Wills Eye Resident Series: Decreased vision and nyctalopia in a 61-year-old man, *p. 70*

REVIEW of OPHTHALMOLOGY®

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DIVINING IOL POWER

The technologies and techniques for predicting the best lens power preop. **P. 24**

ALSO INSIDE:

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.

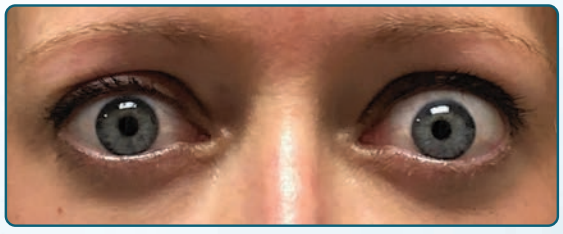
Preexisting Inflammatory Bowel Disease: TEPEZZA may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

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

NEWS

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AUGUST 2021

Aetna's Prior Authorization Policy Spawns Opposition

On July 1st, Aetna implemented a new policy requiring prior authorization for cataract surgery. Ophthalmologists, as well as the American Academy of Ophthalmology and the American Society of Cataract and Refractive Surgery, are up in arms, saying that this new policy is disruptive and burdensome and will result in delays in care for thousands of patients.

David B. Glasser, MD, the secretary for federal affairs at the Academy, says the policy is based on the belief that there's a great deal of unnecessary cataract surgery being performed. "Aetna has told us they have internal data suggesting that about 4 to 5 percent of surgeries may be unnecessary, but they didn't offer any details," he says. "Historically, the number of unnecessary cataract surgeries isn't zero, but it's very low—about 2 percent, depending on the criteria applied. It doesn't make sense to subject every single cataract surgery to prior authorization for a problem that constitutes only a very small percentage of surgeries."

The policy change was announced in the spring, but Aetna failed to provide a way to obtain prior authorizations until just a few days before it went into effect on July 1, says Dr. Glasser. "It's been inefficient," he says. "We've already had reports of at least one emergency case that wasn't approved, despite Aetna's statement that emergency cases could be approved immediately through their 800 number instead of their online portal. We have real concerns that there may be poor outcomes due to delays in care."

The case in question involved a patient with a cataract and retinal detachment requiring emergency surgery in Harrisburg, Pennsylvania. The cataract obscured the view of the posterior segment and retina. "Cataract surgery was initially denied," Dr. Glasser says. "It could have been a couple weeks for approval to come through, and the patient couldn't wait that long. The surgeon removed the cataract. In situations like this, we hope the surgeon would perform the surgery and deal with the insurance later, but this situation really isn't acceptable."

Review was unable to speak to an Aetna spokesperson for comment, but received instead a statement from the company that expressed Aetna's outreach efforts to inform the ophthalmic community of the policy and reassure them that patients would receive "timely access to appropriate, necessary care."

Previous communications with Aetna didn't define what the company considered medically necessary, says Dr. Glasser. *Review* was also sent a link to Aetna's cataract clinical policy bulletin, but the policy bulletin was last updated in April 2020 and revised in August 2020, so it's unclear whether the criteria online reflect exactly the criteria for the July 1, 2021 preauthorization policy.

Dr. Glasser says the AAO has heard complaints about Aetna's online portal rejecting approvals, requiring staff to go back and file more details. Refiling may take up to two weeks, he says. "We've heard from practices that need to schedule combined cataract and glaucoma surgery—not on an emergency basis—that are getting mixed messages from Aetna: The telephone folks say no precertification is needed, but the online portal says it is. There's really a lot of confusion surrounding this."

ASCRS and AAO have connected with the leadership at Aetna and are keeping lines of communication open. "We've reached out to our members with information they can give to their patients to explain this

(Continued on p. 14)

AETNA FRACAS: THE CODES IN QUESTION

CPT codes 66982, 66984, 66987 and 66988 are affected by the new policy. One of the latest revisions from August 2020 states that "cataract removal surgery is considered not medically necessary if ... the member does not require surgery." You can find Aetna's clinical policy bulletin in the Resources tab on aetna.com. Search for CPB 0508 or visit aetna.com/cpb/medical/data/500_599/0508.html.

Information on ASCRS' advocacy efforts can be found at ascrs.org/advocacy/legislative/prior-authorization.

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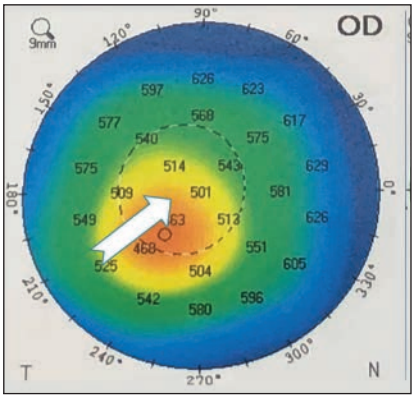

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AUGUST 2021

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REVIEW of OPHTHALMOLOGY

WALTER C. BETHKE, EDITOR IN CHIEF

EDITOR'S PAGE

Ophthalmology Goes Live

John F. Kennedy famously—though, it turns out, erroneously—said that the Chinese word for "crisis" is actually a combination of the symbols for "danger" and "opportunity." In a similar vein, we should come up with a word to describe the feeling of going to live conventions during a pandemic that combines "excitement" and "caution."

As I write this, I've just returned from the 2021 American Society of Cataract and Refractive Surgeons meeting in Las Vegas, the first large, live meeting ophthalmology's had since the 2019 American Academy of Ophthalmology meeting (I hope we all enjoyed that meeting, knowing now what was in store for us a couple of months later).

Even though ASCRS' official numbers had the attendance as, understandably, decreased in comparison to past meetings that didn't occur during a global pandemic, I'm sure the other attendees would agree that it felt great to be in-person again. Gone was the need to stare at a screen for hours, as speakers spoke over each other due to a Zoom audio delay. This was replaced by live sessions with speakers and panelists who made you feel completely engaged with the material. The other benefit, as ophthalmologists will attest, was the chance of meeting with a colleague, ending in a coffee or a lunch, where you learn not only what's new with the person you're speaking to, but also what's new in their practice. What do they think about the new lens they just started using? How do they handle cataract patients who are complaining about poor vision post-op? Can you believe the proposed reimbursement cuts? The immediacy of these types of interactions, made possible by everyone being in the same place, was refreshing and something the digital world still hasn't been able to duplicate.

That was the "excitement" part of our new word for live meetings. The "caution" part appeared when I opened some local news sites and read, "Las Vegas Declared Worst Metro Area in the Nation for COVID-19 Transmission."[1] That's like reading, "Planes Crashing at Unprecedented Rate" as you tear into your airplane pretzels. Fortunately, I, and I'm guessing almost everyone else at the meeting, was vaccinated, and some 99 percent of the new COVID-19 cases are occurring in unvaccinated people. Still, one worries about the possibility of breakthrough infections, spreading the virus without getting sick yourself, and the effects of mutations like the Delta variant.

However, if we're to live our lives and return to some semblance of normalcy, caution may be the price we pay, at least for now. Until normal life returns, maybe we can hope for just a little bit of the two things that compose the word "happiness" in Chinese: luck and a blessing.

— *Walter Bethke*
Editor in Chief

1. KLAS News, Las Vegas. https://www.8newsnow.com/news/health/coronavirus-health/las-vegas-ranked-as-worst-big-metro-area-in-the-nation-for-covid-19-transmission/.

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Cataract Pre-authorization

(Continued from p. 5)

situation," says Dr. Glasser. "We're asking for support of a bill in Congress that will streamline and increase transparency of the preauthorization process and eliminate preauthorization for procedures that are routinely approved. We're also asking members to ask patients who've had their surgeries rescheduled or are put out by this to write to their congressperson and let them know it's affecting Medicare Advantage beneficiaries covered by Aetna.

"We talked to Aetna just a few days prior to the policy implementation and expressed our concerns," Dr. Glasser continues. "They didn't seem concerned, but now that it's clear their system isn't working well, hopefully we'll be able to convince them they need to make significant changes."

However, Terry Kim, MD, the immediate past president of ASCRS, told *Review* in mid-July that Aetna isn't responding to them at all now. "Cataract surgery is one of the most successful ophthalmic procedures and medical procedures in general," he says. "There's a very high level of patient happiness. This move certainly sends the wrong message and limits access to surgical care. We don't want other insurance companies to follow suit."

"The bottom line is that we need to see this policy paused and ideally canceled," says Dr. Glasser. "The program isn't necessary, given the small number of cases that are likely to be denied. It's going to be a waste of time and money for physicians and for patients who've been rescheduled and also have to change plans for family members to take them to surgery. We also think this policy won't save Aetna much money with all the time and money they'll have to spend administering it."

Factors That Portend Worse Cataract Outcomes

A team looking into the prognostic factors associated with low postop visual acuity in patients experiencing vitreous loss during cataract surgery identified ocular comorbidities, secondary intraocular lens implantation, cystoid macular edema development and additional surgical complications as playing a role.

The retrospective, noncomparative, interventional case study evaluated 179 patients experiencing vitreous loss during cataract surgery (60 percent of the patients were male) with a mean age of 73 years, axial length of 23.5 mm and follow-up of 12 months. The researchers assessed demographics, best-corrected visual acuity, axial length, presence of ocular comorbidities affecting central vision, timing of IOL implantation, position of the implanted lens and presence of corneal sutures. Low visual outcome was defined as best-corrected visual acuity <20/40.

Multivariable logistic regression analysis discovered that low visual outcomes were independently associated with persisting postoperative complications (odds ratio: 6.25), preexisting ocular comorbidities (odds ratio: 4.45) and secondary intraocular lens implantation (odds ratio: 10.36). Conversely, pars plana vitrectomy for dislocated fragments of lens material, patient age of more than 70 years, patient gender, axial length, experience level of surgeon, corneal suturing and anterior chamber lens implantation were not found to have significant associations with low visual outcomes.

The study's authors concluded that clinicians, specifically those involved in delivery of cataract surgery and its follow-up care, should be aware of these findings in order to give their cataract surgery patients a more accurate prognosis. ◀

1. Mimouni M, Schaap-Fogler M, Polkinghorne P, et al. Prognostic factors for low visual acuity after cataract surgery with vitreous loss. J Ophthalmol 2021;2021:6691904.

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

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

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Fore!

Musings on life, ophthalmology and the practice of medicine.

MARK H. BLECHER
CHIEF MEDICAL EDITOR

Ophthalmologists, as a specialty, consider themselves to be detail-oriented perfectionists. We're proud of that. We're concerned with mastering our craft through meticulous repetition. The oft-asked questions are: How many cataracts have you done? How many injections? How many tube shunts? etc. It starts with residency interviews, and then continues through our training years and in our quest for a job. Numbers frequently mean money, but they also represent your level of skill, and the phrase "practice makes perfect" should have been written about ophthalmologists. Once mastered, the ability to reproduce these perfect results time after time, eye after eye, is the hallmark of a skilled surgeon. As I used to say to my residents when teaching cataract surgery: "Perfect rice every time." (OK, I had to stop saying that since no one had a clue that I was comparing their surgery to an instant-rice commercial from the '60s.) Anyway, here we are as a profession, still demanding perfect rice.

By now you likely have no idea where I'm going with this, so I'll tell you: Golf. That game where you whack at a little ball and almost always underperform your own expectations. The opposite of perfect rice every time, golf is a seemingly imperfectible game, which, on the face of it, makes it ill-suited for ophthalmologists. Also, golf is a major time commitment. As the old joke goes, where else would you find a doctor on Wednesday except at the golf course? So, when colleagues went out to play golf, I saw it as an entire day of the week devoted to imperfection.

For the reasons stated above, as well as a disinclination to embarrass myself in public, I've resisted learning how to play the game. Despite my friends' and colleagues' recent suggestions that I now take it up, I'm still not sure it's a good avocation for me. What purpose will it serve, other than killing time? Is it exercise? Not really. Is it relaxing? Maybe—but, then again, I'm pretty type A. Is it a good reason to get outdoors? Probably, but I've also got chores galore waiting for me in my yard. My biggest question is: Can I get really good at it? Because that's what being an ophthalmologist is all about.

Maybe, however, the fact that golf eludes perfection is precisely why I should play it. In my second act—Mark 2.0—I'm working on being less intense, less unforgiving of myself and others, and more accepting of imperfection. Maybe all of life's not about perfect rice.

Most importantly though, I'm trying to be present. A few years ago, I was supervising the resident clinic. It was the usual madhouse, but the chief resident was overseeing the chaos with his usual good nature and preternatural calm. I admired that and asked him how he did it. Aside from his having good genes, he referred me to Eckhart Tolle's book "The Power of Now," with which many of you are no doubt familiar. The book was an amazing read and helped me to begin to understand the value of being "in the moment," which is now almost a cliché admonition for surviving modern life. Enlightening? Yes … but oh-so-difficult to achieve.

There are many ways to get there, to be present in the moment, and one size doesn't fit all. For some, its meditation. Others choose yoga. For others, perhaps, it could be golf. Yes, golf. As I contemplate what truly useful reason I might have to take up the game, it occurs to me that you can't play golf without being there, in the moment. And while I would be hard pressed to ascribe a higher calling to the game, it could provide the opportunity to focus on the present—and perhaps to be taken down a peg or two and be left without artifice or pretense. No perfect rice on a golf course. It might be just what the doctor ordered ... just not on Wednesdays. ◀

This article has no commercial sponsorship.

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

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Fitting PRK into Your Surgical Plan

Surgeons detail the patients who benefit most from PRK and share tips for managing postop discomfort.

SEAN MCKINNEY
SENIOR EDITOR

Although LASIK is still the king of refractive surgery in general, PRK still has a significant place in today's mix of refractive surgery procedures for the foreseeable future—and is sometimes used even more often than before. In this article, surgeons explain how they position the procedure and why they rely on it in a variety of cases. They also offer advice to help you determine which patients benefit the most from the procedure.

One and Only

Farrell C. Tyson, MD, FACS, of Tyson Eye in Cape Coral, Florida, knows of surgeons in his region who offer PRK as their only form of refractive surgery. "We've seen a number of colleagues go full circle," he says. "I believe they don't want to deal with flap complications. Plus, PRK is more cost-effective. We see practices promote it as 'bladeless laser vision correction,' giving it the aura of a new innovation."

Not everyone agrees with this approach, however. Unlike some refractive surgeons, Arturo S. Chayet, MD, the medical director of Codet Vision Institute, Tijuana, Mexico, doesn't think the term PRK stigmatizes the procedure or suggests that it's outdated, even though the procedure is more than 25 years old. "To call PRK by an alternative name, such as advanced surface ablation or bladeless refractive surgery, is a big mistake, creating confusion," he says. "We always call it PRK at our practice. We make sure the patient understands that we offer state-of-the-art PRK and state-of-the-art LASIK."

At Tyson Eye, meanwhile, Dr. Tyson also sticks to the PRK label, using the procedure in about 5 percent of all of the refractive surgeries he performs. Generally, he says he reserves it for conditions that are causing irregular corneas, such as epithelial basement membrane dystrophy. Besides creating a refractive result, he notes that PRK on these patients enables him to buff down irregularities in the anterior corneal layer.

"One recent case we had is an example of when PRK can be most helpful," says Dr. Tyson. "We did keratometry, and you could see slight steepening of the cornea, inferiorly. That's when I decided to switch to PRK. The patient in question had forme fruste keratoconus."

Dr. Tyson says he also turns to PRK when a post-RK patient presents for repeat refractive surgery. "We get a lot of patients who come in as post-RK cases," he says. "I don't want to make a deep-flap cut on them. I'd rather buff out the residual refraction. PRK enables me to do that cleanly."

Even Daniel S. Durrie, MD, who co-created sub-Bowman's keratomileusis and now offers every type of refractive surgery, finds a place for PRK in his practice. "Looking back over the past 10 years at our practice, I'd say the percentage of patients undergoing PRK has been very stable at 10 to 15 percent," says Dr. Durrie, who runs Durrie Vision in Overland Park Kansas. "The main indications are pre-existing epithelial disease or thin corneas."

Deciding Between LASIK and PRK

Many refractive surgeons lean toward LASIK. "Recovery from LASIK is a lot nicer and slicker than PRK," says William Bond, MD, FASC, medical director of Bond Eye Associates in Peoria and Pekin, Illinois. "But there's always that moment of truth when you're making the flap. You've got to get the eye more wide-open. And there's the possibility of a flap problem or some complication that you just won't get with PRK. For example, I'll choose PRK for the patient with a small orbit, where the strong bone structure is in the way and I can't get the eye open enough. That makes me worry that I'm going to have a problem with suction."

Also, he continues, "I watch for a residual bed that's too thin for LASIK. We have to keep in mind that the flap doesn't contribute any structural strength to the cornea. Therefore, if you have too thin of a cornea or too high of a correction, PRK is a lot safer. Some conventional wisdom also suggests ectasia is less likely with PRK in certain cases. For example, if someone has a slightly irregular

This article has no commercial sponsorship.

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

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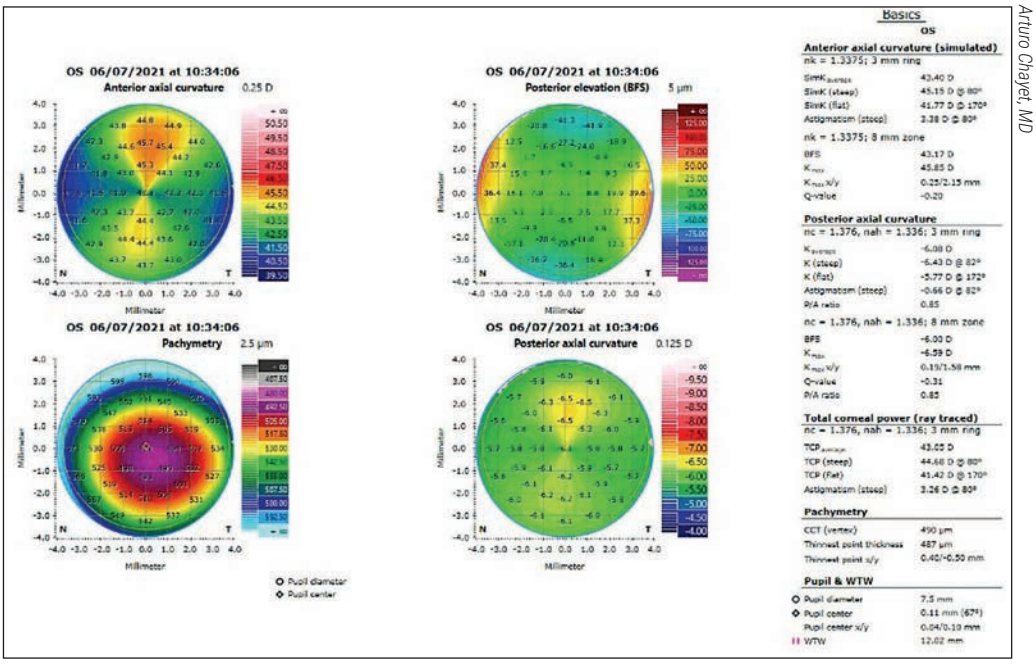
corneal map, you might want to slant toward PRK, considering that PRK will help you avoid ectasia in some cases.

"Can minute differences in the maps really suggest a risk of ectasia? It's debatable, but I like to play it safe. You should be doing what you'd do if you were the patient. Taking away less tissue with PRK, possibly staying on slightly stronger legal ground, is also not a bad idea."

Dr. Bond says he performs 500 to 1,000 refractive surgery procedures per year, including 15 to 35 percent that turn into PRKs. "I typically do PRK about 20 percent of the time," he notes. "You have patients who can't hold still, or a double-digit myope whose cornea isn't overly thick. Sometimes, I have a little problem with a flap; after that, I might use PRK, in as many as one-third of my procedures. On the other hand, you'll get a patient who has a very difficult time healing after surface ablation and experiences a lot of pain. An experience like that may push my PRK percentage back down. It's like baseball. You're only as good as your last time up at bat, and you're always trying to figure out your best approach and learn as you go."



Arturo Chayet, MD

Figure 1. This 22-year-old male, with a refraction of -2.50-4.40 X 168, wasn't a candidate for LASIK because his central corneal thickness, at 490 µm, was too thin. The patient successfully underwent PRK, followed by treatment with mitomycin-C.

Making sure patients fit the right profile for LASIK or PRK is also important, he adds. "Make them aware of the increased stability of refractive surgery without a flap (especially in the event of trauma)," he says. "I try to help them project into the future to determine if they just might end up doing something career- or lifestyle-wise that would not be good for a LASIK patient. Despite all of your counseling, though, you need to leave the decision to the patient. I've done LASIK on rodeo clowns that came to us as a group. That's what they wanted, despite the risks that I reviewed with them."

Dr. Bond notes that he only rarely considers implanting phakic intraocular lenses. "I've done them, yes, and I've had good luck doing them," he recalls. "However, you raise the risk of more serious complications in these cases. With PRK, your complications are completely outside the eye. With LASIK, you could see issues involving the flap. If you put an ICL into a 22-year-old patient, however, you could cause a cataract or endophthalmitis or some other problem. You've moved up to your bigger-league complications, whether they're common or not."

Conservative Approaches

Like Dr. Bond, many other surgeons prefer to err on the side of caution. As a surgeon who doesn't focus primarily on refractive surgery, corneal specialist Brandon Ayres, MD, is one of these doctors.

"For any patient with a corneal thickness of 500 µm or less, even if the safety parameters for doing LASIK are met, I consider the cornea thinner than usual and I'll do PRK," says Dr. Ayres, co-director of the Cornea Fellowship at Wills and an instructor at Jefferson Medical College, Thomas Jefferson University in Philadelphia. "That's purely my own rule. I don't know if there's any substance behind it. I just sleep better if I know I'm being safer for this patient."

Penny A. Asbell, MD, FACS, MBA, FARVO, Barrett G. Haik Endowed Chair for Ophthalmology in the College of Medicine at the University of Tennessee Health Science Center, says many patients favor LASIK "because it provides a relatively quick visual recovery and because of the reduced discomfort initially. However, at six months, most of the reported results of LASIK and PRK are pretty equal in terms of vision. Deciding which type of surgery to perform has to do more with what you, as the surgeon, are comfortable doing. If you like LASIK and do a lot of LASIK, fine. However, LASIK as a technique poses more risk than surface ablation. If you don't do a lot of refractive surgery because that's not your primary focus in your practice,

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Arturo Chayet, MD

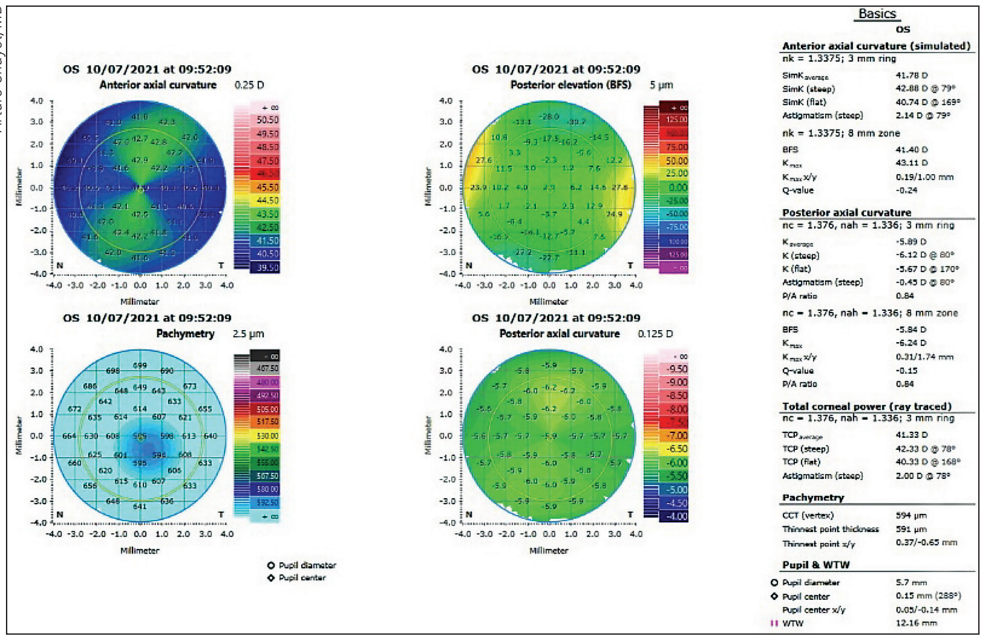


Figure 2. This 21-year-old female was a perfect candidate for LASIK, presenting with orthogonal, symmetric and regular astigmatism. With a refraction of -2.75-2.50 X 169, her central corneal thickness was 594 µm and her pupil size was 5.7 mm.

it's probably less risky to do PRK, in terms of avoiding something major going wrong. You can go either way and, of course, you want to be able to do both because there are some patients who may require one or the other, depending on your findings and their preferences."

Dr. Chayet is a high-volume cataract and refractive surgeon who performs PRK if he sees any risks that could arise from lamellar incisional surgery, including LASIK and SMILE. This amounts to about 20 percent of his cases.

"For example, PRK may be indicated in patients with non-orthogonal asymmetric astigmatism," he says. "This would be on a case-by-case basis, not always. I look for asymmetric thickness maps or abnormal epithelial maps. If you have the luxury of using some of the devices that provide biomechanical analysis, such as a Pentacam and keratoconus-screening software, you can detect these issues. Any time you have a thin cornea, you should be thinking about performing PRK on that patient. There are very few reports of ectasia following PRK."

When new patients call his practice, inquiring about any form of refractive surgery (typically LASIK), Dr. Chayet's staff reviews both PRK and LASIK with them. "There are no differences between these procedures as they're presented to our patients," he says. "They're priced the same and equally effective. If patients want to have LASIK as a first choice, we will offer them LASIK if they're good candidates. But if there's anything that gives us concern about doing LASIK, then we'll offer PRK as the first choice. The only consideration we have to keep in mind, which may encourage more patients to undergo LASIK if they're good candidates, is the longer healing time and brief period of discomfort after PRK."

Discomfort and Healing

Surgeons say they use varied approaches to minimize post-PRK discomfort, safeguard against infection and promote wound healing. Among the possibilities are bandage contact lenses, NSAIDs, topical antibiotics, topical steroids, ketorolac tromethamine ophthalmic solution, topical cyclosporine, preservative-free tears, oral steroids and oral analgesics (such as hydrocodone bitartrate/acetaminophen).

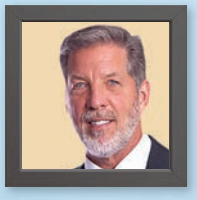
Dr. Chayet says he's never used NSAIDs on the wound surface. "I don't recommend using those agents," he says. "We also don't use anesthetics. Instead, we apply bandage contact lenses and topical steroids. We'll also provide a non-opioid oral analgesic, such as oral ketorolac tromethamine (Toradol), and we don't use alcohol on the surface. Patients have some discomfort for about two days. We tell them before the procedure what the postop period will be like, ensuring realistic expectations. Discomfort and longer healing time haven't really been issues in more than 90 percent of our patients. Most don't complain, and they're satisfied with the results of their surgeries."

Meanwhile, Dr. Chayet says he prevents corneal haze after performing PRK by treating his patients with the antimetabolite mitomycin-C for 20 seconds. "I only use it for ablations of more than 70 µm or in cases when I feel there's a higher chance of post-PRK haze," he says. He keeps the MMC away from the limbus to avoid toxicity and concentrates it on the central cornea. "I haven't encountered any problems with this approach," he adds.

Dr. Chayet acknowledges that PRK still has its drawbacks, even among the best candidates. "We can't give PRK patients opioids in Mexico, so we're limited in that way," he says. "Ketorolac still isn't perfect, and we're always looking for other solutions. There's interest in developing better topical analgesia, which hopefully we can use some day without interfering with re-epithelialization of the treated area of the cornea." ◀

DISCLOSURES

None of the surgeons interviewed for this article discussed products made by companies with which they have a financial relationship.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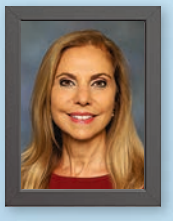
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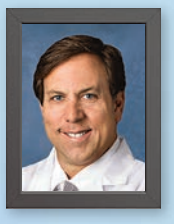
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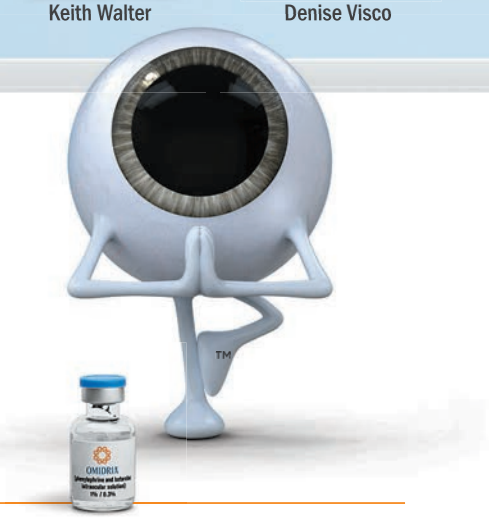

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References: 1. Omeros survey data on file. **2.** OMIDRIA [package insert]. Seattle, WA: Omeros Corporation; 2017. **3.** Al-Hashimi S, Donaldson K, Davidson R, et al; for ASCRS Refractive Cataract Surgery Subcommittee. Medical and surgical management of the small pupil during cataract surgery. *J Cataract Refract Surg*. 2018;44:1032-1041.

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The technologies and techniques surgeons use to predict the best lens power.

CHRISTOPHER KENT
SENIOR EDITOR

Refractive cataract surgery is an ever-evolving field. Biometric measurements are getting more accurate; our understanding of which anatomic factors affect lens position continues to improve; patient expectations continue to increase; and formulas for calculating lens power keep getting more sophisticated—and are starting to rely on artificial intelligence.

Here, experts share the latest information and advice.

Which Optical Biometer?

With many optical biometers available, does it matter which one you use? "Today we have a dozen different types of biometry units that can provide reliable information, including the recently introduced Heidelberg Anterion and the Alcon Argos," notes Terrence P. O'Brien, MD, the Charlotte Breyer Rogers Distinguished Chair in Ophthalmology and director of the Refractive Surgery Service at Bascom Palmer Eye Institute of the Palm Beaches. "That's good, because competition has forced manufacturers to keep improving their instruments.

"Here at Bascom Palmer we're fortunate to have multiple instruments available," he says. "In our experience, these modern biometers are all very accurate in terms of measuring axial length, with a very small standard deviation. However, there's still room for improvement when measuring corneal power—we do see some disagreement there."

Uday Devgan, MD, FACS, FRCS, chief of ophthalmology at Olive View UCLA Medical Center, a clinical professor at the UCLA School of Medicine, and in private practice at Devgan Eye Surgery in Los Angeles, says he doesn't believe that one optical biometer will produce significantly better outcomes than another. "Doing the best possible lens power calculation is more important," he says. "The difference in axial length measurements between machines is on the order of one or two hundredths of a millimeter—about 10 or 20 µm. Even if two biometers come up with slightly different axial length measurements, the difference will be negligible. The lens power's going to end up the same.

"Some instruments make additional measurements, such as Zeiss's True Cornea measurement," he continues. "That could make a difference for some patients, but I'm not convinced it will make a significant difference overall. Comparing the optical biometers is like comparing a Mercedes, a BMW and an Audi. You may prefer one over another, but they're pretty similar. Getting the lens power calculations right will make a much bigger difference than refining those measurements or adding new ones."

Making Sense of the Formulas

"It's somewhat daunting to figure out which formula will give you the most reliable data for IOL power and toric placement," notes Dr. O'Brien. "For practical reasons, I understand that many colleagues use one or two formulas exclusively; some will only check multiple formulas if the axial length is unusually

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Dr Devgan has an ownership interest in Advanced Euclidean Solutions, the company behind IOLcalc.com and the Ladas Super Formula, and in CataractCoach.com, a free teaching website. **Dr. Holladay** is a consultant for Carl Zeiss, M&S Technologies, Oculus, Sonomed, Acutome, Visia Imaging, Zeimer Ophthalmics, Heidelberg Engineering, Medisoft Imaging and Ellex. **Dr. O'Brien** reports no financial conflicts.

long or short. In any case, the available formulas are improving over time. The Barrett Universal was a game changer for many people; that's one that some surgeons have migrated to as their only formula. Warren Hill has the RBF, which is excellent, and he constantly refines it as he gets more data.

"I still enter my data into several formulas and compare the results," he continues. "In addition to the Barrett and Hill RFB, I learned a lot from Dr. Jack Holladay, and I still use his Holladay 1 and 2 formulas. For me, just seeing the variability between formula results allows me to start zeroing in on where I want to be. A lot of variability can alert me that there may be something abnormal, such as a shallow anterior chamber or a dense cataract. You can also use the results from multiple formulas to help educate the patient. The fact that the formulas are not totally in agreement helps to keep the patient's expectations realistic."

Dr. O'Brien says that if he gets widely variable answers from different formulas, he goes back and looks at the raw data to make sure there wasn't a problem. "For example, we take multiple measurements using topography and other devices such as the Pentacam," he says. "If a Pentacam taken on one day and an optical biometry scan taken on another day are quite different, that makes me wonder if the patient's eyes were drier on one day than the other.

"If you don't want to use more than one or two formulas," he adds, "I'd suggest plugging your data into the Barrett Universal 2 and the Hill RBF. If those two are in reasonable agreement, you can be pretty confident your refractive outcome will be close to what you anticipated."

To understand why some formulas are more successful with certain eyes, it helps to know a little about the evolution of these formulas. Jack Holladay, MD, MSEE, FACS, president of Holladay Consulting in Houston and the developer of the Holladay 1, 2 and Refractive Formulas, explains that a number of factors led to many early formulas having trouble avoiding refractive surprises in long or short eyes. "When optical biometry began to appear around 2000, Wolfgang Haigis, PhD, was very instrumental in the calibration of the IOLMaster," Dr. Holladay says. "He measured thousands of eyes to accomplish this, but none of them were longer than 26 mm, and only a few were shorter than about 20 mm. So he extrapolated his measurement curves in both directions.

"The problem with extrapolation," Dr. Holladay continues, "is that it's not based on data. All of the early formulas were developed using ultrasound-measured Ks. When the IOLMaster came out in 2000, clinicians began to switch to that, but nobody realized that Wolfgang had extrapolated those long- and short-eye values. Then about 10 years ago, Doug Koch, MD, and Li Wang, MD, showed that the measurement conversion between ultrasound and optical biometry isn't a straight line. For example, someone with a long eye might get a 36-mm measurement using the IOLMaster, while ultrasound would measure that eye as 34 mm—the correct measurement. The error gets progressively worse the longer the eye. Meanwhile, the other optical biometers were calibrated to the IOLMaster, so they all had the same problem.

MEASURING THE POSTERIOR CORNEAL SURFACE

"Most surgeons understand that measuring the power of the back surface is potentially useful information," says Jack Holladay, MD, MSEE, FACS, president of Holladay Consulting in Houston and the developer of the Holladay 1, 2 and Refractive Formulas. "On average, the back of the cornea reduces the total corneal power by about 12 percent. For example, for a 7.5-mm anterior radius cornea with a keratometric power of 45 D, the front surface power would be 50.13 D and the average back surface power would be 6.49 D, with a net power of 43.78 D. Every lens power formula uses an average index of refraction to compensate for this reduction in total power of the cornea. But if the back surface isn't average, that can result in an error when calculating the lens power that's needed."

How often will it make a significant difference in our lens power calculation? "Studies show that adding the posterior measurement doesn't make very much difference in 80 percent of the population, because their back corneal surface is pretty much average," he notes. "But 20 percent have unusual back surfaces; in those patients you may get a better result because you took the back surface into account. And of course, you can't know which one in five patients will benefit from the additional measurement, so ideally you should always measure it."

Dr. Holladay adds an important consideration. "If you do measure the actual power of the posterior corneal surface, you don't want to start including that adjustment before plugging your numbers into the formula," he says. "The formulas already make an adjustment for that. To avoid this problem, the latest technologies that measure the back surface are simply adjusting the reported power to account for how far above or below normal the back surface is. For example, Zeiss has now incorporated OCT into the IOLMaster 700 so that it can measure the posterior cornea. What they call "Total K" is the keratometric K adjusted by how far the back surface measurement is from average (plus or minus).

"The other manufacturers are working on adding this capability to their instruments, too," he notes. "Meanwhile, you can now measure the astigmatism on the posterior corneal surface as well as the spherical component, which can lead to a more accurate measurement of net astigmatism. Measuring the back of the cornea will help improve outcomes, but it's still early in the game."

—CK

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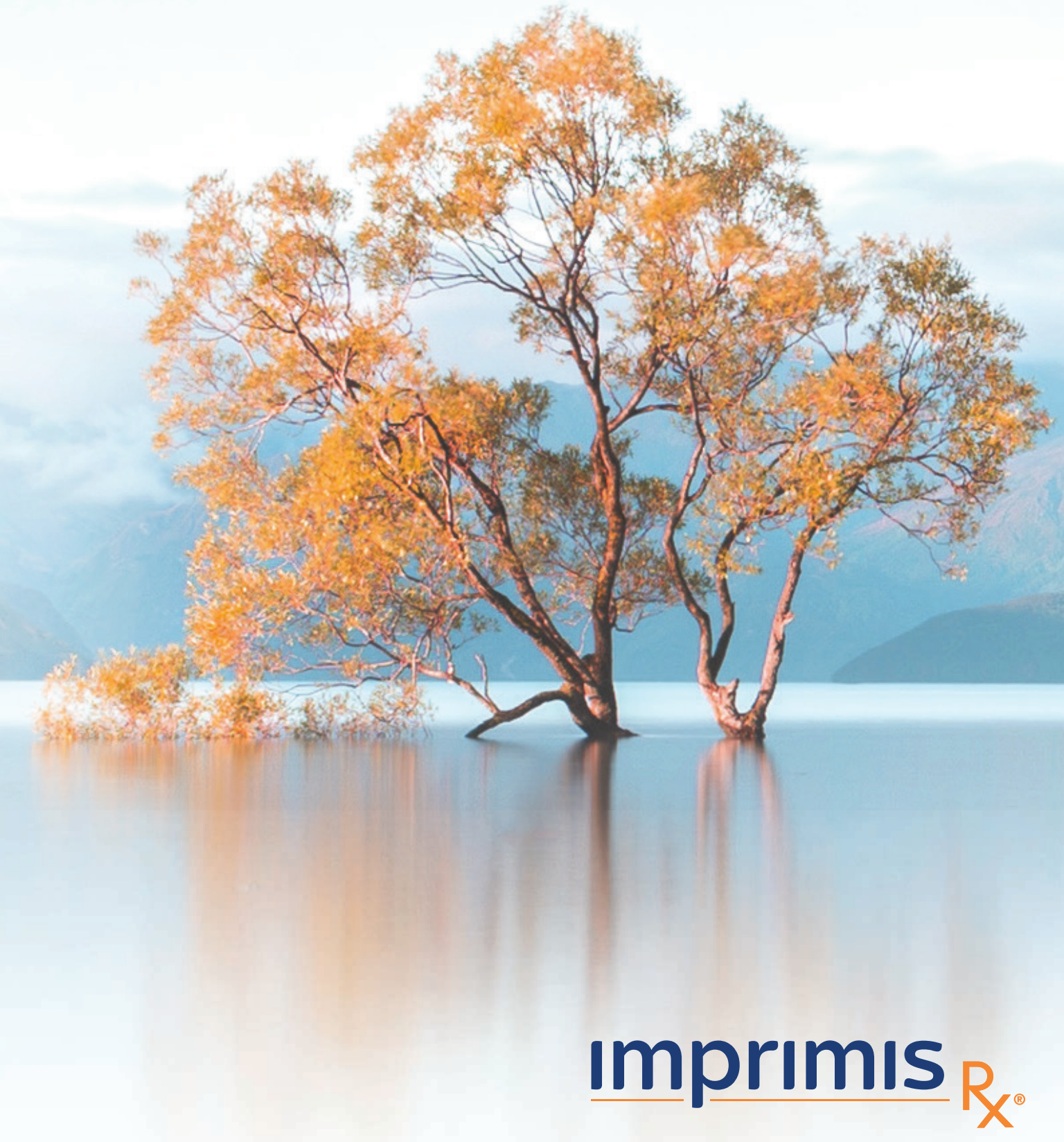

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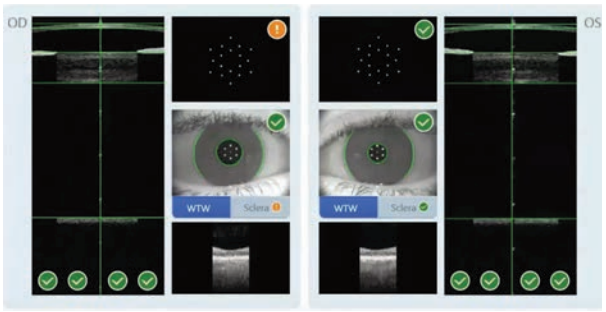
"Drs. Koch and Wang then published a regression that can be used to correct for this error," he adds. "Today, the more recent formulas, such as the Barrett, Olsen and Holladay 2, compensate for this, so clinicians don't need to use a conversion factor to compensate for it themselves."[1]



Zeiss says the IOLMaster 700 can measure both eyes in 45 seconds. Here, the system flags suspicious keratometry.

Office Setup for Success

Surgeons offers these suggestions to help ensure better outcomes:

• ***Take the time to learn your biometry machine.*** Dr. O'Brien points out that many clinicians don't really know much about the details of using the optical biometers. "Most of us haven't even learned the basics of what they can do—and more importantly, what it looks like when they don't do things properly," he says. "That's why we have our fellows work with experienced technicians and do biometry on a few patients from scratch. We want them to appreciate all of the steps along the way, and the variables that can lead to less-precise data. Most of our fellows tell us later that it was a really valuable experience."

• ***Train several technicians to be experts.*** "Many practices will designate one person to do this, and cross-train someone else as a backup person," notes Dr. O'Brien. "The thing is, you need to have a technician who is so familiar with the test that he or she can perform it in their sleep. Then, when something in the data is off, they sense right away that it may be unreliable.

"I suggest training several people to become real experts in using whichever biometer your practice has," he concludes. "That's the only way to ensure that all readings are of acceptable quality."

• ***Use the latest technology.*** "Our IOLMaster 700 provides an OCT of the macula along with the data," Dr. O'Brien points out. "That allows us to confirm that the patient was properly fixating, and we can see the fovea and make sure the contour is correct. We also may detect pathology such as an epiretinal membrane, vitreomacular traction or cystoid macular edema."

• ***Be alert for potentially problematic patients.*** "Extreme refractive errors are a red flag," Dr. O'Brien notes. "Someone who's a -18-D myope is likely to have very abnormally long axial length and possibly a staphyloma. In those cases, you're going to want to get not only A-scan but B-scan ultrasound readings to make sure you're measuring properly, and not measuring in the canyon of a staphyloma in the posterior segment. In eyes that are challenging—the high myopes, extreme hyperopes, and patients who've had prior LASIK or RK—more information is better."

Getting Accurate Measurements

These tips can help:

• ***Always measure both eyes.*** "This is important because the second eye serves as a check for the first eye," notes Dr. Devgan. "The eyes should produce similar physical measurements; if they don't, you need to stop and look carefully at how the data was collected and the condition of the eyes."

• ***If you need to use ultrasound, measure both eyes and compare the result to your optical biometry measurement in the better eye.*** "Some patients have such a dense cataract in one eye that you can't get an optical biometry measurement because light can't get through," notes Dr. Devgan. "In that situation, you have to do an A-scan ultrasound. Here again, you want to take this measurement in both eyes. If the measurements are close, that's a good sign that the measurements are accurate. But even more important, if the other eye can be measured with optical biometry, you can compare the A-scan measurement to the optical measurement. If they agree, that tells you that you're A-scan technique was good."

• ***Make sure the ocular surface is pristine.*** "Getting an accurate corneal power is especially important because it changes the lens power in almost a one-to-one ratio," Dr. Devgan points out. "If your corneal measurement is off by 1 D, your lens power will be off by 1 D—and the measured corneal power can be drastically different if the ocular surface isn't in good shape.

"A problem could be as simple as untreated dry eye," he continues. "It could be epithelial basement membrane dystrophy; it could be a pterygium on the cornea; it could be someone who wears contact lenses full time and just removed them five minutes before your exam, leaving the cornea warped. All of these can play a role in the accuracy of the K-reading, and that can change your lens calculation dramatically."

"You probably don't need to treat every patient's ocular surface," notes Dr. O'Brien. "However, you should check for surface problems in every patient—especially those who may be at higher risk because of age, gender, prior eyelid surgery or systemic medications known to adversely affect tear production or the ocular surface, as well as those patients who've had prior refractive surgery, which can affect innervation and corneal sensation. And you should have a low threshold for treatment; if you find something that's less than ideal, take the time to address it before

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taking the biometry measurements. Treating the ocular surface for a few weeks is preferable to having a postoperative surprise."

• ***Take your measurements on an eye that hasn't yet been touched.*** "In some practices, a patient's IOP is checked before the measurements are taken for the IOL power calculations," notes Dr. Devgan. "That's a mistake. Getting the IOP involves touching the eye and disturbing the epithelium, and that can alter the corneal measurement you get afterwards, throwing off your lens power calculation. In our clinic, everyone seeing me for a cataract consult has biometry measurements done before entering the exam room to have their vision and pressure checked."

Verifying Data Quality

"When people refer patients to me because of a poor outcome, the biggest mistake often turns out to be the quality of the individual measurements on which the lens choice was based," says Dr. O'Brien. "I think it's extremely important for surgeons to verify that the quality of the data is good—especially the corneal power reading. There are a number of ways to do this:

• ***Look at the reflection of the LED mires on the cornea.*** "If they're not sharp, you're going to have garbage in, garbage out," Dr. O'Brien says.

• ***Check the standard deviation.*** "These devices also give us a standard deviation for each measurement," notes Dr. O'Brien. "That helps us know if it falls within acceptable limits. For corneal power, we say a standard deviation greater than 0.3 D is a red flag; when determining the meridian for astigmatic correction, a standard deviation greater than 3.5 degrees is a red flag. In my experience the IOLMaster 700 and the Lenstar measure the axial length very precisely, and in most patients the corneal power is within those parameters as well. However, you have to check to be sure."

• ***Get a second measurement.*** "This is another way to verify the accuracy of the measurement if there's any doubt about it," says Dr. O'Brien. "If possible, I'll use a second instrument. However, even two measurements from the same device can be valuable, especially if you take them on two different occasions. Changing factors—such as the condition of the patient's ocular surface—can affect the reading. Once you have a second reading, check to verify the consistency of the data. This is especially helpful if you're implanting a toric lens."

Choosing the Right Lens Power

Surgeons offer these tips to minimize postop refractive surprises:

• ***If choosing between two lens powers, err on the side of myopia.*** "If you're faced with two slightly different power calculation outcomes—or you have one answer that falls between two lens powers—choose the higher lens power," says Dr. Devgan. "That way, if you're off, you'll err on the side of slight myopia. A small amount of myopia postop isn't a bad thing; it increases your range of vision in the intermediate zone.

"The other reason for doing this is the ease of resolving a problem if you end up with one," he continues. "Let's say you do end up with a myopic outcome; you aimed for plano and ended up at -1 D. If the patient doesn't like being -1 D, that's a slam dunk to fix, an easy LASIK or PRK treatment. But if you aim for plano and end up +1, hyperopic PRK or LASIK isn't nearly as stable or accurate as myopic PRK or LASIK. Myopic PRK or LASIK takes away central corneal tissue, but hyperopic LASIK or PRK steepens the central cornea by lasering away a doughnut shaped section of tissue. That's much less accurate."

• ***When dealing with eyes that have had previous refractive surgery, consider using the ASCRS website calculator.*** "Today it's quite common to do cataract surgery on eyes with prior LASIK, PRK or even

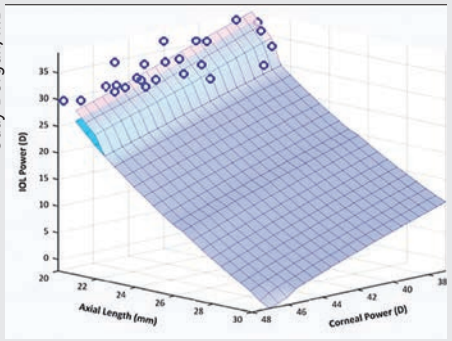
(Continued on p. 59)

ARTIFICIAL INTELLIGENCE JOINS THE FRAY

A notable trend in lens power formula development is the addition of artificial intelligence to the equation. Uday Devgan, MD, FACS, FRCS, chief of ophthalmology at Olive View UCLA Medical Center and a clinical professor at the UCLA School of Medicine in Los Angeles, is part of the group headed by John Ladas, MD, PhD, that's been developing an artificial intelligence approach to lens power calculations known as the Ladas Super Formula 2.0. (Dr. Devgan also has an ownership interest in the company developing it.) "Today, many surgeons use Barrett and Hill RBF," Dr. Devgan notes. "But for me, the most accurate formula is the Ladas Super Formula 2.0, which we've worked on for more than 20 years. The power is calculated using artificial intelligence, based on data from the more than 4,000 ophthalmologists who use IOLcalc.com. Most surgeons using this AI-based system are reporting 94- to 95-percent accuracy.

"This system should be available in clinical machines in the next few years," he adds. "But right now, if you're willing to enter your data manually, you can use this software to calculate your lens power at IOLcalc.com." [A video explaining the Ladas Super Formula 2.0 can be viewed at cataractcoach.com/2021/06/26/1146-the-future-of-iol-calculations/.]

—CK



Artificial intelligence learns that eyes with short axial lengths need to have the IOL power adjusted for the best refractive outcome.

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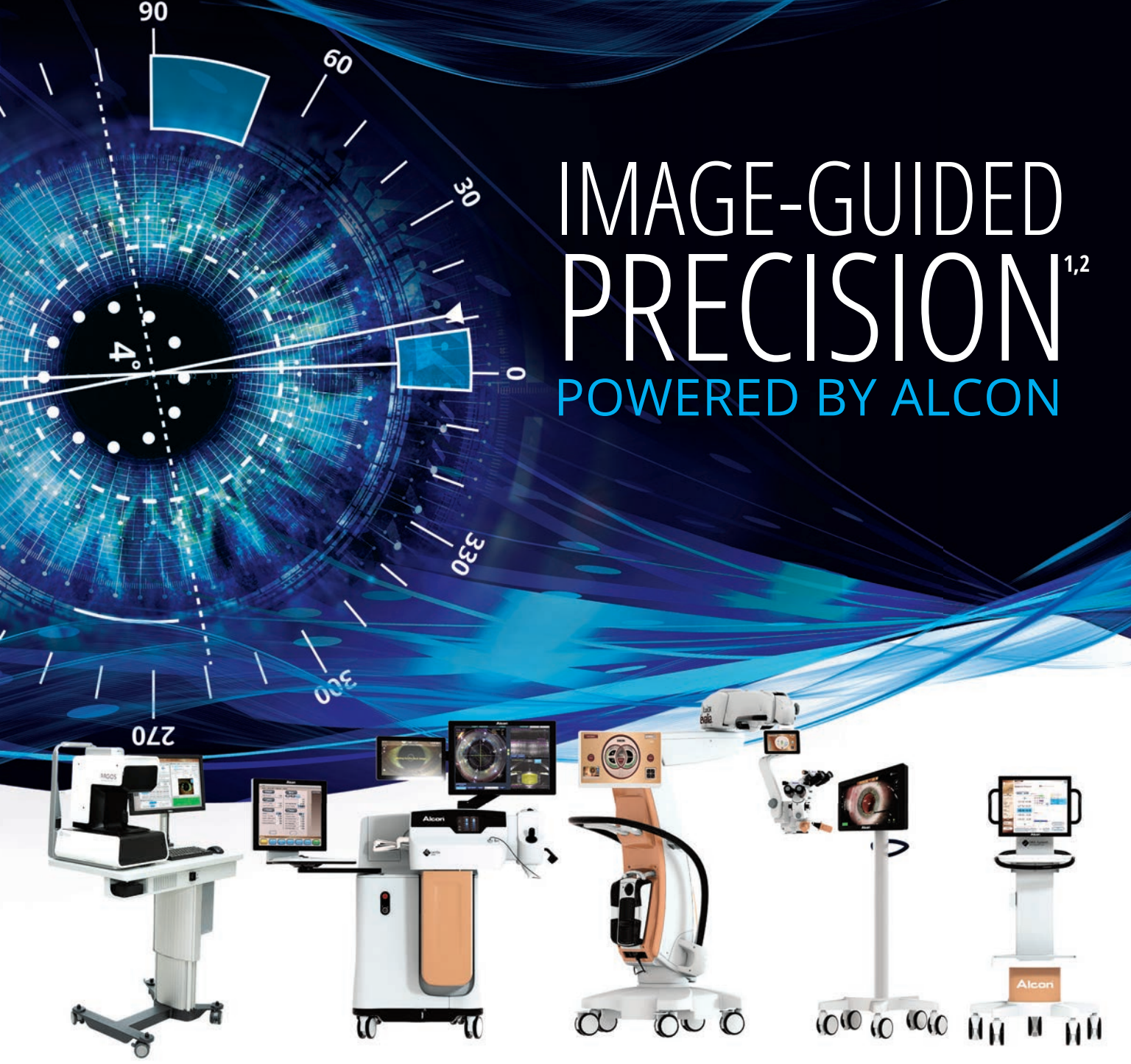

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SCRATCHING THE SURFACE OF ABNORMAL CORNEAS

Treating irregular astigmatism is an art. Experts offer guidance for performing the most cutting-edge laser procedure.

CHRISTINE LEONARD
ASSOCIATE EDITOR

Today's patient population of irregular astigmats differs from 10 or 15 years ago, when the bulk of cases were caused by previous refractive surgery. "In the early days, the laser technology wasn't as good and there were misconceptions about eye registration," says Aleksandar Stojanovic, MD, PhD, medical director of SynsLaser Clinic in Tromsø and Oslo, Norway. "For example, hyperopes usually have a big discrepancy between the center of the pupil and optical center of the cornea. As a rule, patients use their optical center for vision, so centering the laser on the center of the pupil caused irregular optics for those eyes. This generated a large number of irregular astigmatism cases. Now, we tend to see more ectatic causes."

Here, experts break down irregular astigmatism management, from making the diagnosis to performing off-label topography-guided PRK.

Preference for Topo-guided

Dr. Stojanovic, the ophthalmologist responsible for introducing LASIK and cTEN to Norway, says he uses both placido-disc-guided and Scheimpflug-guided topography for treating irregular astigmatism. "My American colleagues use TG-PRK as well, always off-label, because there's no other way to correct the corneal optics," he says. "The aim of TG-PRK is primarily to correct the astigmatism to the degree that the patient isn't bothered by visual disturbances, and to increase as much as possible their corrected visual acuity. Wavefront-guided isn't good enough because we don't get enough data to base our treatment on."

Most surgeons prefer topography-guided to wavefront-guided treatments in irregular corneas for this very reason. "Most wavefront-guided machines measure about 1,200 to 1,300 data points, whereas topography-guided machines can measure more than 20,000 data points," explains Raymond Stein, MD, FRCSC, medical director of the Bochner Eye Institute in Toronto, Ontario, and professor of ophthalmology and vision sciences at the University of Toronto. "This means less interpolation between the collected data points, giving us greater treatment potential. We can address variations in corneal elevation more precisely by flattening steep areas and steepening flat areas by certain amounts. This spares tissue, which is important since we're often dealing with corneas of abnormal thickness."

He adds that unlike in standard PRK, iris or limbal registration is used in topography-guided treatments. "This can be very helpful in terms of compensating for cyclotorsion, ensuring the treatment is exactly as the surgeon intends," he says.

Is It Ectasia?

Distinguishing between ectatic conditions (e.g., keratoconus, pellucid marginal degeneration or ectasia after LVC) and non-ectatic conditions is key, says Dr. Stein. He explains that non-ectatic conditions such as EBMD, amiodarone keratopathy and Salzmann's nodular degeneration are contraindications for TG-PRK, because performing TG-PRK on a non-ectatic eye can

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Drs. Stojanovic, **Stein** and **Kershner** have no related financial disclosures.

All images: Raymond Stein, MD, FRCSC, DABO

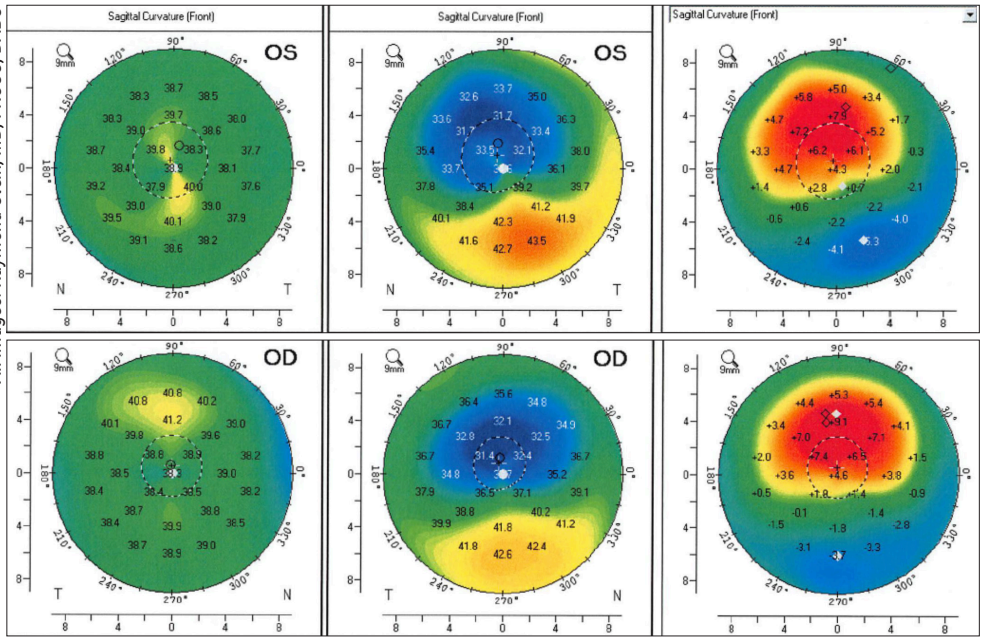

Figure 1. Postop (left), preop (center) and difference maps (right) of an atypical case involving a 32-year-old male who underwent TG-PRK for significant irregular astigmatism prior to left-eye cataract surgery. The patient had previously undergone LASIK OU at age 20 and wore scleral lenses for irregular astigmatism. His BCVA was 20/40 OD and 20/80 OS. Corneal thickness was 443 µm OD and 428 µm OS. The TG-PRK induced significant myopia by steepening the central cornea, as seen in the difference maps. Six months after the ablation when the topography was stable, the patient underwent cataract surgery and received an aspheric toric implant aimed at -2.5 D. At one week postop, the patient's visual acuity was J2 (-2.25 -0.25x90 20/20).

induce more corneal irregularity. "Patients with pseudokeratoconic presentations secondary to a non-ectatic condition typically have a normal stroma, with only an irregular epithelium," he says. "If you go in with TG-PRK, once you remove the epithelium, you'll induce irregularity into the cornea.

"Instead, we treat EMBD and Salzman's with a superficial keratectomy, which is essentially epithelial debridement," he says. "We remove the irregular epithelium; this can regularize the cornea and improve vision. Other secondary causes such as a superficial punctate keratopathy secondary to dry eye or a blepharokeratitis are treated aggressively, usually with lid management and preservative-free artificial tears."

He stresses careful interpretation of topographic maps to make the correct diagnosis. "Identifying the etiology requires corneal topography or tomography and a complete ophthalmic examination," he says. "Anterior curvature changes without significant posterior elevation on tomography are suggestive of non-ectatic corneas. Slit lamp exams may also reveal the underlying cause of corneal steepening."

Astigmatic Origins

Dr. Stojanovic says a high-quality preoperative exam is the most important part of the procedure, followed by evaluating the results and knowing how to use them. "The actual ablation is very straightforward," he says.

Astigmatism is complex. "You need to know where the astigmatism comes from," he explains. "Your approach will depend on the origin. Additionally, we need to know the higher order aberrations influencing the patient's manifest refraction. We can't treat only the astigmatism measured on the exam and then treat the HOAs. We must use the astigmatism measured amidst the HOAs in a mixture of totals, so we can isolate the astigmatism component from the HOAs. Using wavefront aberrometry to get the optics for the whole eye, we can then subtract lenticular optics and look only at corneal optics."

Robert M. Kershner, MD, MS, FACS, a professor and chairman of the Department of Ophthalmic Medical Technology at Palm Beach State College and president and CEO of Eye Laser Consulting Global in Palm Beach Gardens, Florida, points out that just because aberrations are present doesn't necessarily mean they need correcting, if the patient's functional vision is good. "It's never as simple as creating a perfect optical system so the patient sees clearly," says Dr. Kershner. "I've examined Air Force pilots with perfect vision and found their optical systems chock full of aberrations. Sometimes correcting the irregularities we see isn't beneficial to the patient's optical outcome. We also need to be careful about where those aberrations are.

"When you do a Shack-Hartmann wavefront analysis and look at the various levels of HOAs, you can prove that these optical aberrations are present. What you don't know is where in the optical system they reside," he explains. "The shape of the fundus, the anterior and posterior lens, the inner and outer cornea and the scleral shell may all be contributing to the aberrations. In phakic patients, it's very difficult to parse out what's lenticular and what's fundus.

"Typically when we measure astigmatism on the cornea and

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

TRUST THE #1 PRESCRIBED ANTI-VEGF FDA APPROVED FOR WET AMD, DME, AND MEfRVO*

*IBM Truven MarketScan data: number of injections administered from Q4 2018 through Q3 2019; Data on file.

Proven first-line efficacy

- **Powerful efficacy** and **robust anatomic outcomes** across all indications as shown in phase 3 clinical trials[1-8]
- A broad range of indications and **dosing flexibility** across several FDA-approved indications[1]

Demonstrated safety profile

- **Demonstrated safety** profile across 4 VEGF-driven retinal diseases: Wet AMD, DR, DME, and MEfRVO[1]

A legacy of clinical experience

- **9 years** of extensive real-world experience[1]
- **≈13 million** doses administered to **>1 million** eyes since launch (and counting)[9]

EYLEA® (aflibercept) Injection 4 U℠

A COMPREHENSIVE PATIENT SUPPORT PROGRAM TO HELP FACILITATE ACCESS TO EYLEA

- 82% of payers offer access to EYLEA first line, covering **>272 million** patients[9,†]
- As of June 30, 2020, EYLEA4U® has provided **>4.4 million** total support services to eligible patients prescribed EYLEA[9]

†Data represent payers across the following channels: Medicare Part B, Commercial, Medicare Advantage, and VA. Individual patient coverage is subject to patient's specific plan.

DISCOVER WHAT ELSE YOUR PATIENTS COULD SEE WITH EYLEA AT HCP.EYLEA.US

anti-VEGF, anti–vascular endothelial growth factor.

ADVERSE REACTIONS

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

INDICATIONS

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

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2019. **2.** Heier JS, Brown DM, Chong V, et al; for the VIEW 1 and VIEW 2 Study Groups. Intravitreal aflibercept (VEGF Trap-Eye) in wet age-related macular degeneration. *Ophthalmology*. 2012;119(12):2537-2548. doi:10.1016/j.ophtha.2012.09.006 **3.** Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. *Ophthalmology*. 2014;121(1):193-201. doi:10.1016/j.ophtha.2013.08.011 **4.** 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 **5.** Campochiaro PA, Clark WL, Boyer DS, et al. Intravitreal aflibercept for macular edema following branch retinal vein occlusion: the 24-week results of the VIBRANT study. *Ophthalmology*. 2015;122(3):538-544. doi:10.1016/j.ophtha.2014.08.031 **6.** Boyer D, Heier J, Brown DM, et al. Vascular endothelial growth factor Trap-Eye for macular edema secondary to central retinal vein occlusion: six-month results of the phase 3 COPERNICUS study. *Ophthalmology*. 2012;119(5):1024-1032. doi:10.1016/j.ophtha.2012.01.042 **7.** Holz FG, Roider J, Ogura Y, et al. VEGF Trap-Eye for macular oedema secondary to central retinal vein occlusion: 6-month results of the phase III GALILEO study. *Br J Ophthalmol*. 2013;97(3):278-284. doi:10.1136/bjophthalmol-2012-301504 **8.** Wykoff CC. Intravitreal aflibercept for moderately severe to severe non-proliferative diabetic retinopathy (NPDR): 2-year outcomes of the phase 3 PANORAMA study. Data presented at: Angiogenesis, Exudation, and Degeneration Annual Meeting; February 8, 2020; Miami, FL. **9.** Data on file. Regeneron Pharmaceuticals, Inc.

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

03/2021
EYL.21.02.0021

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

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

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

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

4 CONTRAINDICATIONS

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

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

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

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. 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 central retinal vein occlusion (CRVO) in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following branch retinal vein occlusion (BRVO) in one clinical study (VIBRANT).

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

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

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

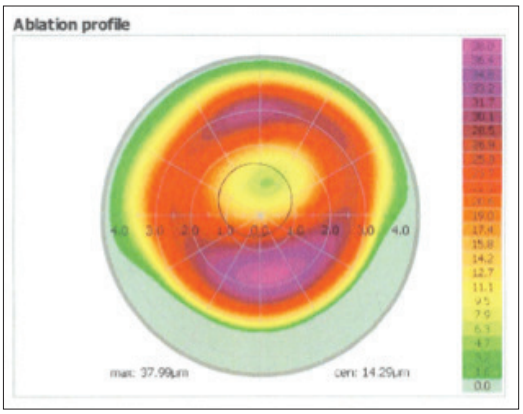
REGENERON

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

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

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

EYL.20.09.0052



The ablation profile OD of the patient in Figure 1.

astigmatism on the cornea and compare it to refractive astigmatism, we find that the cornea can reflect a higher degree of astigmatism in the central 3-mm than the patient actually has optically," he adds. "However, there's no absolute correlation between the two."

Planning Ablations

Topography-guided technology has given surgeons access to many more corneal details than before. Using Alcon's Allegretto excimer laser system, Dr. Stein says he has two options for ablation planning. "One is with a standard software with the Oculyzer II (WaveLight GmbH, Germany). With this approach, we take eight color images of the cornea and review them. If they're all good-quality, we take the average and input this data into the laser. The difficulty with this standard treatment is that we never know how much myopia, hyperopia or astigmatism we may induce when we do TG-PRK.

"The other way we plan ablations is with a newer software developed for Contoura (Alcon) by ophthalmologist Mark Lobanoff, MD, in Minneapolis," he continues. "The Phorcides Analytic Engine accounts for the change in refractive error just by doing the TG-PRK. We can use this in relatively normal corneas as well, for standard and topography-guided LASIK and PRK. The data for this software has shown outstanding outcomes in reducing mild degrees of irregular astigmatism."

After imaging the cornea, Dr. Stein uses either software to develop a treatment protocol with a certain optical zone. "Generally we like to use a 6- or 6.5-mm optical zone," he says. "Occasionally, we'll have to shrink the optical zone to 5.5 or 5 mm, but if we do that, there's a greater chance of regression. In general, we can use a large optical zone in patients with a dioptric difference of 10 D or less who also have corneas thicker than 460 µm at the thinnest point. We've found larger optical zones to be more effective at reducing irregular astigmatism."

For modern LVC, the optical zone diameter typically falls in the 6- to 6.5-mm range. "The optical zone should be large enough to go beyond the borders of the pupil in low-light situations," Dr. Kershner says. "When we first began doing refractive surgery, before LASIK, most optical corrections fell into the 5- to 5.5-mm zone, because we assumed the pupil wasn't going to get much larger than that, except pharmacologically. For most cases that worked.

"Newer lasers now have computer algorithms that can do a blend, which tends to ablate a little more in the center and less in the periphery to maintain the asphericity that's typical of a human cornea," he explains. "If you do that, it lessens but doesn't entirely eliminate the optical aberrations. You're still doing a refractive correction, i.e., removing tissue within the visual axis, and the element of concern here is the pupil size."

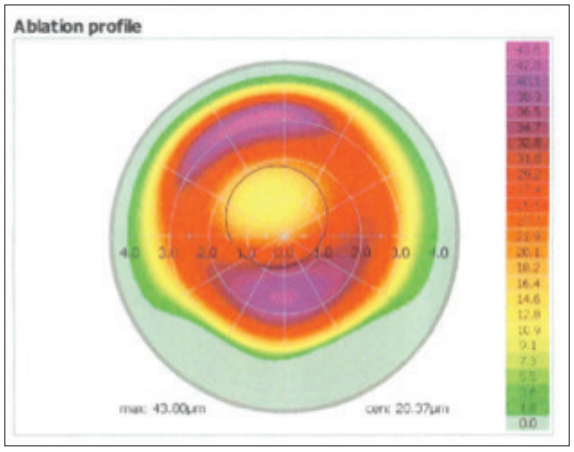
Low-light situations can dilate a blue-eyed person's pupil up to 6 or 7 mm—which exceeds the typical optical correction zone—leaving them with unsatisfactory night vision and symptoms such as fuzziness, halo or double images. "A darker pigmented individual might not be as conscious of these problems at night because their pupils don't dilate as much," Dr. Kershner says. "That's one of the drawbacks of surface ablation or excimer laser ablation with LASIK: It's not a perfect process when you have to remove tissue from the center of the cornea and flatten it. It's important to inquire about the importance of nighttime vision. Many patients won't think to share this information unless you ask them directly."

Surgery Day

Dr. Stein's patients undergo imaging and refraction on the day of surgery, but he remarks that it's important for contact lens wearers to be out of their contacts for an extended period prior to imaging, so the cornea can revert to its natural shape. He advises a washout period of at least a month for hard lenses, but sometimes longer depending on the number of years of wear. For soft contact lenses, he says one week is typical.

After identifying the optical zone he uses for the ablation, often a 6.5-mm zone with a transition zone to 8.3 mm, he removes the corneal epithelium with a 50-µm phototherapeutic keratectomy. "We typically limit the stromal ablation to 50 µm to allow enough residual thickness for a cross-linking procedure," he says. "The combination of TG-PRK and CXL has a good chance at reducing irregular astigmatism. However, for patients with irregular astigmatism secondary to radial keratotomy, we tend not to perform CXL with TG-PRK. The success of CXL at decreasing diurnal vision fluctuations has been highly variable in these eyes."

After the laser ablation, Dr. Stein applies ice to the cornea. "We've found this significantly reduces patients' postoperative pain," he says. He uses a frozen sponge soaked in BSS as a "popsicle" and applies this to the cornea for 10 seconds.



The ablation profile OS of the patient in Figure 1.

Dr. Stein then dries the cornea and applies a disc containing mitomycin-C for all of his PRK patients, whether they received standard PRK or TG-PRK. "We apply this for about one minute and then remove the disc," he says. "We've found the MMC decreases the incidence of postoperative corneal haze. Then we irrigate the cornea with balanced saline to remove the MMC. If CXL is indicated, we perform it. Then we instill prednisolone acetate 1% and an antibiotic drop such as moxifloxacin 0.5%. We follow this with a bandage soft contact lens."

After treatment, he has the patient wait in a recovery room for 10 to 15 minutes before undergoing a slit lamp examination to ensure the contact lens fits properly. "We like to see very little movement of the contact lens," Dr. Stein says. "If it's too loose, the patient will be uncomfortable."

He sends the patient home with a nonsteroidal drop for the first 48 hours, an antibiotic drop to be administered four times daily until the contact lens comes out and a four-times-daily steroid drop, with the dose tapered over one month. He sees the patient back the following day, five days later to remove the bandage contact lens, and then typically at one, three and six months. "At six months we'll often repeat the tomography, although the epithelium may not be totally mature and changes can occur even at one year," he notes.

Follow-up

How you define a successful procedure sometimes depends in large part on the patient's happiness. "The vital sign of the eye is: Can you see or can you not?" Dr. Kershner says. "Simply doing a Snellen acuity test doesn't tell you much. It's not a real-life situation, such as sitting in a dark room looking at a jet-black letter on a white surface. Real life is potential glare from car headlights or reading small text on a computer screen."

He advises using all modalities of functional vision testing—in particular, contrast sensitivity and visual acuity under varying light conditions—to ensure that the patient sees well in a variety of real-life situations.

"There's no fooling the patient," he says. "You could achieve a perfect result and correct all of their refractive error and completely neutralize their topographic and wavefront maps, but if the patient can't read the chart or can't read a menu under dim lighting, it's not a win. If they can read the chart and see clearly and function normally, then it was a success, even if you left them with some uncorrected astigmatism. The goal isn't 20/20, it's 20/happy."

Annual follow-up exams that include tomography are key for ensuring the cornea has been regularized and stays that way after TG-PRK. Dr. Stein says that patients should undergo imaging, no matter what their level of UCVA. "You can't see early ectasia at the slit lamp," he points out. "It's rare that a patient will require a retreatment due to progressive ectasia, but it's a real concern. If the clinician picks it up at an early stage, you can save the patient's sight by doing corneal cross-linking."

Tomographic imaging is especially important for cases of irregular astigmatism secondary to keratoconus, pellucid marginal degeneration or ectasia after LVC. "We make sure that the cornea isn't steepening in any area, especially in the area that was steep before," says Dr. Stein. "This is a sign of progressive disease. We typically do tomography and difference maps six months to a year after LVC. This tells us how we accomplished the improvement in corneal regularity; it shows the areas we've steepened or flattened. The epithelium may not be totally mature at six months, and changes can occur even at one year."

TG-PRK Limitations

Patients will get the most benefit from TG-PRK if the dioptric difference across their corneas is 10 D or less, says Dr. Stein. "If there's marked irregularity of the cornea, it can be difficult to regularize because of the way the software works," he explains. "If a patient has, for example, 10-D of difference across the cornea, the software would flatten the steep area by 5 D and steepen the flat area by 5 D, and that's about the most the laser can do. Generally, less than a 10-D difference is an important threshold, as well as having enough cornea to work with—you want to have a thickness of at least 450 to 460 µm."

If the dioptric difference is too great or the cornea is too thin for TG-PRK, one approach you can try is PTK, he says. "When the cornea is irregular, it'll typically have an irregular epithelium," says Dr. Stein. "Where the cornea is steepest, the epithelium will be thinner, and where the cornea is flatter, the epithelium will be thicker. By doing PTK of a constant amount, we end up removing a little more tissue over the steep part of the cornea, and that can reduce irregular astigmatism."

Dr. Stein cautions that TG-PRK may worsen any corneal scarring already present. "Fortunately, most of the corneas we operate on are clear, so that isn't an issue."

One additional challenge with TG-PRK is the indirect nature of the

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correction. "We can't directly steepen or flatten anything," says Dr. Kershner. "If you want to steepen one area, you have to indirectly flatten an area 90 degrees away."

"Topography-guided PRK isn't perfect," he continues. "Corneal behavior isn't an exact one-to-one ratio when it comes to steepening and flattening. If you flatten one area by a given amount, in theory you've steepened the cornea 90 degrees away by the same amount, but it doesn't always work out perfectly. You have to be very careful about balancing it, like a teeter-totter. It's impossible to flatten one part without the other end coming up."

He says this is where surgeons often run into trouble. "In the quest to eliminate astigmatism, ablating too much tissue to get the patient right where you want them can lead to an ectatic cornea. Now you've got a real problem on your hands. You don't want to put a patient through a corneal transplant.

"It helps to know where the patient started in their refractive surgery journey," he adds. "Now, we're seeing the population who had excimer laser refractive surgery years ago who are now in the cataract age group, and they're showing up for cataract surgery but we don't know where their cornea started.

"If you've been taking care of a patient for years and have their early records, you can see what corneal topography, keratometry and wavefront data they've had," he says. "This puts you in a better position to analyze your approach and know what you shouldn't attempt. Many of the patients we're seeing now had radial keratotomy, and we should be concerned about reopening old incisions and the like."

Strategies for Success

Here are some tips for improving your irregular astigmatism patient's visual acuity:

• ***Get to know the patient.*** "The key to success is getting to know your patient," says Dr. Kershner. "I know that's hard with a busy office and having to see many more patients than you used to, to make the same amount of money. It's hard to take that time, but you need to—especially with a refractive surgery patient. If you don't know their needs, you'll get burned."

He says discussing expectations, explaining the worst outcomes, and asking what the patient will be happy with are important to include in your counseling. "Always underpromise and over-deliver."

• ***Stay alert for false ectasia patterns.*** These may result from measurement errors or previous decentered ablations. "If the patient fixates below the central axis of the videoscope, you'll see a pattern of inferior steepening," Dt. Stein says. "Be sure to check the pupil position relative to the center of the topographic map and repeat the imaging."

He adds that a decentered hyperopic ablation is more likely to produce a pattern resembling ectasia. "A focal area of steepening on anterior curvature topography or anterior elevation tomography may be mistaken for ectasia," he says. "Unlike keratoconus, however, you won't see significant posterior elevation on tomography."

• ***Never increase the power of the correction or shift its axis.*** "Patients can't tolerate this," says Dr. Kershner. "This is due to neuroadaptation. It's a process ingrained in the brain to varying degrees. Younger people can neuroadapt more quickly to an alteration in optical input to the visual cortex, but the older you get, the more difficult it becomes."

"If you change the patient's axis, the magnifying effect of plus-cylinder astigmatism creates some degree of meridional optical perception differences," he continues. "They can end up with a meridional anisometropia or meridional amblyopia. This is especially common

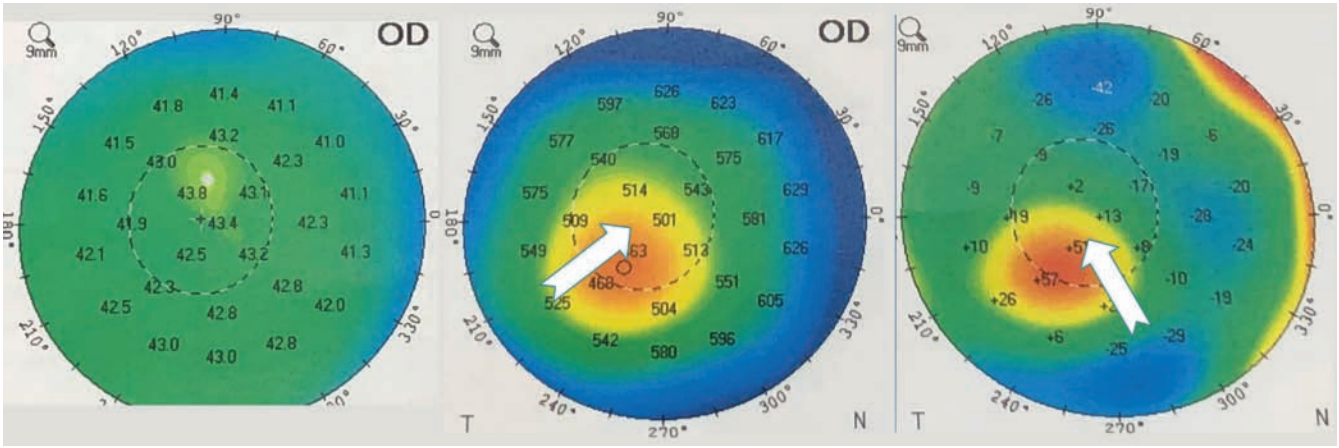

Figure 2. It's important for patients to undergo annual tomography post-LVC to screen for ectasia, no matter what the UCVA is, experts say. Changes are likely to occur first in posterior elevation. This patient underwent LASIK in 2007 (left), but 2019 imaging (center and right) revealed ectasia development despite UCVA 20/20. The patient's pachymetry map (center) and posterior elevation (right) are shown.

in the genetic population of Native Americans. If you alter a patient's optical apparatus to change their visual perception, the brain can't neuroadapt to live with it."

• ***Consider each case individually.*** "TG-PRK can also be used when irregular astigmatism is caused by lamellar keratoplasty, penetrating keratoplasty, arcuate relaxing incisions and corneal scores," says Dr. Stein. "Every case should be considered on an individual basis in order to determine the risks and benefits of treatment."

• ***Treat only the surfaces you can measure.*** "How you deal with the epithelium is important," says Dr. Stojanovic. "Don't remove it mechanically, because that will change the corneal optics completely. If we remove the epithelium, then the surface we're treating isn't the one we're measuring, it's the stroma. Transepithelial topography-guided PRK is the only way we can safely ablate irregular corneas at this point."

Dr. Stojanovic says stromal surface topography-guided ablation is possible using epithelial thickness maps, but it's not widespread yet. A case study from 2015 successfully used the treatment to significantly reduce a patient's surgically-induced stromal surface irregularities and improve topography and visual quality.[1]

One thing to note with transepithelial ablation is the difference in ablation rate between the epithelium and the stroma. With good epithelial mapping, however, this is less of an issue. "There's a slight difference in ablation rates, but we're aware of it, and we know the average thickness of the epithelium when we're removing it with PTK," says Dr. Stein. "We like to use a large optical zone and transition down. Typically the optical zone is about 7 mm with the PTK, with a blend out to 9 or 9.5 mm. If we remove 50 µm with the Allegretto, we know we can induce a mild degree of myopia, say -0.75 D. We can account for this when trying to give patients the best uncorrected vision."

• ***Be aware of the posterior cornea's influence.*** "We can't treat the posterior cornea, so if the irregular astigmatism is mainly due to posterior corneal irregularities, it's better not to treat that patient because they won't get better," says Dr. Stojanovic. "It's inaccessible to us, at this point. Wavefront-guided PRK would take the posterior cornea into account, but this approach isn't usually good enough to handle irregular corneas."

New Treatment Modalities

Dr. Stojanovic says that emerging modalities for irregular corneal optics are taking into account the posterior cornea and its influence on total corneal optics. "In the future, we'll have total corneal ray-tracing-guided ablation for very customized care," he says. "Alcon has released a ray tracing system, but right now it doesn't separate corneal ray tracing from total-eye ray tracing. Oculus' Pentacam AXL Wave also has total-eye ray tracing."

Ray tracing optimizes refractive surfaces in the eye until the measured wavefront equals the simulated ideal wavefront for a particular patient. It does this by calculating an ablation profile for a laser using data from several measurements, including anterior and posterior corneal topography and the crystalline lens. While wavefront also considers the entire eye's optical properties, it's based on approximation, and its calculations are derived from a single measurement method, making it inherently less precise and less ideal for true customized treatment, say experts.[2] ◀

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FOLLOWING PROGRESSION IN GLAUCOMA PATIENTS

Experts discuss how they take structure and function into account.

MICHELLE STEPHENSON
CONTRIBUTING EDITOR

Glaucoma is a progressive disease that must be monitored over time. For years, identifying glaucoma progression relied heavily on clinical assessment of the optic nerve, comparison of disc photos over time and visual field analysis. OCT has given physicians another tool to keep track of patients' glaucoma, and they can combine its findings with the results of other modalities to try to get a fuller picture of the patient's disease. Here, glaucoma experts explain how they follow progression in their patients.

The Toolbox Expands

According to Richard Lehrer, MD, who is in practice in Canton, Ohio, before visual field testing became popular, ophthalmologists examined the optic nerve and checked the patient's pressure. "In the 1960s, if a patient's pressure was less than 21 mmHg, he or she didn't have glaucoma, and if the pressure was more than 21 mm Hg, he or she had glaucoma," Dr. Lehrer says. "At that time, people were losing vision, and ophthalmologists didn't really understand why. Once visual field testing became popular, it became routine standard of care to monitor for progression with visual field testing. Before OCT testing, we would follow all patients with stereo disc photos and disc drawings. We would do them on a regular basis and compare them. Studies have shown that manual optic nerve examination, even by very experienced observers, isn't as reliable as comparing photographs. It's not as reliable as OCT testing measuring nerve fiber layer and ganglion cell layer parameters."

A recent study found that OCT is very sensitive for the detection of progression in early glaucoma (though several of the authors have financial interests in OCT technology).[1] The utility of the nerve fiber layer declines in advanced glaucoma, but the ganglion cell complex remains a sensitive progression detector from early to advanced stages, the authors said. The study included 356 glaucoma suspect/preperimetric eyes and 153 perimetric glaucoma eyes that were analyzed every six months for at least four semi-annual follow-up visits. Follow-up length was 54.1 ±16.2 months for glaucoma suspect/preperimetric eyes and 56.7 ±16 months for perimetric glaucoma eyes.

Fourier-domain OCT was used to map the thickness of the peripapillary retinal nerve fiber layer and ganglion cell complex. OCT-based progression detection was defined as a significant negative trend for either nerve fiber layer or ganglion cell complex. Visual field progression was determined if either the event or trend analysis reached significance.

Progression was detected in 62.1 percent of perimetric glaucoma eyes and in 59.8 percent of glaucoma suspect/preperimetric eyes by OCT, significantly more than the detection rate of 41.8 percent and 27.3 percent by visual field. In severity-stratified analysis of perimetric glaucoma eyes, OCT had a significantly higher detection rate than visual field in mild perimetric glaucoma (63.1 percent vs. 38.7 percent), but not in moderate or advanced perimetric glaucoma. The rate of nerve fiber layer thinning slowed dramatically in advanced

This article has no commercial sponsorship.

Dr. Cantor is a consultant for Zeiss. Drs. Lehrer and Stiles have no financial interests in any of the products discussed.

perimetric glaucoma, but ganglion cell complex thinning rate remained relatively steady and allowed good progression detection even in advanced disease. The Kaplan-Meier time-to-event analyses showed that OCT detected progression earlier than visual field in both groups.

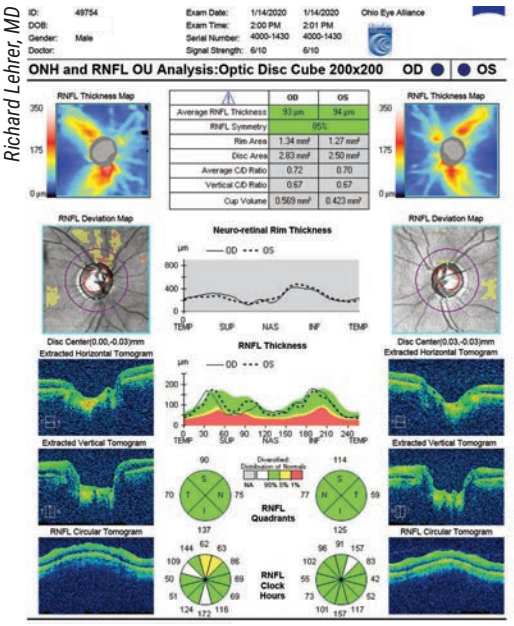
Because glaucoma is a complicated disease, it requires more than one method of following its progression, according to Michael Stiles, MD, who is in practice in Overland Park, Kansas. "We must look at both structure and function," he says. "We've always been under the impression that measurable structural change will precede measurable functional change, but the Ocular Hypertension Treatment Study and other large studies have shown that functional loss can be recognized before structural loss. So, even in the early stages, following both structure and function is important."

Louis Cantor, MD, who is in practice in Indianapolis, agrees. "There's no one test that will tell you definitively if a patient is progressing," he says.

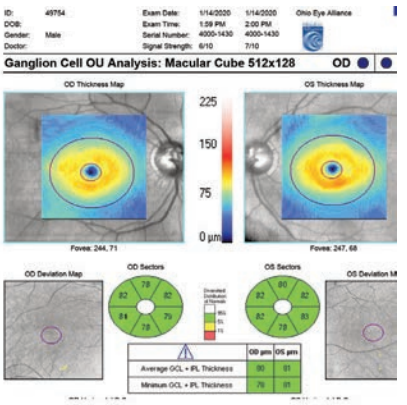
Consistent, Persistent, Significant

Dr. Cantor says that there are three things to consider when evaluating possible progression: Is it consistent? Is it persistent? And, is it significant?

"First, the progression must be consistently observed on multiple tests," he says. "It's challenging to diagnose progression based on one measurement being up one day on any given test. We can't hang our hat on any one thing in glaucoma, so things have to correlate and be consistent with each other. If something looks worse in a patient's field, but the pressure is as low as it's always been, the optic nerve looks the same, and the patient isn't noticing any changes, then we are less likely to believe that the field is worse.



Richard Lehrer, MD



A 70 y.o. man followed for 12 years as a glaucoma suspect has IOPs in the 15 to 18 mmHg range, and he's developing cataracts. CCT is 524/520 µm and HVF 24-2 visual fields are full. In 2020, he developed superior RNFL thinning OD with no significant change in GCC thickness.

However, if that same patient comes in with a worse field, something on the nerve fiber layer looks worse, the pressure is up, and the patient feels that his or her vision is worse, that all adds up to progression."

In addition to being consistent, the progression must be persistent, Dr. Cantor says. In other words, measurements need to be repeated to ensure that it's a persistent finding. "Many times, things look worse, but then when you repeat the measurement, it's really not worse," he says. "Sometimes the scan quality of an OCT isn't perfect, and when we repeat the measurement, what we thought looked worse is no longer there. Anytime we feel that a patient has progressed, we need to confirm that it's true progression by repeating testing and making sure it's a persistent finding. If we see the same visual field defect twice or three times in a row, that means something."

The final consideration is whether the progression is significant. "Many people with glaucoma get a little bit worse with time, but we're looking for patients who are at highest risk of future functional impairment or what we call loss of vision-related quality of life," Dr. Cantor says. "What we're most looking for and what most people are concerned about is patients who demonstrate that they're getting worse quickly. In a visual field, this means losing 1.5 to 2 decibels of sensitivity per year. These are the patients who are most likely to run into trouble. Patients who are only losing 0.5 decibel per year, even from progressive glaucoma, usually aren't going to experience any significant functional impairment during their lifetime. Another factor to consider is the patient's age and life expectancy. A 30-year-old with advanced pigmentary glaucoma who's getting worse slowly may be in real trouble, whereas an 85-year-old who's getting worse quickly but with mild glaucoma will probably never run into trouble with functional impairment in his or her lifetime."

Functional and Structural Changes

When following glaucoma and making decisions about when to adjust treatments, ophthalmologists consider both structural endpoints and functional endpoints. "Structural changes are a very compelling reason to think about upping your therapy to reduce the pressure more.

Ultimately, even when the structural change hasn't yet caused visual loss, it probably will, but, again, you need to take age and life expectancy into account. Also, other conditions, such as brain tumors, can cause structural changes to the nerve, as well," Dr. Lehrer says.

Dr. Cantor uses OCT to examine the nerve fiber layer. "I must admit that I often find it difficult to ascertain progression in the nerve fiber layer, particularly in moderate to moderately advanced glaucoma, and certainly in advanced disease because there's so little nerve fiber layer left to follow," he says. "Nerve fiber layer and optic nerve parameters are much more sensitive for following progression during the earlier stages of disease, just by nature of our testing and what the optic nerve looks like. When 75 to 80 percent of the nerve is gone, there's very little left to follow with OCT. We can look at macular parameters and other indicators, but it gets very hard, and we rely more on the visual field. Conversely, the field isn't very sensitive for early disease and early progression, but is much more sensitive in moderate to moderately advanced and advanced disease. So, the test we use to monitor progression is influenced a great deal by the stage of glaucoma. The patient with early disease can be progressing, and his or her optic nerve is getting worse, but nothing shows up on the field by our current technologies."

Dr. Lehrer agrees. "It's important to look at the diagnosis to see if it's mild, moderate or severe glaucoma and how much damage the patient has," he says. "Certain things will work better in mild disease, and other things can be better in more severe disease. For instance, if you're following severe glaucoma with OCTs, they're not quite as useful because you reach a floor effect where it just doesn't get any thinner after a while. At that point, fields are a much better way to follow things. Whereas, if you're looking at mild disease, you may start to see changes sooner in the structural testing like OCT, versus seeing changes on fields and monitoring the disc. I think those are important factors. The other thing that I've started doing in extremely mild and ocular-hypertensive patients is photopic negative response (PhNR) and ffERG testing. These may show signs of progression prior to some of the structural changes or visual field changes."

Dr. Stiles follows glaucoma progression using primarily OCT and visual field. "In visual field testing, the 24-2 testing strategy is typically used, but we're seeing a higher interest in using 10-2 to pick up more disease closer to fixation," he says. "In the past, we've always been under the impression that pericentral disease only occurs in later stages of glaucoma. But we're finding in certain glaucomas that the first manifestation of visual field loss is sometimes pericentral visual field defects, so 10-2s are being more commonly incorporated in screening and follow-up."

A recent study found that both visual function and the optic disc must be monitored with equal diligence, because either may show the first evidence of glaucomatous damage.[2] This longitudinal randomized clinical trial included 168 eyes of 152 ocular hypertensive participants aged 40 to 80 years.

Of the 168 eyes, 41 reached an endpoint by both visual function and optic disc criteria; 40 eyes reached only a visual function endpoint, and 87 reached only an optic disc endpoint. Times to reach isolated disc or field endpoints were similar. Visual field endpoints were more likely in eyes that showed the following optic nerve head features: an optic nerve head hemorrhage; thinning of the optic disc rim; or enlargement of the horizontal cup-to-disc ratio. Optic disc endpoints were more likely in eyes that showed some evidence of a nasal step or a partial arcuate visual field defect, or an increase in the pattern standard deviation.

In addition to testing, Dr. Cantor recommends asking patients about glaucoma progression and vision changes. "Many patients are aware that their glaucoma is getting worse," he says. "Even if the visual field looks the same, the patient may say that his or her vision feels worse. If I can't find another reason for it, that raises suspicion because patients are usually correct. I don't know that we listen to patients well or even ask them about their perception of their vision. I now ask every glaucoma patient about his or her vision at every visit. Then, we go from there. I think we leave the patient out a lot and rely too much on testing, when our testing may not be as sensitive as the patient sitting in front of us."

The Future

Artificial intelligence is an exciting new technology. "Trying to standardize what's truly progression and what's artifact or inherent anomalies of the optic nerve will be helpful in having a more specific and sensitive diagnosis of glaucoma, as well as following progression," Dr. Stiles says.

A recent study found that numerous artificial intelligence strategies provide promising levels of specificity and sensitivity for structural and functional test modalities used for the detection of glaucoma.[3] Combining structural and functional inputs has been shown to further improve diagnostic ability. Regarding glaucoma progression, artificial intelligence strategies may detect progression earlier than conventional methods, or potentially from a single visual field test, according to the researchers. ◀

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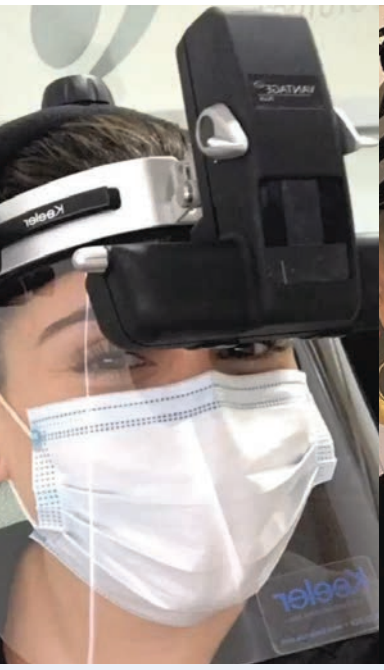


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CAN PATIENTS JUST DROP PRESBYOPIA?

Pharmacological treatment of this form of progressive near vision loss may usurp surgery. Here's what you need to know.

SEAN MCKINNEY
SENIOR EDITOR

David Wirta, MD, remembers prescribing glaucoma medications consisting of 4% and 8% concentrations of pilocarpine when he was a resident at UCLA. "Back then," he recalls, "miosis was a side effect of pilocarpine that adversely affected patients when they walked into dark rooms." Today, he serves as a principal investigator of four topical medications that will soon temper and use these same side effects to help presbyopic patients see better. One of the investigational agents, AGN-190584 from Allergan, should reach the market by the end of this year, and the other, CSF-1 from Israeli-based Orasis Pharmaceuticals, is expected to soon follow. "We're entering a whole new world," says Dr. Wirta, owner of the Eye Research Foundation in Newport Beach, California. "Reformulations of pilocarpine (a cholinergic muscarinic receptor agonist) and other miotics will change how we manage presbyopic patients from here on out."

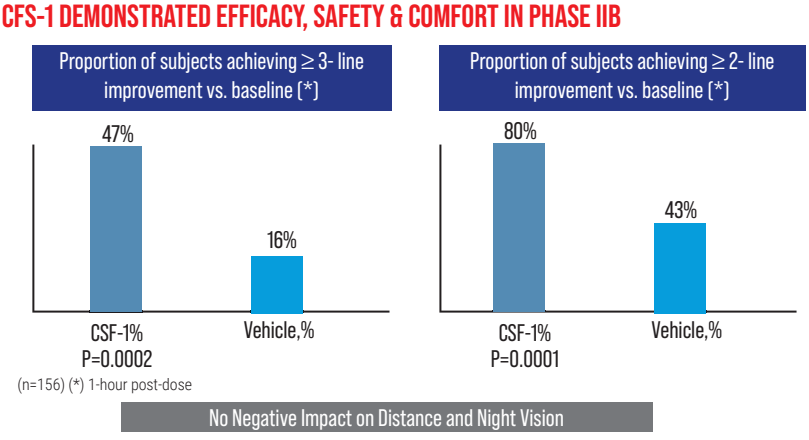

Figure 1. Above are results from a Phase IIb study of the Orasis CFS-1 drop for treating presbyopia. The columns on the left show that 47 percent of subjects using the drop achieved a three-line or better improvement in near vision compared to 16 percent using the vehicle. The columns on the right show that 80 percent of subjects taking the CFS-1 drop achieved a two-line or better improvement in near vision compared to 43 percent using the vehicle.

In this report, ophthalmologists and 12 manufacturers update you on what lies ahead. Half of the companies are developing topical reformulations of generics used in glaucoma treatment and cataract surgery for decades. The drive to meet the needs of 120 million-plus patients in this unique way has attracted more than $100 million in investor support and positioned entrepreneurial executives to blast the internet and airwaves with consumer advertising, supplanting surgical approaches of yesteryear.

New Day Coming

"Pharmacologic treatment of presbyopia is about to meet a great unmet

This article has no commercial sponsorship.

Dr. Wirta is a principal investigator of AGN-190584 (Allergan), MicroLine (Eyenovia), Brimochol (Visus Therapeutics) and CSF-1 (Orasis). **Dr. Donnenfeld** is a consultant for Allergan and chair of the clinical advisory committee for Brimochol. **Dr. Schiffman** is chief medical officer and head of R&D at Visus Therapeutics. **Dr. Dell** is a member of the advisory board of and investor in Lenz Therapeutics.

need," says anterior segment surgeon Eric Donnenfeld, MD, of OCLI Vision, at Island Eye Surgicenter in Westbury, New York. Dr. Donnenfeld is a consultant for Allergan and chairperson of a clinical advisory committee for another developer of topical treatment in this space, Visus Therapeutics in Irvine, California. "Unfortunately, many of the surgical therapies that have been used to treat presbyopia really haven't panned out. Presbyopic LASIK, scleral inlays and corneal inlays have all been fraught with problems, and we've learned that many plano presbyopic patients aren't willing to undergo these procedures. We need better opportunities for patients. What's nice about presbyopic drops is that they represent a reversible therapy that patients can stop at any time. The drops' efficacy appears to be really quite good. They are derived from proven medications with long histories."

By the end of this year, product developers at Allergan, an AbbVie company, expect the U.S. Food and Drug Administration to act on an NDA filed in February for AGN-190584 (pilocarpine 1.25%) ophthalmic solution, an investigational, novel, optimized formulation of pilocarpine designed as a topical, once-daily drop delivered by a proprietary vehicle. The application is based primarily on data from two Phase III clinical studies (GEMINI 1 and GEMINI 2), which have evaluated the efficacy, safety and tolerability of AGN-190584. The most updated data on AGN-190584—the complete Phase III GEMINI 1 study results—were revealed at the 2021 ASCRS meeting in Las Vegas on July 25.

The GEMINI 1 clinical study evaluated 323 participants randomized in a one-to-one ratio of vehicle (placebo) to AGN-190584. AGN-190584 was instilled bilaterally, once-daily, for 30 days in participants with presbyopia.

2019 Clinical Study Data Corroborate Prior Clinical Data, With Duration Up to 12 Hours

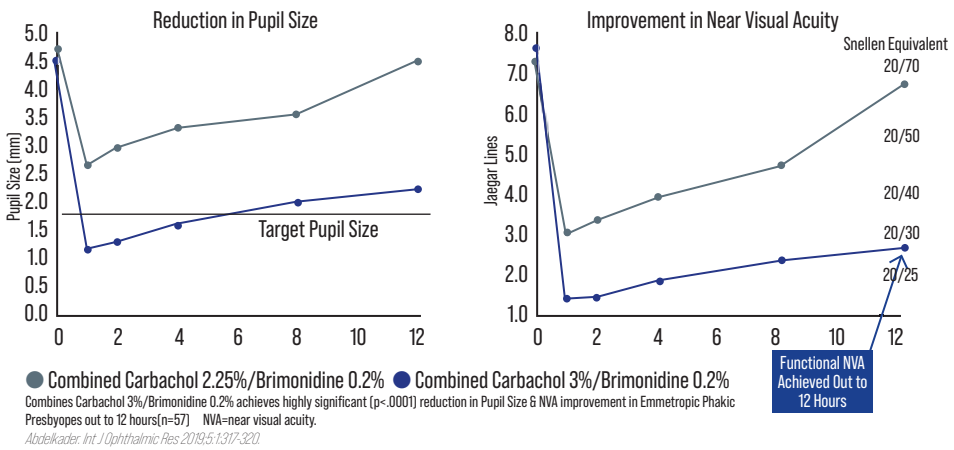

Figure 2. Above are the results from a 2019 clinical study of combined Carbachol 2.25%/ Brimodine 0.2% versus combined Carbachol 3%/Brimonidine 0.2%, showing that the stronger concentration maintained a pupil size below 2.5 mm for 12 hours post-treatment while achieving functional near visual acuity that lasted for up to 12 hours.

The primary and key secondary endpoints were met. Compared to those receiving the vehicle, a statistically significantly greater proportion of AGN-190584-treated participants gained three lines or more in mesopic, high-contrast and binocular DCNVA at Day 30, including at hour three (22.5 percent, $p<0.0001$) and at hour six (9.7 percent, $p=0.0114$).

The results demonstrated AGN-190584 had a rapid onset of 15 minutes and duration of up to six hours in mesopic DCNVA, without loss of distance vision, after administration at Day 30. Additional endpoints showed that 75 percent of participants treated with AGN-190584 achieved a ≥2-line improvement in mesopic DCNVA and that 93 percent of participants achieved ≥20/40 vision in photopic DCNVA. Improvements were also observed in DCIVA up to 10 hours at day 30. No treatment-emergent serious adverse events were observed in AGN-190584-treated participants.

Next in Line?

In terms of possible timing of approval, other entrants in the field include the following:

- ***CSF-1 (Orasis).*** Orasis CEO Elad Kedar and industry observers believe that CSF-1, containing a low concentration of pilocarpine (undisclosed at this point) and a proprietary vehicle, will possibly be the second drop to reach the market with FDA approval. The company is currently conducting its Phase III NEAR-1 and NEAR-2 clinical trials, launched in October 2020. Mr. Kedar says the multicenter, double-masked, parallel-group studies, each involving 300 participants, are structured similarly to a Phase IIb study, which showed a gain of at least two lines of near vision in 80 percent of patients and at least three lines of near vision in 47 percent of patients. The Phase IIb study also found no reduction in distance vision or night/low-light vision, he says.

  Mr. Kedar says the key to success when treating presbyopia by reducing the diameter of pupils is to not burden the patient with excessive miosis, which can negatively affect distance vision, night vision and visual field. By striving for comfort, Mr. Kedar says his team has formulated a drop that minimizes side effects such as headache, brow ache and red eye. "While the specific elements of our vehicle are proprietary, I can say our

careful balance allows us to achieve the desired therapeutic effect in a concentration significantly below the glaucoma range for pilocarpine," he says.

With respect to a potential launch date, Mr. Kedar adds: "We're currently focused on completing the ongoing Phase III trials, with the data readout anticipated later this year. FDA submission and review will follow shortly thereafter."

• ***Brimochol*** (Visus Therapeutics). Unlike other topical presbyopic treatments, Brimochol is a combination product with two active ingredients—the parasympathomimetic carbachol and the selective alpha-2 adrenoceptor agonist brimonidine tartrate. Rhett Schiffman, MD, MS, MHSA, chief medical officer and head of R&D at Visus, notes that carbachol, mimicking the effect of acetylcholine on the muscarinic and nicotinic receptors, has been used to decrease IOP in glaucoma patients by inducing miosis for more than 50 years. It's also marketed as an injectable formulation to constrict the pupil during cataract surgery.

Brimonidine blocks the dilation of the pupil under dark conditions and appears to inhibit some of the adverse effects of carbachol or pilocarpine by inhibiting alpha-2 receptors on the ciliary body, Dr. Schiffman adds. "We also have good evidence that brimonidine increases the half-life of carbachol," says Dr. Schiffman. "Previous published data indicate that this combination product can have very beneficial effects on your visual acuity for eight to 12 hours. A single dose in the morning would last you all day."

Another feature of Brimochol that may attract patient interest is that brimonidine, the active agent in Lumify, reduces ocular redness, which is associated with the use of pilocarpine and carbachol.

Visus initiated its Phase II study of Brimochol in March 2021 to evaluate the safety, tolerability and efficacy of two formulations, Brimochol and Brimochol Free (for dry eyes) in a three-arm crossover study, according to Dr. Schiffman. "Visus estimates FDA approval in Q4 2024 if everything goes as planned," he says.

Push of a Button

New York City-based Eyenovia, a clinical stage ophthalmic biopharmaceutical company, is developing a proprietary pilocarpine solution called MicroLine that's administered in a "microdose," minimizing adverse effects. Eyenovia's unique proprietary Optejet spray dispenser, featuring an automated push-button function, activates a 7-ml burst of the cholinergic muscarinic receptor agonist, reducing potential systemic exposure and toxicity, according to the company. MicroLine's Phase III VISION-1 clinical trial found that fewer than 3 percent of study participants reported headache and brow ache, compared to a 20 to 25 percent incidence observed in some other studies of eye drop formulations of pilocarpine.

"A typical eye drop may be 20 to 50 ml, depending on viscosity," says Dr. Wirta, a principal clinical investigator of MicroLine. "Because only 7 ml of the formulation is delivered by Eyenovia's Optejet dispenser, this formulation doesn't spill onto the patient's face and beyond the targeted area of the eye. Although miosis by itself can still contribute to adverse effects, this lower dose may be a factor in MicroLine's reduced adverse effects.

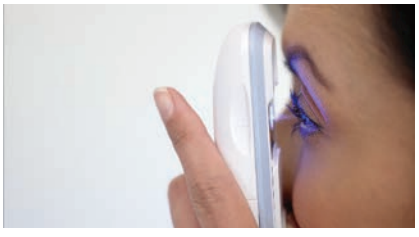

Figure 3. Eyenovia's Optejet spray dispenser, if approved by the FDA, would enable presybopes to self-administer an automated 7-ml burst of pilocarpine with the push of a button, as needed, without having to tilt their heads back for instillation of a drop. The small dose is also designed to reduce potential systemic exposure and toxicity.

The effect of the treatment peaks one hour after administration, providing up to three lines in improved vision. This is an on-demand treatment designed to be used with readers or prescribed lenses, as needed, and it provides improved vision up to three hours or more, depending on individual response."

Eyenovia's VISION-1 study evaluated the safety and efficacy of the company's 1% and 2% pilocarpine Micro-Array Print (MAP) formulations versus placebo, all administered with the Optejet dispenser. A higher proportion of subjects met the primary endpoint of three-line or greater improvement in near vision with 2% MicroLine, compared to placebo (Odds Ratio=7.7; statistically significant difference $p<0.05$). A higher proportion of subjects achieved two-line or greater improvement in near vision with 2% MicroLine as compared to placebo (Odds Ratio=10.8, statistically significant difference $p<0.05$). Eyenovia plans to initiate a second Phase III registrational trial, VISION-2, later this year.

Unique Approach

Lenz Therapeutics of San Diego, formerly called Presbyopia Therapies, has reorganized and eliminated the previous trade name of its developmental product, whose active ingredient, aceclidine, is a parasympathomimetic agent used in the treatment of open-angle glaucoma as a topical drop.

Steven J. Dell, MD, a Lenz Therapeutics scientific advisory board member and investor in the company, says a 1998 study indicates that aceclidine has the potential to function as a best-in-class treatment of presbyopia by uniquely targeting the iris sphincter.[1] The muscarinic acetylcholine receptor agonist demonstrates the ability to stimulate the pupil with minimal effect on the ciliary muscle, compared to the more significant effects on the ciliary muscle created by pilocarpine and carbachol, the other active ingredients in today's emerging topical

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presbyopia treatments, according to Dr. Dell, who is also the medical director of Dell Laser Consultants in Austin, Texas.

He notes that aceclidine, pilocarpine and carbachol stimulate the iris sphincter to create a pinhole effect, which is desirable, but not all three spare the ciliary muscle significant and undesirable stimulating effects. Strong stimulation of the ciliary muscle is undesirable in the treatment of presbyopia because it causes lens shift, increased lens thickness and varying induced levels of myopia, he continues. "For example, only 900 nmol/L of aceclidine triggers the sphincter muscles, but 22 times that amount would be required to trigger the ciliary longitudinal muscle," he says. "This is a high independence ratio versus what is found in the actions of the other miotics."

In 1977, he adds, researchers used these three miotics to elicit a pinhole effect and measured the corresponding impact on the lens created by the ciliary muscle, echoing the impact on the ciliary muscle found in the 1998 study.[2]

Dr. Dell says Lenz Therapeutics' aceclidine product will be a daily eye drop. "We completed a successful Phase II study," he says. "The product was well-tolerated. The most common side effect was mild discomfort on instillation and there were no serious adverse events. Our current focus is on Phase III clinical development to enable FDA submission and bring the product to market."

Second Combination Drug

Another emerging topical presbyopic treatment combines phentolamine ophthalmic solution 0.75% and low-dose 0.4% pilocarpine, according to the United States National Library of Medicine's clinical trial website. The product in development is Nyxol, manufactured by Ocuphire Pharma in Farmington Hills, Michigan.

A Phase II interventional trial that currently involves 150 randomized, parallel-assigned participants, with quadruple masking (participant, care provider, investigator and outcomes assessor) was begun on February 15 and is expected to conclude in September 2021, according to the FDA. Participants qualified for the trial if they had near visual acuity of 20/50 or worse.

Ocuphire says the primary endpoint of the trial is the percentage of patients with at least three lines (15 letters or more) of binocular distance-corrected near visual acuity (DCNVA) improvement on a standard near vision eye chart in photopic lighting conditions. Secondary endpoints at multiple timepoints include improvement of three lines of DCNVA without any loss of distance vision, pupil diameter and improvement in DCNVA of one or two lines when compared to placebo, phentolamine ophthalmic solution 0.75% alone and low-dose pilocarpine alone.

Alternative Mechanisms of Action

Not all topical treatments of presbyopia will be used to stimulate miosis. Novartis' UNR844 is a prodrug that penetrates the cornea and uses lipoic acid choline ester to reduce di-

sulfide bonds in the lens which, over time, restrict the lens from changing shape via ciliary muscle contraction and relaxation. The age-related disulfide bonds also contribute to the development of nuclear sclerotic cataracts.

The company's prospective, randomized, double-masked, placebo-controlled Phase I/II study enlisted 75 patients, ages 45 to 55 years, with presbyopia. At baseline, participants' distance-corrected near vision was below 20/40 in both eyes. Fifty patients received UNR844; 25 received placebo. Patients received drops for 91 days and were then monitored for seven months. According to a company spokesperson who asked to remain anonymous, findings included:

- Bilaterally, 74 percent of patients receiving UNR844 improved to 20/40 or better, versus 33 percent of those receiving placebo. Although 82 percent of patients receiving UNR844 finished the study at 20/40 or better (compared to 48 percent receiving placebo), some of them started with bilateral vision of 20/40 or better. "This is because the inclusion criteria required that monocular vision be worse than 20/40 in each eye," the spokesperson says. "However bilateral vision can be better than monocular. The 74 percent versus 33 percent numbers here excluded them (subjects with bilateral vision of 20/40 or better) from the analysis."
- Fifty-three percent of those receiving UNR844 experienced an improvement of at least 0.2 logMAR; only 22 percent receiving placebo achieved this.

The drug caused no change in visual acuity, manifest spherical equivalent or pupil diameter.

- Seven months after study completion, 39 percent of treated subjects maintained their improvement in bilateral vision (defined as an improvement of at least 0.2 logMAR), compared to only 6 percent of the placebo group. A Phase IIb study of UNR844 in patients with presbyopia was initiated in June; the first interpretable results are expected in 2022.

Another unique mechanism of action for presbyopia-correcting therapy is employed by Yolia True Vision, which involves self-administration of proprietary enzyme eye drops that increase corneal malleability, followed by the wearing of individually customized contact lenses that reshape the cornea's sphericity to produce multifocal vision.

The treatment, approved by the Mexican FDA, Cofepris, is part of Yolia Health's platform of similar treatments. CEO and co-founder Alberto Osio reports that his company is currently treating emmetropes with presbyopia and post-refractive patients with presbyopia. "We will soon begin testing our myopia progression treatment," he adds. "We've also been successful at creating multifocal corneas and therefore will use the same approach for controlling the progression of myopia. In addition, Yolia has recently entered into a commercial partnership in Asia."

Benefiting from the U.S. FDA's willingness to accept data established in Mexico, Mr. Osio says he is hoping for expedited evaluation and approval of his company's treatments by the FDA in 2023. ◀

1. Ishikawa H, DeSantis L, Patil PN. Selectivity of muscarinic agonists including (+/-)-aceclidine and antimuscarinics on the human intraocular muscles. J Ocul Pharmacol Ther 1998;14:4:363-73.
2. Francios J, Goes F. Ultrasonographic study of the effect of different miotics on the eye components. Ophthalmologica 1977;175:6:328-38.

WHAT HAPPENED TO SURGERY FOR PRESBYOPIA?

Although most early innovators of invasive treatments for presbyopia are in retreat, at least one U.S. company refuses to be counted out. The VisAbility Micro Insert System (Refocus Group, Aliso Viejo, California) consists of four 5.8-mm-long micro-thin polymethylmethacrylate (PMMA) scleral implants, each smaller than a grain of rice. The implants are placed just below the surface of the sclera about 4 mm from the limbus in the four quadrants of both eyes using a specially modified sclerotome system to ensure uniformity. Each implant has two parts; the second, smaller part locks the first part in place inside the scleral tunnel.

The VisAbility Micro Insert System is based on a theory that age-related enlargement of the lens decreases space between the lens and ciliary muscle, contributing significantly to presbyopia. The VisAbility system is intended to adjust the tension of the posterior zonules, altering the spacing relationship between these structures. In an IDE clinical study (VIS-2014), 360 presbyopic subjects 45 to 60 years of age had the procedure in the primary eye, followed by surgery in the fellow eye of 348 of the subjects at least 14 days later, according to Mike Judy, CEO of Refocus-Group. The primary endpoint of 20/40 or better DCNVA at 40 cm and at least 10 letters of improvement in the primary implanted eye was achieved in 79.1 percent of primary eyes at 12 months, 84 percent of primary eyes at 24 months.

A follow-up study from the completed IDE found 90 percent (52/58) of all eyes maintained 20/40 or better DCNVA. In addition, 67 percent (39/58) achieved 20/32, and 52 percent (30/58) achieved 20/25 or better at the last visit 48 or 60 months postop. Distance vision remained stable in all enrolled eyes. No serious ocular adverse events were reported.[1]

"VisAbility treatment (under FDA study review) has the potential to provide a permanent solution for treating presbyopia without impacting the lens and cornea, since it's implanted in the sclera," says Mr. Judy.

Another form of surgery for presbyopia is the Pearl Procedure, developed by Soosan Jacob, MS, FRCS, DNB, director and chief at Dr. Amar Agarwal's Refractive and Cornea Foundation in Chennai, India. (You can watch a video of the procedure at youtu.be/8H4Ns1b8L3M.) The procedure uses a biological tissue implant (rather than a synthetic implant) to create a hyperprolate central cornea that improves near and distance vision. Dr. Jacobs reports that she plans to continue to increase the use and refinement of this surgery.

Meanwhile, two presbyopic surgical approaches once promoted as promising are idle in the United States for now. "CorneaGen has stopped marketing and promoting the KAMRA Inlay," notes Tami Kelly, Brazer Communications for CorneaGen. The same status applies to Supracor, a procedure developed by Bausch + Lomb that involves the use of laser ablation to create a multifocal cornea. "We aren't planning to introduce Supracor in the United States at this time," says Kristy Marks of Bausch + Lomb.

1. 2021 ASCRS Electronic Abstract Submission by Frank Bucci, MD

Cataract Surgery with Zonular Issues

An experienced surgeon shares his strategies for achieving good short- and long-term outcomes.

SHAKEEL R. SHAREEF, MD
CLEVELAND

One of the many challenges cataract surgeons sometimes face is weak or missing zonules, a situation that's often associated with pseudoexfoliation. (We know that pseudoexfoliation not only affects the zonules, but can also infiltrate and affect the ciliary body; that combination can lead to zonulopathy.) Here, I'd like to share some of the strategies I use to minimize complications during surgery—and postoperatively—when working with such patients.

Searching for Warning Signs

One of the reasons zonular weakness is challenging is that it's not always obvious before surgery that the problem exists. Sometimes the signs are subtle and easily missed at the slit lamp. For example, you may not notice a small amount of white fibrillar material on the iris or the anterior lens capsule.

In fact, if the problem is mild enough, it's even possible to miss it during surgery. One study found that 70 percent of patients with subluxed IOLs, years after their cataract surgery, had pseudoexfoliation that wasn't detected or reported in the notes made by the original surgeon. For these reasons, I take the advice offered by my former colleague, the late Alan Crandall, MD: Assume that every cataract surgery patient with a family history of glaucoma has pseudoexfoliation. (As I tell my residents, there's no such thing as "routine" cataract surgery.)

During a routine examination you may find signs that a patient has a pseudoexfoliation issue. For example, you may note an unusual discrepancy, such as an asymmetry between the eyes in anterior chamber depth, or a hint of lens subluxation. Deposits of fibrillar material on the anterior lens capsule or sphincter are a giveaway, and phacodonesis or iridodonesis, poor dilation, abnormal lens or iris movements and a small pupil are other warning signs. Any discrepancy that can't be explained should put you on the alert. In that situation you need to be prepared for possible trouble.

Perhaps even more important is any direct evidence of weakened zonules, especially at the lens equator. In particular, with dilation you may be able to see focal areas of invagination of the lens capsule. Whenever there's focal weakening of the zonules—especially if there's a loss of zonules—the capsule won't be uniformly on stretch. The lack of stretch in one area will create a dip, and areas still under stretch may form a hump, creating a scalloped edge with hills and valleys. The valleys mark areas of zonular weakness or loss. This is a classic scalloped lens edge, and it indicates you'll have a problem at the time of capsulorhexis.

Respecting the Zonules

In most cases of pseudoexfoliation, the surgery goes very well despite the problem. However, if you see a sudden deepening of the chamber, that indicates the presence of zonulopathy. That should kick in a whole set of strategies to minimize the chance of a potential adverse outcome.

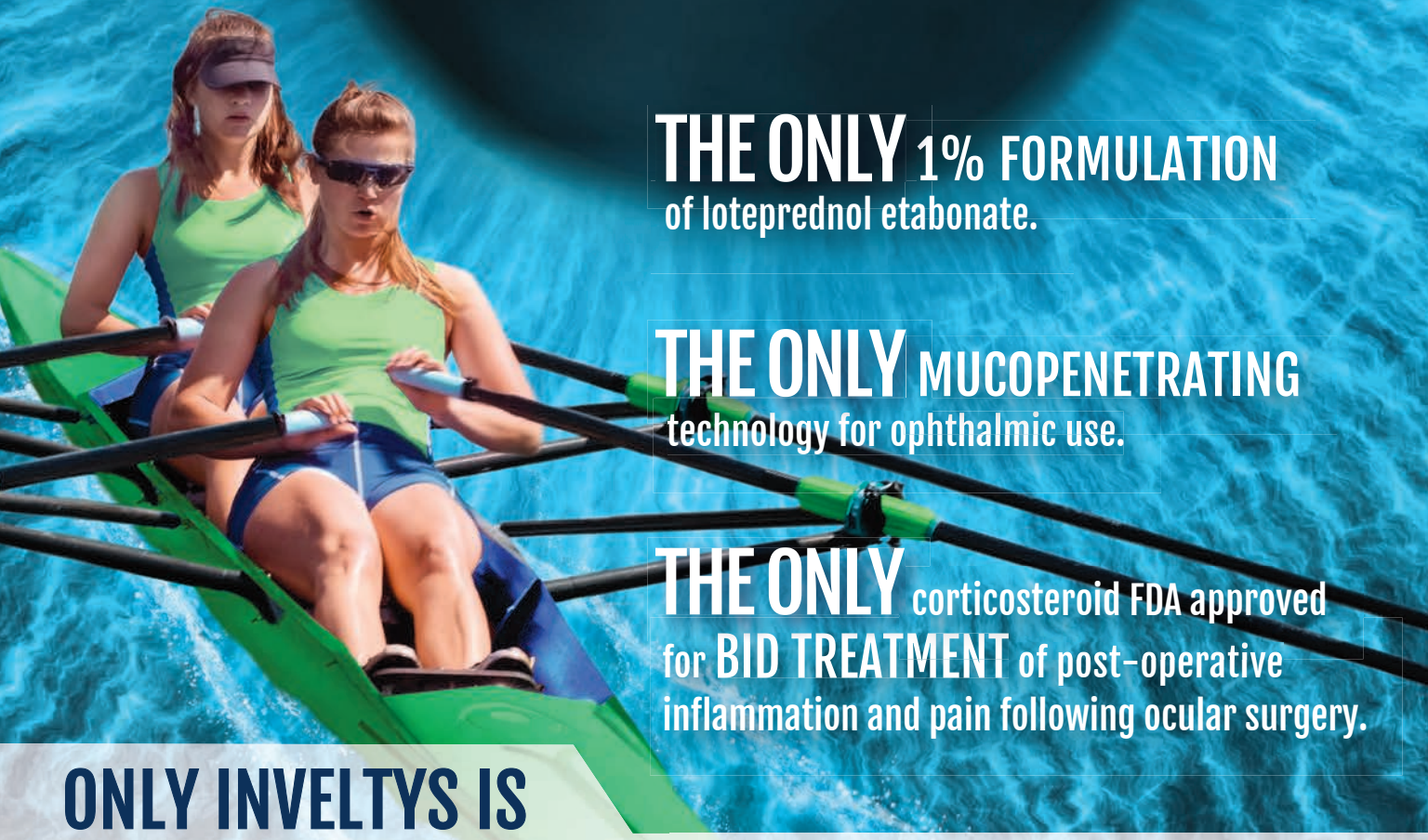
The fact is, during cataract surgery it's easy to make zonulopathy worse. Therefore, we need to take some essential precautions to avoid that. In essence, we need to minimize the stress we create in the x-axis or the y-axis by minimizing the side-to-side and up-and-down motion of the capsular-bag-zonular complex. This will avoid damaging the weakened zonules more than they've already been compromised. Accomplishing this involves maintaining a stable anterior chamber; doing a careful hydrodissection/delineation; using tangential forces during phaco and irrigation/aspiration rather than radial; and inserting and rotating the IOL slowly and carefully.

Here are some specific strategies that will help to protect the zonules:

• ***Be sure to widen a small pupil.*** It's impossible to do a safe surgery if you can't see well. (Of course, this is a problem you may face whether or not the patient has pseudoexfoliation or weak zonules.) You can use a cohesive viscoelastic of your choice to viscodilate the pupil; some surgeons recommend a push-pull technique using hooks to widen the

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.



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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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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.

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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.

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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.

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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.

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US-INV-2000053 August 2020

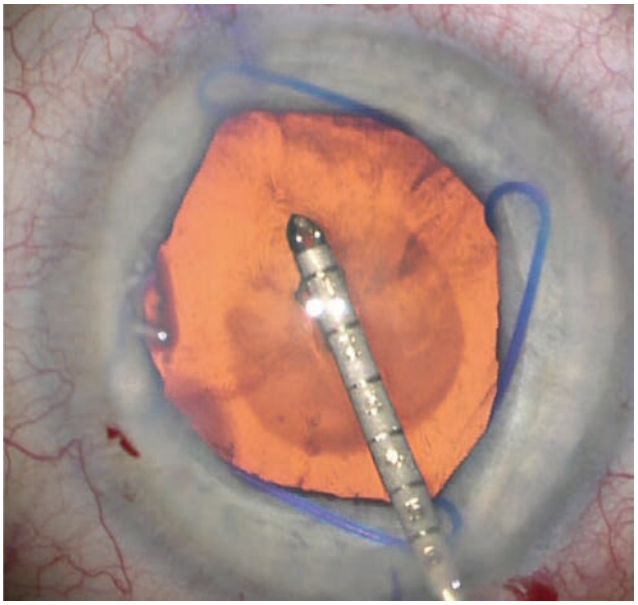
opening. Some surgeons use scissors to make small micro-sphincterotomies that relax the pupil. Iris hooks or a device like the Malyugin Ring are other options. (If you use a Malyugin Ring, consider placing one of the circular scrolls right underneath your keratome incision; this can help to prevent the iris from exiting through the incision.)

• ***Make sure your capsulorhexis isn't too large or too small.*** To help minimize stress forces in the x-axis, you need to have a capsulorhexis of adequate size—at least 5.5 mm. If the capsulorhexis is too large, you may not have the edge of the capsular tear sitting over the edge of the optic. If it's too small, you can get phimosis and shrinkage over time, creating stress on the zonules at the equator and accelerating the zonulopathy 360 degrees.

A small capsulorhexis also makes it difficult to do the surgery in a way that reduces zonular stress during the operation. For example, if you can lift the endonucleus into the anterior chamber and phaco it there, rather than in the capsular bag, you'll prevent all of the forces associated with phacoemulsification from impacting the zonules, but if the capsulorhexis is small, it'll be very hard to do this.

One strategy I find helpful when creating a capsulorhexis is to use the Microsurgical Technology (MST) forceps. They have ruler markings starting from the tip that can help the surgeon create an ideal-sized capsulorhexis opening by confirming the diameter of the capsulorhexis you've made. (*See picture.*) I measure it after I've created the capsulorhexis. If necessary, you can always enlarge it.

• ***Consider implanting a one-piece IOL.*** A one-piece IOL unfolds very slowly, without causing much tension; that gives you time to orient the haptics in the plane and axis you want. It's very zonule-friendly. In contrast, the haptics of a three-piece lens open very rapidly; the lens pops out of the lens injector. I don't have any evidence that a one- or three-piece lens will result in a better outcome in pseudoexfoliation, but they open differently. A one-piece lens gives you more control and thus may allow you to avoid zonular stress.



MST forceps with ruler markings can help a surgeon confirm the size of the capsulorhexis. (Note the Malyugin Ring scroll that's been placed directly beneath the keratome incision; this helps prevent iris herniation through the incision.)

• ***Do a thorough hydrodissection and hydrodelineation.*** You don't want to attempt to rotate the lens nucleus in the bag unless you have a complete separation of the capsular/zonular apparatus from the cataract itself; that's why it's very important to do a very good hydrodissection. Note: Having a fluid wave isn't sufficient to do a rotation. I tell residents: The goal is to direct that force of fluid to separate the nuclear material from the lens capsule at the equator.

I like to use the Chang cannula for this part of the surgery; it has a 90-degree-angled flat tip. Because of the cannula design, I can start doing the hydrodissection right underneath my keratome incision temporally, underneath the capsulorhexis edge and continue to irrigate going superiorly; then I do the same thing going in the other direction, again starting near the incision.

I also use the cannula to make sure the hydrodissection is complete. The distal point of the beveled tip can be used to impale and rotate the lens in the bag. Usually the hook is lying parallel to the plane of the cataract; I'll rotate it 90 degrees and embed it into the cataract, and then rotate it. Once I get good rotation, I know I've separated the lens from the capsule/zonular complex.

• ***If you're dealing with profound zonulopathy, do a viscodissection.*** That will not only separate the cataract but also elevate it out of the bag. If the cataract is soft enough, you can do a hydrodelineation to separate the nucleus from the epinuclear and cortical material, producing the ring sign. Then, because I'm right-handed, I go in with a flat instrument using my left hand, while I viscoelastic-elevate that piece into the chamber with my right hand. Next, I phacoemulsify the nucleus. Finally, I go after the remaining equinuclear and cortical material with additional viscodissection outside of the cortex.

• ***When sculpting, don't push.*** Residents and glaucoma fellows often want to push the phaco handpiece into the cataract. Instead, let the phaco tip lead you. When you're doing longitudinal phaco the device will clear the path for you, without pushing. Think of it as being like mowing the lawn with an automatic mower. The mower will pull you in the direction you're cutting the grass. It's leading you; you're not pushing it.

If you do push while sculpting, you're tugging on the zonules in the

subincisional space, pushing the whole lens-zonular complex into the zonules 180 degrees away from you. You want to minimize that stress. So, let the phaco handpiece do its job. And once you're done, don't phaco coming backwards. That will minimize any damage to the corneal endothelium.

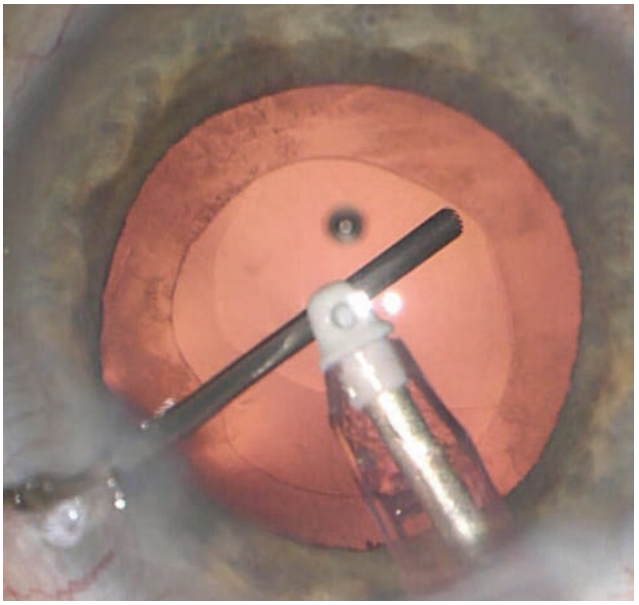
• ***Maintain a stable chamber.*** This is about minimizing the forces in the y-axis by preventing chamber shallowing or collapse. Strategies that can help accomplish this include:

— *Make a 2- to 2.2-mm keratome incision.* If you make the incision 2.4 mm or bigger, I believe the chamber will collapse no matter what you do. So make the incision snug around your phaco and irrigation/aspiration sleeve. You want a very controlled environment.

— *Make your incision triplanar.* I also tell residents, when you make your keratome incision, it can't be biplanar. In the presence of zonulopathy, the lens and iris can shift. But if you make a nice 2.2-mm triplanar incision, nine out of 10 times the chamber will hardly shift at all.

— *Avoid pressure changes when moving instruments in and out of the eye.* I use my 27-ga. cannula to firmly inject BSS into the chamber while I simultaneously turn off the continuous irrigation in my phaco handpiece and gently pull it out, very slowly. This strategy achieves two things. First, because the irrigation is off, the iris won't follow you out through the keratome incision. Second, the BSS will keep the chamber formed so you don't get a trampoline effect and a sudden collapse of the anterior chamber, which could have a very problematic impact on the zonules. (Note: This strategy partly works because I use a 2.2-mm keratome incision.)

Another way to maintain a stable anterior chamber is to inject viscoelastic as you turn off the irrigation/aspiration. Once I have a stable chamber, I put my I/A handpiece in the eye; I remove the cortical and epinuclear plate, if there is any; I may even take out some of the debris underneath the anterior capsule that can contribute to phimosis. With my other hand I'll go underneath the I/A tip while it's still irrigating and then go underneath the edge of the capsulorhexis. (*See image, above.*) Then I fill the bag with viscoelastic while turning off the I/A. (If you leave it on, it will aspirate some of the viscoelastic.)



One way to maintain a stable anterior chamber is to inject viscoelastic as you turn off the irrigation/aspiration. Here, viscoelastic is injected into the capsular bag, causing a fluid wave; the I/A handpiece is kept in the eye with the irrigation off.

I don't want to remove the I/A handpiece during this process, because it could collapse the chamber. Instead, I leave it in, almost like an anterior chamber space maintainer. Once the whole bag is filled up, and the viscoelastic is bulging into the anterior chamber, I'll gently take out the I/A handpiece and the chamber will be maintained.

• ***Peel tangentially, not radially.*** When I need to peel away cortex from the lens capsule, for example during the divide and conquer technique, I peel it in a tangential direction, like peeling the skin off an orange once you've cut it into pieces. When you pull radially, you're pulling on the zonules. I'll take my phaco handpiece and impale the desired piece without phacoing it, and then using vacuum, I peel the tissue back from an edge that's already been hydrodissected. This minimizes damage to the zonules.

The tangential approach is critical, sweeping from one side to the other. I tell residents, go to the West Coast and walk to the East Coast and peel everything. In radial peeling, you're going underneath the edge, grabbing a piece of cortical or nuclear material and pulling it to the center; that pulls directly on the zonules. Tangential peeling minimizes that.

• ***When rotating the cataract, consider using two instruments.*** If you use the divide-and-conquer technique, you want to make sure you're rotating the whole lens before you start your sculpting; but rotating the material with one hand stresses the zonules significantly. Adding a second instrument to help the phaco handpiece do the rotation can eliminate most of the zonular stress. For example, push on one heminuclear piece while you pull on the other heminuclear piece in the opposite direction. This will help you maintain control inside the bag during the rotation and minimize the stress put on the zonules.

• ***If necessary, use iris hooks to stabilize the capsule during the surgery.*** Sometimes you may notice that the entire capsular bag complex is weak. In some patients there's such significant zonulopathy that you can start a partial capsulorhexis and find yourself worried about the rest of the bag collapsing. In this situation you can use iris hooks to

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support the capsulorhexis itself (rather than the iris). That can minimize the y-axis stress while you do your phacoemulsification.

If you have more than three clock hours of weakness in the zonules, you'll need multiple iris hooks to hold it up. It just depends on the extent of the zonulopathy. Later you can put in a support ring and suture it to the sclera; once that's done, you take the hooks out.

Capsular Tension Rings and Segments

Capsular tension rings basically help with centration. So if you see that the capsular bag has shifted a little bit, but the shift is mild and the bag isn't completely off-center, a CTR may solve the problem.

A few things to keep in mind:

• ***A CTR won't prevent postoperative subluxation.*** It will help with centration at the time of cataract surgery, especially in patients with two or three clock hours of zonulopathy, but it won't help prevent subsequent subluxation years later.

• ***A CTR won't prevent postoperative phimosis.*** Whatever the mechanism of capsular phimosis is, a CTR doesn't seem to counter it. So, it's important to make a good 5.5-mm capsulorhexis.

• ***When you put the ring in, avoid any capsular laxity at the equator.*** Fill the capsular bag with cohesive viscoelastic. If it's not fully inflated when you put the ring in, it can actually damage the zonules.

• ***Use a second instrument when delivering the CTR into the bag.*** This can help you manipulate the ring without stressing the zonules.

• ***Inject the CTR in the direction of the zonular laxity.*** This helps to avoid putting stress on the remaining zonules.

Even though the CTR won't prevent late subluxation or dislocation, my retina colleagues tell me that if that IOL/capsular bag and CTR complex decides to take a dive onto the retina, having the ring in the bag will help them retrieve it. They can simply grab the edge and lift it up. The CTR keeps the capsular bag on stretch pretty much 360 degrees, making it easier to grasp.

> **"It's crucial for us to take steps to minimize the likelihood of postoperative complications."**

If there's a need for zonular support covering four or more clock hours during cataract surgery, a CTR typically isn't going to suffice. In that situation a fixate-able capsular tension segment may be what you need. These segments have eyelets that can be used to secure them to the sclera. Often these segments only cover a few clock hours, as is the case with the Ahmed segment, but you can also use what's called a modified Cionni Ring, which is a CTR, but with eyelets. (You can also fixate the capsule with multiple shorter segments. If you place one segment and see the whole bag tilt 180 degrees away from where you're suturing the one eyelet, then putting in a second one in the opposite side makes sense.) Note that if you're putting in a segment, it's important to also place a CTR within the bag to uniformly stretch it.

The advantage of using a suture-able segment is that you can just slide the segment into the bag within the clock hours at which the laxity is present; the eyelet allows you to create two-point fixation to the sclera using a CV 8-0 Gore-Tex suture. The eyelet is designed to be above the plane of the arc, protruding upward and anterior outside of the capsulorhexis edge, so it's accessible, while the curved CTR segment covering about 120 degrees sits inside the capsular bag in the lens equator to keep it on stretch. We simply make a little groove in the sclera, 1- or 1.5-mm posteriorly, and pass the sutures through the groove. We bury the knot in the groove, so we don't need to make a flap.

This approach provides support where the zonules are missing, so the patient can have a well-centered IOL. (It also ensures that the lens won't fall posteriorly later on.)

One other thing to keep in mind: The size of the CTR matters. CTRs come in multiple sizes, and getting the appropriate size is crucial to making sure the outward force created by the ring is appropriate for the eye. Depending on the axial length of the eye, the manufacturers make a recommendation of what size CTR to use.

In our practice we've created a table and posted it on the wall. It tells us the recommended CTR size that's appropriate for a given eye's axial length. So when I'm in that situation, I have my IOL printout and ask the nurse, "What's the axial length for this eye?" (I'll visually confirm it as well.) Then the appropriate sized CTR is requested from the reference table.

Doing What We Can

Ironically, it's difficult to assess the effectiveness of any preventive strategy we use, because clinical experience has shown that dislocation or subluxation of the capsulorhexis-IOL complex can take an average of eight and a half years to occur. That time lag makes it difficult to draw any firm conclusions about the effectiveness of our efforts. Nevertheless, it's easy to do things during surgery that can worsen the problem. Thus, it's crucial for us to do everything in our power to identify a potential issue and take steps to minimize the likelihood of postoperative complications.

ABOUT THE AUTHOR

Dr. Shareef is a professor at Case Western Reserve University/University Hospitals in Cleveland. He has no financial ties relevant to anything discussed in this article.

(Continued from p. 30)

RK," notes Dr. Devgan. "There's no one amazingly accurate way to measure these eyes. However, the American Society of Cataract and Refractive Surgery has an online calculator that lets you plug in whatever data you have, and it will use whichever of the 20 or so different formulas that are available to do the calculations. If you don't have all of the data, it will use the formulas that are compatible with whatever data you do have. It will give you a spread of answers, rather than one conclusive answer. Again, I suggest erring on the side of ending up slightly myopic, by choosing a higher lens power." [You can access the calculator at ascrs.org/tools/post-refractive-iol-calculator.]

• ***Be aware that there are two different types of short eyes.*** Dr. Holladay points out another factor that clinicians may not be aware of: There are two very different types of eyes that measure as having a short axial length. Identifying which you're treating can significantly impact the accuracy of a refractive outcome.

"One type of short eye is a nanophthalmic eye, where the anterior segment is proportional to the smaller axial length," he explains. "Then, there are axial hyperopes with a very short posterior compartment and axial length, but a perfectly normal anterior segment. Eyes with a short axial length are only nanophthalmic about 20 percent of the time; the other 80 percent are axial hyperopes. If you're operating on an axial hyperope, you'll need a lens with more power because the lens will sit deeper in the eye; if it's a nanophthalmic eye, you'll need less power, because the lens will sit closer to the cornea.

"In a paper my colleagues and I wrote back in 1996[2] we showed that the best measurement to use to make this distinction was the white-to-white measurement," he continues. "Normal eyes, including axial hyperopes, had 12-to 12.5-mm corneal diameters, while nanopthalmic eyes had 9- to 10-mm diameters. So there's a big difference between a nanophthalmic eye and an axial hyperope in terms of this measurement. Furthermore, the nanophthalmic eye often had a steep K and shallower anatomic anterior chamber depth, while the axial hyperope did not. So, those three dimensions of the eye are critical in differentiating whether you're dealing with a nanophthalmic or an axial hyperope eye. That's the reason the optical biometry companies began to add white-to-white, anterior chamber depth and lens thickness measurements, and why the newest formulas take that into account." ◂

1. Wang L, Holladay JT, Koch DD. Wang/Koch axial length adjustment for the Holladay 2 formula in long eyes. J Cataract Refract Surg 2018;44:10:1291-1292. Errata: January 2019 JCRS Jan 45 117.
2. Holladay JT, Gills JP, Leidlein J, Cherchio M. Achieving emmetropia in extremely short eyes with two piggyback posterior chamber intraocular lenses. Ophthalmology 1996;103:7:1118-23.

Therapeutics in the Suprachoroidal Space

A look at different approaches companies are taking to make use of this unique aspect of ocular anatomy.

NEESURG MEHTA, MD, AND GLENN YIU, MD
SACRAMENTO

Sometimes, in order to improve your outcomes with medical or surgical interventions, you don't need a new therapy, you just need to apply your current therapy in a new way or—in the case of the suprachoroidal space—in a new place. The suprachoroidal space is a potential space between the sclera and choroid that glaucoma specialists have long taken advantage of for surgical drainage. Today, the SCS has also become a high-value target for retinal therapeutics ranging from intraocular drug and gene delivery to surgical interventions such as scleral buckling and retinal prosthesis implantation. Here, we'll show you the ways this space is being used, and how it might help improve outcomes.

Anatomy of the SCS

Located between the sclera and the outer border of the choroid, the SCS consists of a gradual transition from the loose lamellar fibers of the choroidal stroma to the more compact fibers of the sclera.[1] Under physiologic conditions, the SCS has an average thickness of 35 µm[1,2] and is collapsed due to the intraocular pressure.[3] In pathologic conditions, serous fluid or blood may collect in the SCS, but won't extend beyond the scleral spur anteriorly or the optic nerve posteriorly.[4] The SCS serves as the intermediary channel for the uveoscleral pathway, by which aqueous flows through the ciliary body into the SCS, through the sclera and out through the lymphatics.[5]

Imaging the SCS

Although standard OCT penetrates poorly through the retinal pigment epithelium and the light defocuses at the choroid,[6] newer advances let us better visualize the choroid and deeper structures. Enhanced depth imaging (EDI)-OCT is obtained by placing an OCT device closer to the eye to create an inverted image with an increased depth of field.[7] Similarly, swept source-OCT employs a tunable swept laser with a longer median wavelength of 1,050 nm (as compared to 840 nm in spectral domain-OCT) to allow deeper tissue penetration and better visualization of deeper structures.[8]

On OCT, the suprachoroidal layer is found at the choroidal-scleral junction and is thought to have an inner hyperreflective band and an outer hyporeflective band.[9] The consensus is that the hyperreflective band represents pigmented cells interspersed between fibroblasts while the hyporeflective band represents the SCS.[9] The hyporeflective SCS can be seen on EDI-OCT scans of the macula in approximately half of healthy adults above age 50, and its presence correlates with hyperopia.[6] The SCS may be more difficult to visualize in those with darker uveal pigment such as those of Asian or African descent.[10] The SCS was noted to be visible in 20 percent of those with exudative AMD, and half with non-exudative AMD,[9] likely because macular fluid may impair SCS visualization.[11]

Accessing the SCS

There are several techniques to access the SCS. Minimally-invasive glaucoma surgery traditionally uses the *ab interno* approach, in which drainage devices such as the now-defunct Cypass Micro Stent (Alcon) and the investigational iStent Supra (Glaukos) are surgically implanted to allow aqueous to flow from the anterior chamber to the SCS without a filtering bleb.[12]

An external approach can also be achieved by transscleral cannulation (iTrack, iScience Interventional).[13] This is performed by creating a full-thickness pars plana scleral flap and threading a microcatheter through the SCS to the intended location. Care must be taken to identify the choroidal-scleral junction to avoid dissecting through the choroid or retina. The catheter has a flashing diode that helps the surgeon visualize the advancing catheter through the surgical microscope.[13] The advantage of this technique is that it allows for precise delivery of the

This article has no commercial sponsorship.

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

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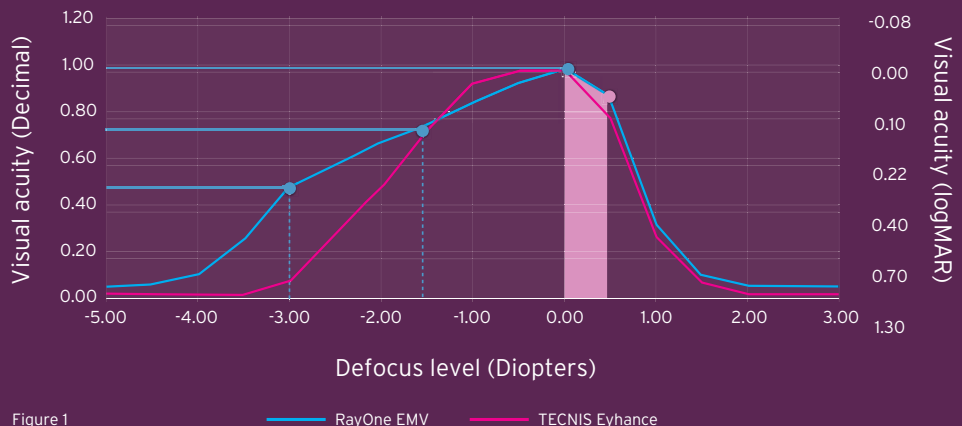

Figure 1

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drug or substance, though there is a steep learning curve and potential risk for choroidal hemorrhage.

Microneedles have been developed to allow easy and safe access to the SCS in the outpatient setting. The microneedles have a depth set to that of the sclera and conjunctiva so that the choroid and retina aren't inadvertently perforated.[14] A hollow-bore 750 um-long microneedle (Clearside Biomedical) is inserted perpendicular to the sclera at the pars plana and often held for ~1 minute to prevent reflux *(See Figure 1).*[13,14] This particular technique is necessary because, unlike standard intravitreal injections, suprachoroidal microneedle injections should be given slowly to minimize patient discomfort.

Pharmacokinetics

Intravitreal injections are the most common route for treating retinal conditions, but efficacy may be limited by biodistribution, tissue penetration and pharmacokinetics. Drug distribution in the vitreous can be non-uniform, as small molecules rapidly distribute through it, while larger molecules are more restricted.[15] The internal limiting membrane may also serve as a barrier, for example, in viral-mediated gene therapy.[15] Materials in the vitreous are cleared anteriorly through trabecular outflow and posteriorly through passive and active transport through the blood-retina barrier and uveoscleral outflow. Therefore, hydrophilic and larger molecules tend to be cleared more slowly.[15]

According to a paper from Clearside's founder and his co-workers, delivery to the SCS bypasses the ILM, spares anterior segment structures unwanted exposure, and provides higher drug concentrations to the retina, RPE and choroid.[14] For example, suprachoroidal fluorescein localizes to the choroid and retina at 25- to 200-times-higher levels than with intravitreal injection.[16] Similarly, bevacizumab injected into the SCS showed an eightfold higher concentration in the choroid compared to injections into the vitreous.[17] Studies in dog and pig eyes have shown that the SCS can accommodate up to 1 mL of fluid as compared to 10 to 50 µL in the vitreous.[18] Although there is a circumferential distribution of fluid with SCS delivery, it doesn't cover the entire space.[14] Distribution is limited anteriorly by the scleral spur and posteriorly by the optic nerve. Because the SCS is distensible, a higher injection volume can possibly cover a larger area.[14]

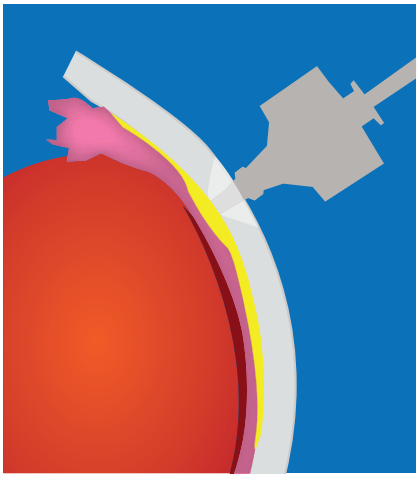

Figure 1. A transscleral microneedle can be used to access the suprachoroidal space.

The three proposed routes of SCS clearance include: 1) from the injection site; 2) pressure-driven, transscleral movement; and 3) diffusion through the choroid and intravascular route.[19] Most molecules are cleared more quickly from the SCS than from the vitreous, although lipophilic molecules such as triamcinolone acetonide form precipitates that dissolve slowly. Suprachoroidal injection of triamcinolone took 120 days to clear as compared to 41 days after intravitreal injections in non-vitrectomized eyes and six days in vitrectomized eyes.[20] In contrast, bevacizumab was undetectable in the SCS seven days after suprachoroidal injection.[17] Molecules up to 500kDa are cleared from the eye two days after SCS delivery, but very large molecules (2MDa) take up to 20 days to be eliminated.[19] Interestingly, polystyrene microparticles (20kDa) may last four months or longer in the SCS,[21-23] possibly because these rigid microspheres can't enter the choroidal circulation easily.[14] These various properties can be taken advantage of to increase the half-life of various therapeutics in the SCS.

Drug Delivery in the SCS

The use of microneedles to deliver triamcinolone to the SCS has been examined in macular edema associated with noninfectious uveitis (NIU), retinal vein occlusions and diabetes.

• ***Clearside studies.*** In Clearside's Phase III PEACHTREE study, 160 patients with macular edema due to NIU were randomized to a suprachoroidally-injected triamcinolone acetonide suspension (CLS-TA) or sham treatment at weeks 0 and 12.[24] Of those receiving CLS-TA, 47 percent gained 15 or more ETDRS letters as compared to 16 percent in the sham arm ($p<0.001$) at week 24.[24] Mean reduction in central subfield thickness (CST) was 153 µm versus 18 µm, respectively ($p<0.001$).[24] The incidence of elevated intraocular pressure and cataract progression were similar between the two arms.

For eyes with RVO-related macular edema, the Phase II TANZANITE study evaluated suprachoroidal CLS-TA combined with intravitreal aflibercept (Eylea, Regeneron) versus intravitreal aflibercept alone.[25] Both arms demonstrated comparable visual acuity, but the need for retreatment was significantly lower in the combination arm compared with the aflibercept-only arm (78 vs. 30 percent; $p=0.003$), suggesting that CLS-TA could reduce injection burden in these patients.[25] The Phase I/II HULK trial also evaluated CLS-TA monotherapy or combination treatment with intravitreal aflibercept

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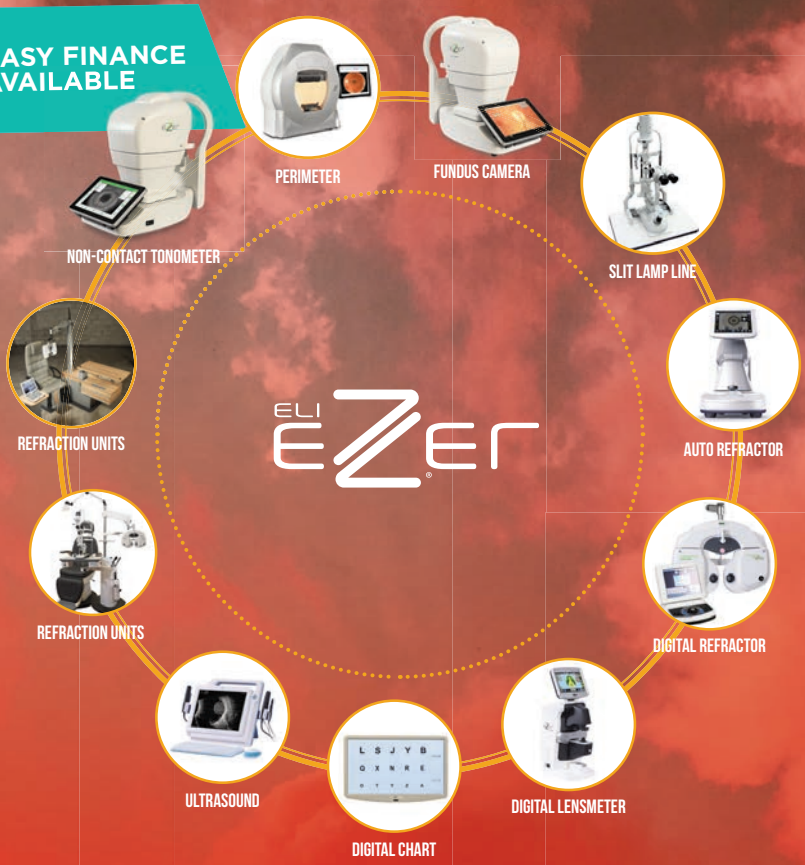

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in patients with diabetic macular edema.[26] The treatment was well-tolerated with few adverse events, though VA gains and CST reduction were greater among treatment-naïve eyes as compared to previously-treated eyes.[26]

Post hoc imaging analyses offer insight into the pharmacokinetics of suprachoroidal drug delivery. While anterior segment OCT of eyes from the HULK study showed SCS expansion immediately post-injection and anatomic restoration at one month,[27] macular EDI-OCT of eyes from the TANZANITE study showed slight but persistent SCS expansion after three months, providing some evidence for sustained drug effect.[28]

Suprachoroidal delivery has also been explored for anti-VEGF pharmacotherapies. Axitinib (Inlyta) is a tyrosine kinase inhibitor that directly blocks VEGF receptors-1, -2, and -3 and is currently approved to treat renal cell cancer.[29,30] In a study from Clearside, a single suprachoroidal injection of axitinib in rabbit eyes achieved a higher concentration in posterior segment structures and more sustained VEGF inhibition than standard anti-VEGF-A therapies.[30]

Initial data from Clearside's Phase I/IIa OASIS trial (NCT04626128) evaluating 0.03 mg suprachoroidal axitinib suspensions (CLS-AX) for patients with previously treated neovascular AMD showed VA and CST improvements, no adverse events and a reduction in intravitreal injection burden over three months in the first cohort (n=6).[29] The study will proceed with dose escalation in cohorts 2 and 3 (0.1 mg and 0.3 mg, respectively).

• ***Gyroscope Therapeutics' studies.*** The SCS also provides a conduit for drug delivery into the subretinal space. The Orbit Subretinal Delivery System (Orbit SDS, Gyroscope Therapeutics) delivers a precise volume of drug into the subretinal space by passing a cannula through the SCS and advancing a microneedle into the space *(See Figure 2)*.[31] As complement dysregulation is a key driver of AMD pathology, the Orbit SDS is being evaluated for an investigational gene therapy, GT005, to increase expression of complement factor I (CFI), which is a negative regulator in the complement alternative pathway.[32] Subretinal injection of GT005 has been found to be safe in mouse and nonhuman primate models.[32] The Phase I/II FOCUS (NCT03846193), Phase II EXPLORE (NCT04437368) and Phase II HORIZON (NCT04566445) studies are under way to evaluate its safety and efficacy in AMD patients with geographic atrophy.[31]

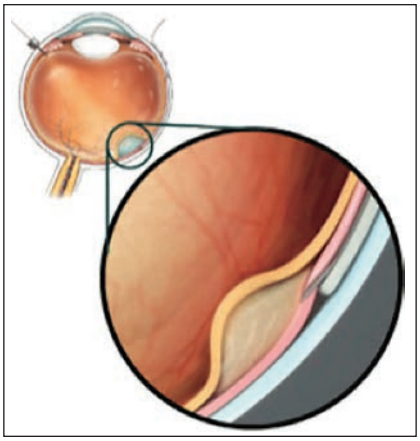

Figure 2. A cannula can be passed through the suprachoroidal space and microneedle into the subretinal space. (Copyright Gyroscope Therapeutics, 2021. Reproduced with permission)

Gene Delivery to the SCS

Subretinal injection of viral vectors is currently the preferred method for viral-mediated gene therapy. However, subretinal injection requires surgery in the operating room, and the therapeutic effect is limited to the area of the subretinal bleb. Suprachoroidal injection provides a potentially easier route of delivery while enabling a broader area of gene transduction.

• ***Delivery of AAV vectors.*** Suprachoroidal delivery of an AAV8 vector expressing green fluorescent protein (GFP) using a conventional needle demonstrated widespread expression on retinal flat mount tissues across rats, pigs and nonhuman primates.[33] Using a similar technique, injection of RGX-314, an AAV8 vector that expresses an anti-VEGF Fab fragment, showed expression levels similar to subretinal injections in rats.[33] Our laboratory compared intravitreal, subretinal and suprachoroidal delivery of AAV8 in nonhuman primates using transscleral microneedles, and similarly found widespread GFP expression. However, the transgene expression was mostly limited to the peripheral RPE that was highest at month one; it declined by month three after injection along with infiltration of inflammatory cells.[34]

In follow-up studies, we found that while intravitreal AAV8-GFP produced low retinal expression and high egress of viral particles to systemic circulation to trigger a neutralizing antibody response to the viral capsid, suprachoroidal delivery of the same vector generated high levels of local GFP expression in the sclera, which is outside the blood-retinal barrier, and thus elicited stronger immune responses to the GFP transgene.[34,35]

Since GFP is a fluorescent jellyfish protein that's foreign to the human body, the SCS remains a compelling route for gene therapies with normal human or humanized transgenes. The Phase II AAVIATE (NCT04514653) and ALTITUDE (NCT04567550) trials to evaluate suprachoroidal microneedle delivery of RGX-314 (RegenXBio), which consists of an AAV8 vector that encodes an anti-VEGF antibody fragment, are currently enrolling patients with neovascular AMD (AAVIATE) and center-involving diabetic macular edema (ALTITUDE).[36,37]

• ***Nanoparticle delivery.*** Suprachoroidal delivery of nanoparticles enables non-viral-based gene therapy that may avoid immunogenicity and achieve higher therapeutic doses.[38]

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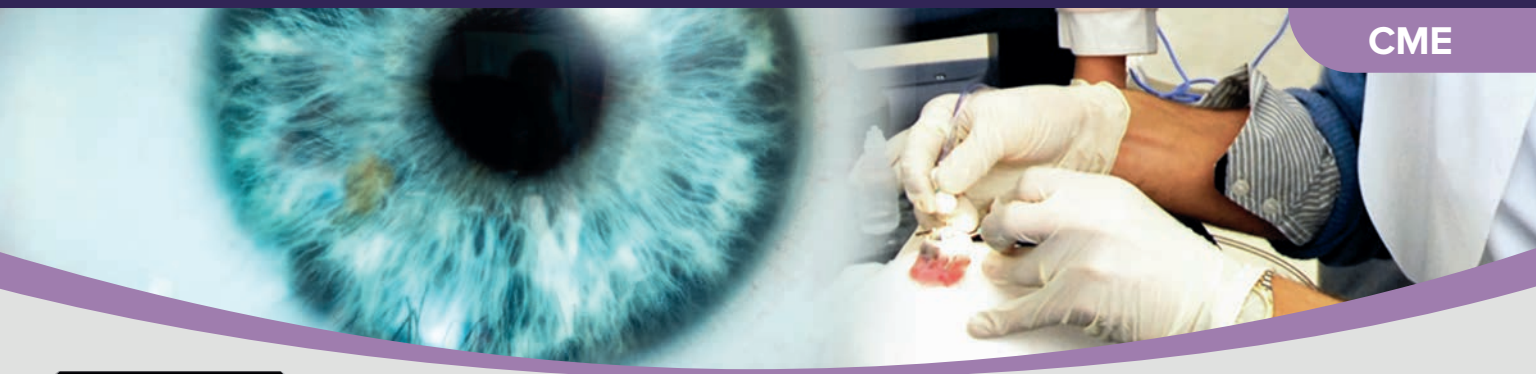

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Subretinal and suprachoroidal delivery of luciferase DNA nanoparticles in rabbits successfully transfects the RPE, choroid and retina.[39,40] Suprachoroidal injections of nanoparticles containing a DNA plasmid enabled transgene expression in rat photoreceptors and RPE for at least eight months, and can be used to produce an anti-VEGF protein to suppress subretinal neovascularization.[41]

Suprachoroidal delivery of viral nanoparticle conjugates has also been evaluated for the treatment of choroidal melanoma. AU-011 (Aura Biosciences) binds to cancer cells through modified heparan sulphate proteoglycans and induces cell death when photoactivated with a non-thermal infrared laser.[42]

Suprachoroidal injection of AU-011 results in tumor regression in rabbits,[42] and is undergoing Phase II investigation in patients with choroidal melanoma.[43]

Vitreoretinal Surgery in the SCS

The suprachoroidal space can also be used in various surgical applications.

• ***Retinal implants.*** The approval of the Argus II retinal implant (Second Sight Medical Products), which uses electrodes to stimulate inner retinal neurons, bypass degenerated photoreceptors and restore basic vision to those with severe vision loss,[44] has generated significant enthusiasm for the development of retinal prostheses. These prosthetics may be implanted in epiretinal, subretinal and intrascleral locations to help patients regain some light and object perception,[44] though different complications are associated with the various locations and surgical techniques.

Implantation into the SCS doesn't require manipulation of the retinal tissue and may avoid disrupting the fragile neurosensory retina of patients with retinal degenerations. The first human clinical trial (n=3) using a suprachoroidal retinal prosthetic in RP patients (Bionic Vision Australia Research Consortium) showed improved light localization in all three participants, but was complicated by subretinal and suprachoroidal hemorrhage that formed three to four days after surgery.[44] In two patients, the hemorrhage resolved completely, while one patient formed a fibrovascular scar at the temporal edge of the device, though this didn't affect its efficacy.[44] The researchers noted that a longer habituation time may be required to properly assess visual acuity. Following the success of this trial, the team tested a 44-channel suprachoroidal prosthesis in cats that showed a good safety profile.[45]

> **"Implantation [of a retinal implant] into the suprachoroidal space doesn't require manipulation of the retinal tissue and may avoid disrupting the fragile neurosensory retina of patients with retinal degenerations."**

• ***Retinal detachment repair.*** In addition to retinal prosthesis implantation, the suprachoroidal space may also be accessed for retinal detachment repair. Injection of viscoelastic into the SCS using a microcatheter introduced through a sclerotomy and advanced to the target area enables suprachoroidal buckling to relieve traction from peripheral retinal breaks in rhegmatogenous retinal detachments. It can also be injected underneath the fovea to repair myopic foveoschisis or macular holes.[46] Although this eliminates the need for and complications associated with silicone bands in conventional scleral buckling surgery, the steep learning curve and risk for choroidal hemorrhage has limited its widespread adoption.

In conclusion, with new technologies and methods to image and access the SCS, many clinical trials are under way to evaluate novel therapies that involve suprachoroidal drug or gene delivery. Suprachoroidal injections can be performed in outpatient settings using microneedles, and the location and pharmacokinetics of the SCS enable more widespread and targeted delivery of drugs and viral vectors to the outer retina, retinal pigment epithelium and choroid while limiting the impact on anterior segment structures. However, the position of the SCS outside the blood-retinal barrier and juxtaposition to the high-flow choroidal vessels present unique challenges for optimizing drugs' durability and minimizing exposure to the host's immune system.

Future innovations to maximize the efficacy and safety of suprachoroidal therapies could further expand the indications for this potentially game-changing route of delivery. ◀

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EDITED BY MEERA SIVALINGAM,MD, MPH
WILLS EYE RESIDENT CASE REPORT

Decreased vision and nyctalopia bring a 61-year-old man to Wills Eye.

ALINA YANG, MD, AND JAMES P. DUNN, MD

Presentation

A 61-year-old white male presented with decreased central and peripheral vision, nyctalopia and photopsias OU over the previous four months. Systemic review was significant for fatigue, difficulty sleeping, decreased appetite, dyspnea on exertion, as well as muscle aches and joint pain. He denied weight loss, fevers, chills, scalp tenderness, jaw claudication, chest pain or gastrointestinal or genitourinary symptoms.

Medical History

Past medical history was significant for obesity (BMI>41), obstructive sleep apnea on CPAP, hyperthyroidism treated with radioactive iodine and thyroidectomy, depression and migraines. His only medication was levothyroxine.

The patient was initially admitted after presenting to a general emergency room, and evaluated by several services, including neurology, cardiology, vascular surgery and ophthalmology. He had a superotemporal branch retinal artery occlusion in the right eye. Subsequent cardiac and vascular workup was overall non-diagnostic for his visual symptoms. This included an unremarkable EKG, MRI and computed tomography (CT) scan of the head and orbits, MRA/MRV, echocardiogram, carotid duplex study, BMP, CBC, LFTs, TSH, A1c and lipid panel. A stress test revealed a moderate-sized partially reversible inferior wall defect, with a left ventricular ejection fraction of 57 percent. The patient was started on a daily aspirin, but declined a statin. His erythryocyte sedimentation rate and C-reactive protein were found to be elevated at 47 and 16.5, respectively, and he was initially started on oral prednisone 60 mg daily for possible GCA. He was then referred to our retina service.

He had quit smoking five years prior after an 80-pack-year smoking history. He denied any alcohol or substance abuse. He was allergic to penicillin. Family medical history included breast cancer, diabetes and hypertension in his mother, and history of stroke in his father.

Exam

Visual acuity on presentation was 20/40 OD and 20/300 OS. Pupils were equal and reactive, with no afferent pupillary defect. IOP was 16 OD and 13 OS. Extraocular motility was full OU. Visual fields were full to confrontation OU.

The anterior exam was normal, except for 1+ nuclear sclerotic cataracts OU. Fundoscopic exam was significant for two Hollenhorst plaques versus platelet-fibrin plugs along the proximal inferotemporal arcade of the right eye, and a small choroidal nevus in the left, as well as arteriolar attenuation and mild peripheral pigmentary changes OU.

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

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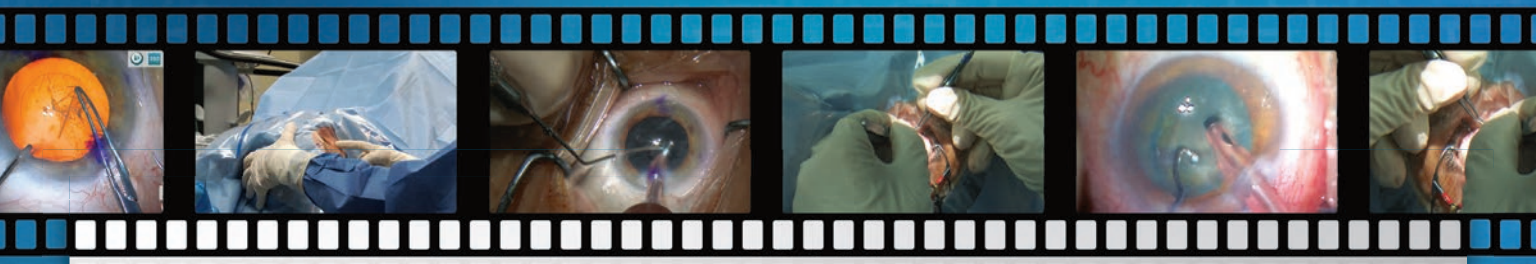

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Work-up, Diagnosis and Treatment

OCT demonstrated disruption of the extrafoveal ellipsoid zones in both eyes *(Figure 1 A, B)*. No cystoid spaces or subretinal fluid were seen. Fundus autofluorescence and fluorescein angiography were within normal limits. Full-field ERG demonstrated near isoelectric responses to scotopic stimuli and combined flash stimuli OU, as well as a severe decrease in amplitude in response to single flash photopic and 30-hertz flicker stimuli, suggesting advanced retinal dysfunction in both eyes. Octopus perimetry demonstrated a superotemporal arcuate scotoma, denser temporally, as well as an inferior arcuate scotoma.

Given the patient's symptoms and workup, autoimmune retinopathies (AIR), including paraneoplastic (pAIR) and non-paraneoplastic (npAIR) etiologies, were at the top of the differential. Acute zonal occult outer retinopathy, hereditary retinal degenerations such as retinitis pigmentosa, cone-rod dystrophy, and toxic-nutritional retinopathies were considered, but thought to be less likely.

The patient reported mild improvement in symptoms after initial treatment with prednisone. However, he was unable to taper below a daily dose of 20 mg of prednisone without developing worsening visual symptoms; he was subsequently started on a steroid-sparing regimen of mycophenolate and tacrolimus. He later developed hemoptysis and worsening SOB, and was found to have a large left lung mass on CT that was then biopsied and showed poorly differentiated carcinoma with focal squamous differentiation. A PET scan showed diffuse metastases involving the liver, adrenal gland, spine, pelvic bones, femurs and multiple ribs. The patient began chemotherapy and palliative radiation for stage IVB non-small cell lung cancer, but sadly did not survive his diagnosis.

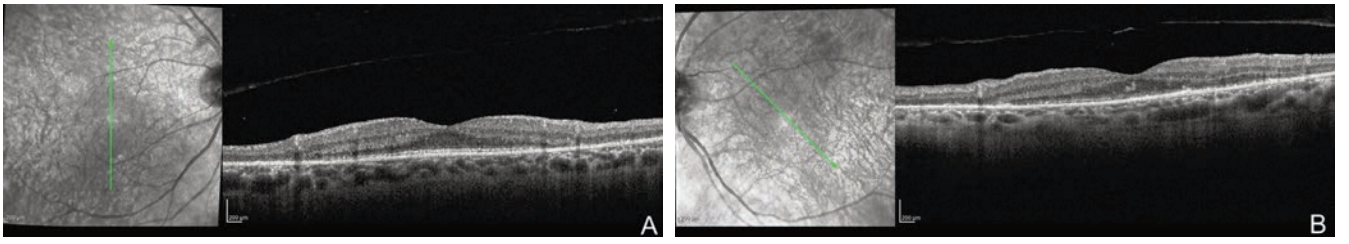

Figure 1. OCT demonstrates disruption of the extrafoveal ellipsoid zones in the right (A) and left (B) eyes.

Discussion

Autoimmune retinopathies comprise a spectrum of retinal degenerative disorders characterized by subacute vision loss, visual field deficits and the presence of circulating antiretinal autoantibodies (ARAs). Depending on the presence or absence of concomitant malignancy, AIR can be broadly classified as paraneoplastic or non-paraneoplastic (npAIR). Paraneoplastic AIR can be further subdivided into cancer-associated retinopathy (CAR) and melanoma-associated retinopathy (MAR).[1] Patient symptoms may reflect dysfunction of the associated photoreceptors and the damaged retinal tissue. CAR classically affects both rods and cones, whereas MAR is characterized by rod dysfunction secondary to antibodies directed toward bipolar cells. Cone dysfunction can lead to reduced visual acuity and central vision, hemeralopia and decreased color discrimination, while patients with rod dysfunction may experience more peripheral field loss, nyctalopia and prolonged dark adaptation.[2,3]

Cancer-associated retinopathy is most often a bilateral disease that can lead to rapid progressive visual deterioration. The differential diagnosis includes MAR, nPAIR, retinal degenerative disorders such as retinitis pigmentosa and cone-rod dystrophy, white-dot syndromes such as acute zonal occult outer retinopathy (AZOOR), toxic-nutritional retinopathy and non-infectious and infectious posterior uveitis. Currently, the diagnosis is made based on clinical presentation, abnormalities on ERG, and the presence of serum ARAs in the absence or presence of malignancy.

The fundus can initially be normal in appearance in CAR, with later stages revealing potential arteriolar attenuation, retinal pigment epithelial changes and pallor of the optic disc.[4] Abnormalities of cone and rod dysfunction may be evident on ERG. Optical coherence tomography can demonstrate loss of outer retinal structures, including the ellipsoid and interdigitation zone, or show cystic spaces or occasionally mild schisis-like changes.[5]

Antibodies to recoverin, a retina-specific calcium-binding protein in photoreceptors, is most commonly associated with CAR.[6] However, the diagnosis of autoimmune retinopathy remains challenging, in part because the presence of ARAs alone is not diagnostic, as well as lack of an accepted gold standard for ARA detection. Authors of one study sent blood specimens from 14 patients with AIR to two different labs and found the concordance rate to be only 36 percent for specimens sent from the same patients.[7] ARAs can be found in other systemic autoimmune diseases, RP and AMD, as well as in retinal degenerations, uveitis and normal eyes.[8,9] A recently published study in JAMA reported the presence of retinal antibodies in 93 percent of the patients without autoimmune retinopathy.[10] In addition, some AIR

cases have been reported in which no ARAs were found.[11] While testing for serum ARAs wasn't ultimately done for our patient, the combined clinical presentation, ancillary testing and subsequent detection of small-cell lung cancer strongly implicated CAR.

An extensive investigation, in partnership with an internist or primary care physician, should be conducted in order to determine a patient's individual risk factors and determine age- and gender-appropriate cancer testing. CAR is most frequently associated with small-cell lung cancer, breast cancer and other gynecologic cancers.[12] In most cases of CAR, vision loss precedes the diagnosis of malignancy; one such interval was reported as much as 11 years prior to diagnosis.[13] In contrast, vision loss in MAR is often accompanied by a recurrence or metastasis of a previously diagnosed cutaneous melanoma.[14]

There are currently no clear prognostic indicators or standard parameters to guide treatment in CAR. A number of largely anecdotal case reports and observational studies have reported on different treatments for CAR, with variable results and improvement in visual function. These treatment modalities include regional corticosteroid injections, systematic immunosuppressive medications (cyclosporine, azathioprine, alemtuzumab, rituximab and intravenous immunoglobulin) and plasmapheresis.[15-18] In any case, prognosis remains poor once widespread retinal degeneration occurs. ◀

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

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

†The safety and efficacy of Xiidra were assessed in four 12-week, randomized, multicenter, double-masked, vehicle controlled studies (N=2133). Patients were dosed twice daily. The mean age was 59 years (range, 19-97 years). The majority of patients were female (76%). Use of artificial tears was not allowed during the studies. The study end points included assessment of signs (based on Inferior fluorescein Corneal Staining Score [ICSS] on a scale of 0 to 4) and symptoms (based on patient-reported EDS on a visual analogue scale of 0 to 100). Effects on symptoms of dry eye disease: a larger reduction in EDS favoring Xiidra was observed in all studies at day 42 and day 84. Xiidra reduced symptoms of eye dryness at 2 weeks (based on EDS) compared to vehicle in 2 out of 4 clinical trials. Effects on signs of dry eye disease: at day 84, a larger reduction in ICSS favoring Xiidra was observed in 3 out of the 4 studies.[1]

Indication

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

Important Safety Information

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

NOVARTIS

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East Hanover, New Jersey 07936-1080

KEN JEONG,
REAL DRY EYE PATIENT.

xiidra® (lifitegrast ophthalmic solution)5%

Dry eyes deserve a change

Important Safety Information (cont)

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

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

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

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

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

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

6 ADVERSE REACTIONS

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

- Hypersensitivity *[see Contraindications (4)]*

6.1 Clinical Trials Experience

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

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

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

6.2 Postmarketing Experience

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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