and a bandage contact lens was placed for a week. Both patients were closely followed, and at the one-month follow-up both were found to have BCVA 20/16 with complete stability of their SMILE interface.[12]

Another case report describes a 40-year-old female who presented with progressive increase in the size of epithelial ingrowth at the SMILE interface on OCT over the span of seven months. Though the patient's BCVA remained 20/20, it was determined that the epithelial ingrowth would be treated given its progressive enlargement. The providers describe using a Nd:YAG laser to break up the collection of epithelial cells and eliminate the epithelial collection at the three-month follow-up visit. The patient continued to have complete resolution of epithelial ingrowth with consistent BCVA 20/20 in all subsequent follow-ups.[13]

In summary, the SMILE procedure is a minimally invasive refractive surgery technique with an efficacy and safety profile similar to the more established procedures LASIK and PRK. Studies have shown that SMILE may offer patients postoperative benefits compared to other refractive surgery techniques, including increased corneal tensile strength, improved corneal sensation/innervation and a potential reduction in postop ocular surface disease. Epithelial ingrowth is an extremely rare post-SMILE complication that often self-resolves with no long-term effect on vision. In the rare cases requiring intervention, both surgical and laser therapies have been proven to remove the nest of epithelial cells, maintain interface stability and ensure no decompensation of patient vision. ◀

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In embryo/fetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost which achieved at least 1770 times the maximum human bimatoprost exposure following a single administration of DURYSTA™ (based on plasma C_{max} levels; blood-to-plasma partition ratio of 0.858).

In a pre/postnatal development study, oral administration of bimatoprost to pregnant rats from gestation day 7 through lactation resulted in reduced gestation length, increased late resorptions, fetal deaths, and postnatal pup mortality, and reduced pup body weight at 0.3 mg/kg/day (estimated 470-times the human systemic exposure to bimatoprost from DURYSTA™, based plasma C_{max} and a blood-to plasma partition ratio of 0.858). No adverse effects were observed in rat offspring at 0.1 mg/kg/day (estimated 350-times the human systemic exposure to bimatoprost from DURYSTA™, based on plasma C_{max}).

Lactation: There is no information regarding the presence of bimatoprost in human milk, the effects on the breastfed infants, or the effects on milk production. In animal studies, topical bimatoprost has been shown to be excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when DURYSTA™ is administered to a nursing woman.

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Potential for Pigmentation: Advise patients about the potential for increased brown pigmentation of the iris, which may be permanent.

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Macular edema, including cystoid macular edema, has been reported during treatment with ophthalmic bimatoprost, including DURYSTA™ intracameral implant. DURYSTA™ should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Prostaglandin analogs, including DURYSTA™, have been reported to cause intraocular inflammation. DURYSTA™ should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

Ophthalmic bimatoprost, including DURYSTA™ intracameral implant, has been reported to cause changes to pigmented tissues, such as increased pigmentation of the iris. Pigmentation of the iris is likely to be permanent. Patients who receive treatment should be informed of the possibility of increased pigmentation. While treatment with DURYSTA™ can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Intraocular surgical procedures and injections have been associated with endophthalmitis. Proper aseptic technique must always be used with administering DURYSTA™, and patients should be monitored following the administration.

Adverse Reactions

In controlled studies, the most common ocular adverse reaction reported by 27% of patients was conjunctival hyperemia. Other common adverse reactions reported in 5%-10% of patients were foreign body sensation, eye pain, photophobia, conjunctival hemorrhage, dry eye, eye irritation, intraocular pressure increased, corneal endothelial cell loss, vision blurred, iritis, and headache.

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

References: 1. DURYSTA™ [Prescribing Information]. Irvine, CA: Allergan, Inc.; 2020. **2.** Data on file, Allergan, 2020. **3.** Standring S. Orbit and accessory visual apparatus. In: *Gray's Anatomy: The Anatomical Basis of Clinical Practice*. 41st ed. Philadelphia, PA: Elsevier Limited; 2016: 666-708.

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