Wills Eye Resident Series: Mysterious ocular swelling in a young woman, *p. 85*

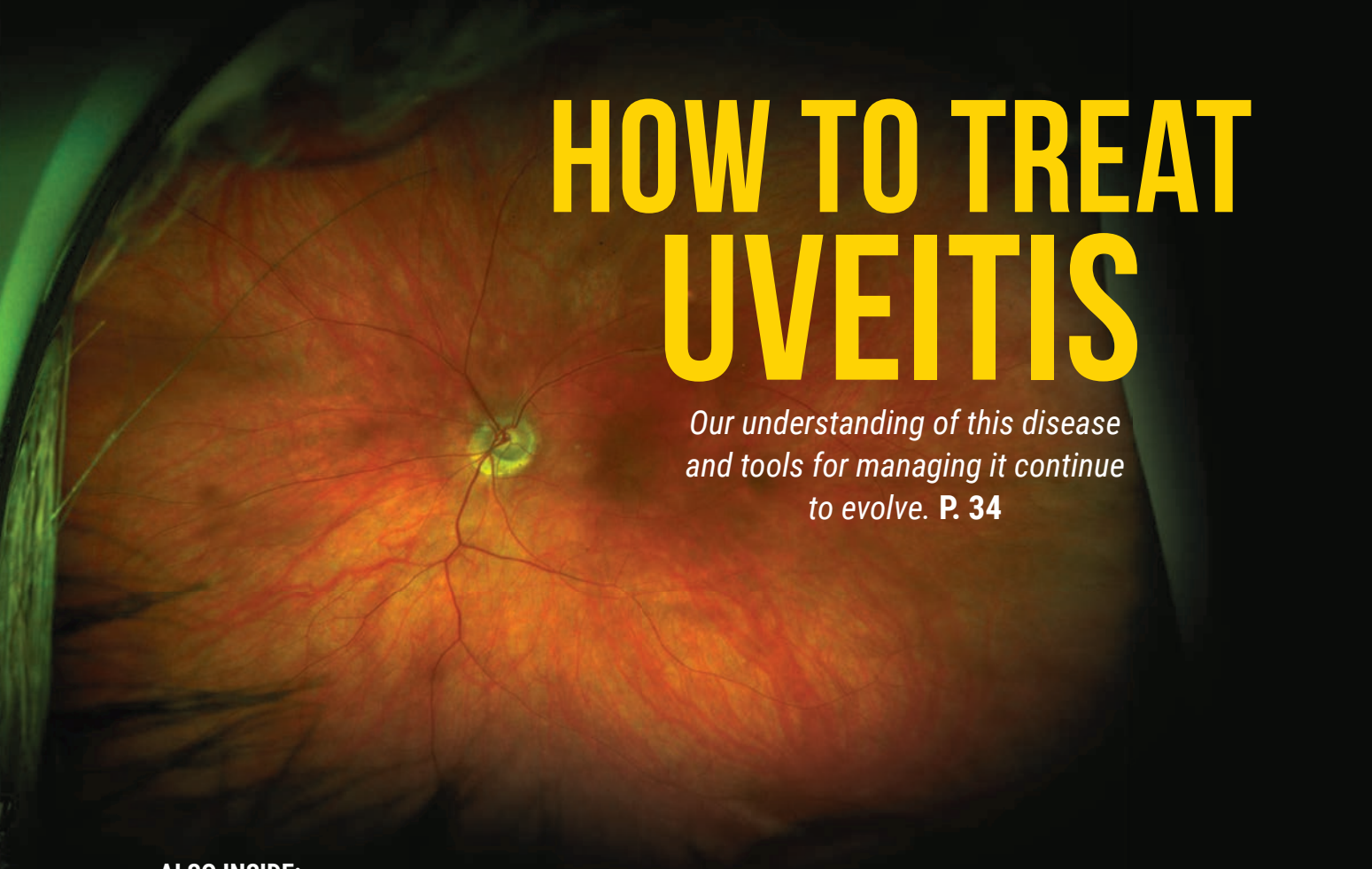
REVIEW® of OPHTHALMOLOGY

May 2021 • reviewofophthalmology.com • Clinical advice you can trust

REFRACTIVE/CATARACT RUNDOWN
Psych Screening for Refractive Surgery
PAGE 29

GLAUCOMA MANAGEMENT
Glaucoma with Retinal Disease
PAGE 76

RETINAL INSIDER
Going the Distance for the Underserved
PAGE 72



HOW TO TREAT UVEITIS

Our understanding of this disease and tools for managing it continue to evolve. **P. 34**

ALSO INSIDE:

- Catching Vitelliform Maculopathy **P. 46**
- The Quest for Excellent Vision After Cataract Surgery **P. 54**
- A Review of Ocular Allergy Treatment **P. 62**

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

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

Indication

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

Important Safety Information

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

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

Important Safety Information (cont)

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

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

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

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

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

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

6 ADVERSE REACTIONS

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

- Hypersensitivity *[see Contraindications (4)]*

6.1 Clinical Trials Experience

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

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

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

6.2 Postmarketing Experience

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

Distributed by:
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936

T2020-87

NEWS

RevOpth
RevOpth
reviewofophthalmology.com

VOLUME XXVIII • NO. 5
MAY 2021

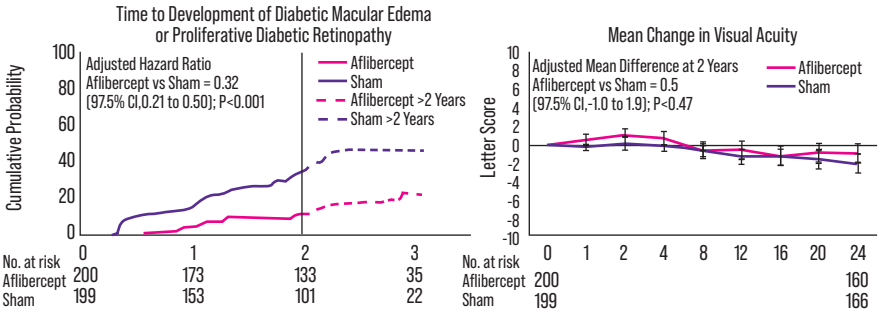
NEI: Early Anti-VEGF Injections May Slow DR Progression

A new clinical study from the DRCR Retina Network, supported by the NEI, found that early initiation of anti-VEGF therapy reduced the development of more advanced diabetic retinopathy at two years. Also at two years, however, the injections' effect on vision was similar to standard therapy used to treat the onset of late disease.

The interim findings of the Protocol W clinical trial were published in *JAMA Ophthalmology* in late March. Raj K. Maturi, MD, of Indiana University and the protocol chair for the study, says the study will help to determine whether there's any benefit to treating patients who haven't yet reached proliferative disease stages.

"The DRCR.net Protocol S demonstrated that anti-VEGF injections were noninferior to panretinal photocoagulation for treatment of PDR," he explains. "In our study, we looked at the moderate and severe NPDR categories to see if early treatment with intravitreal anti-VEGF injections would prevent any of the complications of DR that happen with more advanced disease, and if it'd prevent vision loss. Our data clearly show that the

(Continued on p. 10)



Left panel: Time from randomization to development of PDR or center-involved DME (composite outcome). The vertical line represents the end of the two-year visit window (815 days after randomization) when two-year cumulative probabilities were estimated. Hazard ratio includes all available data through four years and was adjusted for DR severity at the screening visit, study eye laterality and correlation between eyes of participants with two study eyes. Figure was truncated at the timepoint at which data from less than 20 eyes in each treatment group were available.
Right panel: Mean change in visual acuity over two years. Treatment group difference was calculated after multiple imputation of missing data and covariate adjustment for DR severity and baseline VA at the screening visit, study eye laterality, and correlation between eyes of participants with two study eyes.

IN BRIEF

New Johnson & Johnson Vision Phaco Machine Approved
Johnson & Johnson Vision announced FDA 510 clearance and the CE mark for its next-generation phacoemulsification device, the Veritas Vision System. The company says the system "features technologies that enable surgeons to guide through any lens density with less surge and more stability." It also provides advancements in ergonomics to enhance usability during cataract surgery. The machine will be available for purchase later this year.

Topline Results From Phase III NOV03 Trial for Dry-eye Drug
Bausch + Lomb announced topline data from the first Phase III trial (GOBI trial) evaluating the investigational topical drug NOV03 (perfluorohexyloctane) aimed at treating the signs and symptoms of dry-eye disease associated with meibomian gland dysfunction. In the topline data, the drug met both of its co-primary endpoints.

New Viscoelastic Approved
Bausch + Lomb announced the FDA approved ClearVisc. ClearVisc contains sorbitol, a chemical agent that the company says has been shown in a laboratory study to provide protection from free radicals. The company adds that free radicals can contribute to corneal damage. In a multicenter, randomized, clinical study of 372 subjects, ClearVisc met its primary safety and efficacy endpoints and was demonstrated to be non-inferior to Viscoat, B+L says.

Fundraising Pearls for the New Entrepreneur

MATTHEW CHAPIN, MD
Andover, Mass.

If you're an entrepreneur in the middle of raising funds for your new project, and it's in the conceptual stages or in preclinical testing, you're likely meeting with a wide range of investors. You may be speaking with pharma companies and institutional venture funds, of course, but chances are you're also having conversations with "family offices" (private wealth management advisory firms that serve ultra-high-net-worth individuals or families) and individual investors. These last two sources are starting to appear more often in the funding of new technologies, since the ability to secure funding from large institutional venture funds and pharmaceutical companies in general tends to come later in many cases.

This early group of investors may be individual angel investors, patients, established family offices that operate like a venture fund but are new to the field, and individual investors who are new to the field of ophthalmology or health care in general. In this month's column, we'll look at a few key considerations when speaking with this group of early investors.

Most people have experienced (directly or through someone they know) some form of vision-related illness or condition, such as dry eye, which almost everyone experiences from time to time; allergies, which are on the rise; cataracts; presbyopia; macular degeneration; or even inherited retinal diseases. This experience makes investing in ophthalmology personal for many people, and they become what's known as an "emotional investor." In general, these investors tend to be smaller, and may not even be very focused on biotech. As such, they may need extra education on several fronts, including ophthalmology, but also on biotech investments and pharmaceutical development, as well as how to mitigate the risks involved with these particular investments.

To help educate these early investors, it helps to emphasize what makes investing in ophthalmology, specifically, so unique. Outlining the following key areas as the overall "reason to believe" for ophthalmology typically resonates with investors new to the space:

• ***Ophthalmology is an active space.*** In ophthalmology, there's a healthy volume of transactions, initial public offerings and deals with pharma that represent exits for the investors. Its always good to have at least an appendix in your slide deck that highlights and puts into context examples of key deals in the industry and the investment returns they provided.

• ***Exit partners and pathways.*** There's a range of potential exit pharma partners—from the large multinational pharma companies to smaller ones. In this market

niche, a commercial organization can usually be built around targeting the top group of physicians. As we've seen for years, development companies can make the jump from having an investigational drug or device to hiring a sales force once a product is approved or cleared, and then launching the product and building value. Thus, exit to pharma isn't the only endgame. This shows investors that they have options.

In your pitch, show examples of both exit deals to pharma as well as examples of companies that went public and commercialized. This helps set the stage for you to outline various exit scenarios: Is the plan to exit after the Phase II or Phase III trials, or is it to go the distance to an IPO and commercialization? What's the expected interest from pharma for your specific program and drug indication at different stages of development as an aquisition? Or is a license deal with back-end royalties realistic?

As the range of investors broadens, you may find that some investors new to the space prefer a quicker return on their investment and don't have the appetite or the capital to carry a product through to approval, even if approval will lead to a larger valuation and a greater return for them in the end. It's important to be clear what the plan is, show them the options and ensure alignment.

Here are some aspects of ophthalmic drug development that you can emphasize when trying to convince someone to invest in your program:

• ***Opportunity to spread risk, time/cost and return.*** If possible, it may be attractive to have multiple products in development. Companies with multiple products can mitigate risk, maximize the use of their time and spread costs over multiple programs. For example, you could fill an unmet clinical and market need for an anterior segment indication with a topical eyedrop while you also work on your longer-term retina programs.

By diversifying your array of products in development, you can better answer the common question: "What happens if your lead program's study fails?" which may be a question on the minds of investors new to the space who are more risk averse. It's helpful for potential investors to see that your team has the ability to develop alternatives and adapt as needed, to mitigate what otherwise may be "binomial" (pass/fail) risk after a single clinical trial. In other words, be ready with a plan for a "second shot on goal," either in parallel with your trial or following it. One form this second shot might take would be different uses for the same product in other patient populations or study designs—even if they are more niche markets—with lower risks of failure.

(Continued on p. 8)

new!

thera tears® EXTRA® PRESERVATIVE FREE

PRESERVE THEIR MOMENTS WITHOUT PRESERVATIVES

The Extraordinary Relief of TheraTears® EXTRA® Dry Eye Therapy Enhanced with Trehalose is Now Preservative Free

Trehalose is a natural disaccharide found in some plants with moisture retention properties, helping organisms survive without water as an excipient. In ophthalmic products, Trehalose supports and enhances:[1]

- ✓ Protection of corneal cells from desiccation
- ✓ Restoration of osmotic balance to the ocular surface
- ✓ Maintenance of homeostasis of the corneal cells

Learn about our complete line of dry eye therapy products at **theratears.com**

AKORN | EYE CARE

Reference: 1. Jones L, et al. TFOS DEWS II Management and Therapy Report. *The Ocular Surface.* 2017;15:575-628.

M2O-036-00A

Fundraising Pearls for the New Entrepreneur

(Continued from p. 6)

• ***Benefits of local delivery of drugs.*** The fact that many products in ophthalmology are delivered locally means that, in general, there's less systemic absorption and therefore a lower likelihood of systemic side effects. This lets you emphasize safety to investors new to the space. Also, in many cases, there are more streamlined requirements for such things as systemic toxicology for locally-administered ophthalmic drugs, compared to systemic agents.

• ***Ability to directly visualize the target tissue.*** An ophthalmic drug's efficacy can be seen directly by examining the ocular surface or imaging the retina. If you emphasize this, it gives an investor who's new to ophthalmology confidence in your ability to measure and assess the endpoints that are crucial to your clinical trial.

• ***Leveraging known molecular pathways and mechanisms.*** The eye shares many disease processes and pathways with other systems. This helps your cause with investors, since if a pharmacological pathway has already been clinically validated in disease areas outside of the eye—such as dermatology, allergy, immunology or cancer—there's less risk of failure than if you were investigating an entirely untried pathway.

AN EARLY-FUNDRAISING CASE STUDY

Here's a recent example of a development-stage company that just completed its financing, which included non-institutional investors, and dealt with a lot of the considerations mentioned above.

Stuart Therapeutics is a company that recent closed its Series A round of over $11 million to fund development of its platform based on PolyCol, a synthesized polypeptide "collagen mimetic." The contract research organization I work for, ORA, has been providing the company with advisory and clinical trial services for its drug program.

The company's lead PolyCol product, ST-100, is a therapeutic that aims to target and repair damaged collagen in the extracellular matrix, return tissue homeostasis and stimulate wound healing. The lead program is a topical dry-eye product, but the technology appears to have a broader application in the eye.

One of the company's co-founders, Bob Baratta, MD, is an ophthalmologist/entrepreneur; he was joined by other individual key opinion leaders in ophthalmology who came on board as investors and advisors. InFocus Capital Partners, an ophthalmology-focused venture fund, invested in the Series A, and this syndicate brought a high level of credibility to a range of other investors new to the space that were focused on the team, mitigation of risks, time to return/inflection, and the industry dynamics mentioned above.

> **"In many cases, there are more streamlined requirements for such things as systemic toxicology for locally-administered ophthalmic drugs, compared to systemic agents."**

The CEO, Eric Schlumpf, offers his perspectives on the fundraising process with family offices and individuals that were new to the space: "Seeking funding from family offices and larger-appetite angel investors requires a slightly different approach than that of the typical venture capital investor," he says. "One key element is to seek out those that have experience and/or appetite for life-science investments. Otherwise, you can get bogged down quickly with folks who are learning the market space, but ultimately will never invest in you. It's extremely important to have some key endorsements on your side. This was provided by such elements as our well-respected advisory board and partnership with InFocus Capital Partners. These endorsements provided comfort on those due-diligence items that prospective investors new to the field may not be able to cover themselves. Remember that these investors' experience in the industry, breadth of technical and development knowledge and appetite for health-care investment in general are highly variable, so your team's domain knowledge, both in execution and in ophthalmology, is critical. Having an ophthalmologist as a co-founder gave us credibility on any clinical questions, and the balance of the team having startup expertise and program-management capabilities convinced a number of investors to commit."

LOOKING AHEAD

There's tremendous growth in the use of individual angel investors and family offices by start-up companies. Especially for pre-clinical and seed-stage opportunities, we see entrepreneurs closing more deals with investors who are relatively new to the field.

One of the main challenges when speaking with these novice investors is they may not have as much formal experience with such things as clinical-regulatory development, disease mechanisms, the use of animal models to put data in context, the FDA's requirements, reimbursement issues or competition. Though this group of investors that are new to the field will rely on your knowledge, you don't have to go it alone: The expertise of other investors and syndicate partners will help you build your case for investing in your product. Some investors may rely on the technical assessments from others as far as clinical-regulatory issues and pharmacology are concerned, while they focus on your business pitch, your team, your decision-making process and the ultimate path to exit.

Of course, some individuals and family offices won't have the same formal fact-finding process as a large institutional investor, so it may take more of an educational effort on your part. However, in the end, if you follow the steps outlined here, you may help your investors see the path to a return on their investment.

Mr. Chapin is a senior vice president of the Asset Development & Partnering Group at Ora, which offers drug, biologic and device consulting, preclinical and clinical research execution, and development strategy and support in an effort to promote new client and partner initiatives.

Review and comments on this column were provided by Aron Shapiro, partner in the same group at Ora. The author welcomes your comments or questions regarding product development.

Please send correspondence to mchapin@oraclinical.com or visit oraclinical.com.

Helping Heroes See Clear And Stay Safe

"The Vantage BIO is great for ROP screening! It's lightweight, has settings for different pupil sizes, a cool, white LED light and the longest battery ever!!"

Dra. Paulina Ramirez Neria

"I'm a big fan of the All Pupil BIO. I had issues with other models so when I started [my practice], I knew the All Pupil would be my go-to BIO...I greatly appreciate the new custom fit Keeler BIO shields as an added safety layer."

Dr. Annie Bacon

"I chose my [Vantage Plus] for the optics and value...with other brands, I had difficulty focusing up close during my dilated fundus exams. [The oculars] made my eyes feel more relaxed, and I felt like my view was better."

Dr. Michelle Hammond

"[I've] been seeing emergent and urgent cases every day during the COVID19 pandemic. I really like [the Vantage BIO] because [it's a] very good quality and provides a super clear view."

Dr. Reza Moradi

Choose one of the programs below when you purchase a BIO*

(Expires June 30, 2021)

***this program is valid for our wireless indirects: All Pupil II and Vantage Plus**

1

RECEIVE A

$850

credit towards any PPE

2

24-MONTH

0%

lease as low as $128/month*

***All Pupil II: $127.92/month; Vantage Plus: $155/month (shipping and taxes not included).**

3

RECEIVE

10 FREE

bottles of phenylephrine 2.5%, 15mL

***Leasing may also be combined with the PPE credit OR the phenylephrine option.**

Contact us at 800-523-5620 or customerservice@keelerusa.com to learn more or place your order. This promo cannot be combined with any other Keeler offers.

Keeler

– A world without vision loss –

www.keelerusa.com • 3222 Phoenixville Pike - Bldg. #50 • Malvern, PA 19355
Tel No: 1-610-353-4350 • Toll Free: 1-800-523-5620 • Fax: 1-610-353-7814

A Halma company

Early Anti-VEGF for Diabetic Retinopathy

(Continued from p. 5)

chances of developing DME or some of the severe forms of DR are reduced by almost a factor of three with the early use of anti-VEGF agents."

The four-year study includes 328 patients (399 eyes), randomized to receive either 2 mg aflibercept (n=200) or a placebo (n=199). At two years, 16.3 percent of the treated group and 43.5 percent of the placebo group developed center-involved DME with vision loss or PDR (p<0.001). Additionally, aflibercept eyes demonstrated significant differences in DR severity (defined as a change of two or more steps from baseline) compared to the sham group: 44.8 percent vs. 13.7 percent of eyes improved (p<0.001) and 5.2 percent vs. 12.4 percent eyes worsened (p=0.03), respectively. Regardless of treatment group, patients who progressed were treated with aflibercept, according to standard clinical care.

The Protocol W study also examined functional vison as a coprimary endpoint. "Our data very clearly showed that there was no difference in vision between the groups," Dr. Maturi says. Baseline visual acuity was 20/25 or better, and the two-year adjusted mean difference in VA change was 0.5 letters (-0.9 ±5.8 letters for aflibercept vs. -2 ±6.1 letters for sham [p=0.47]).

Medicare provides complete coverage for any patient with DR to get preventive treatment, but there's a potential cost. "The early treatment group required about eight injections over two years, while the treatment-deferred group received an average of one treatment over the entire two-year period," Dr. Maturi explains. "The non-treatment group got far fewer injections and didn't lose any vision, even though the DR looks like it would have progressed, in many cases.

"At four years, we'll see whether the benefit of early injections outweighs the risks," he continues. "Right now, the DRCR recommends watching these patients every four months until they develop PDR-like changes or DME. That's when we suggest treatment be initiated. Of course, there will always be individual cases where earlier treatment may be indicated."

Though the FDA has already approved aflibercept for DR at q8-week dosing regardless of retinopathy level, Regeneron is seeking FDA approval to market the drug with a q16-week dosing interval, which may make it more competitive with other anti-VEGF agents. However, Dr. Maturi notes that currently, "using aflibercept at less-frequent intervals isn't an issue, since it's approved for use up to q8 weeks."

Disclosures: Dr. Maturi receives financial support for clinical trials from Allergan, Genentech-Roche, Allegro Pharmaceuticals, Boehringer-Ingelheim and Aerpio Therapeutics, LLC.

Secondhand Smoke's Danger to Kids' Eyes

Researchers affiliated with a number of hospitals and universities in China recruited children ages 6 to 8 years from the Hong Kong Children Eye Study (n=3,103) to assess whether exposure to secondhand cigarette smoke had an effect on the children's peripapillary retinal nerve fiber layer thickness.

Data about exposure to secondhand smoke, including the number of smokers in the household and amount of smoking taking place, was gathered via a validated questionnaire. All subjects received a comprehensive ophthalmic examination, with peripapillary RNFL thickness measured by spectral-domain optical coherence tomography. Associations were determined via multivariate linear regression, adjusting for potentially cofounding factors.

About one-third of the children (n=1,097) had been exposed to secondhand smoke in their homes. The children who had been exposed to secondhand smoke and those who had not were of similar age, gender, body mass index, birth weight and axial length.

Findings in the study included:

- Families with smokers had significantly lower family income (p<0.001).
- Parents of children living with smokers had a lower education level (p<0.001).
- After adjusting for these factors, exposure to secondhand smoke was associated with a thinner peripapillary RNFL (average difference: 4.4 µm, p<0.001).
- A thinner peripapillary RNFL was also associated with more smokers in the family (p<.001) and a greater amount of smoking taking place in the home (p<0.001).

The authors conclude that exposure to secondhand smoke is associated with a thinner peripapillary RNFL. They note that a thinner peripapillary RNFL can increase the risk of permanent visual impairment later in life, and thus recommend that children not be subjected to secondhand smoke.

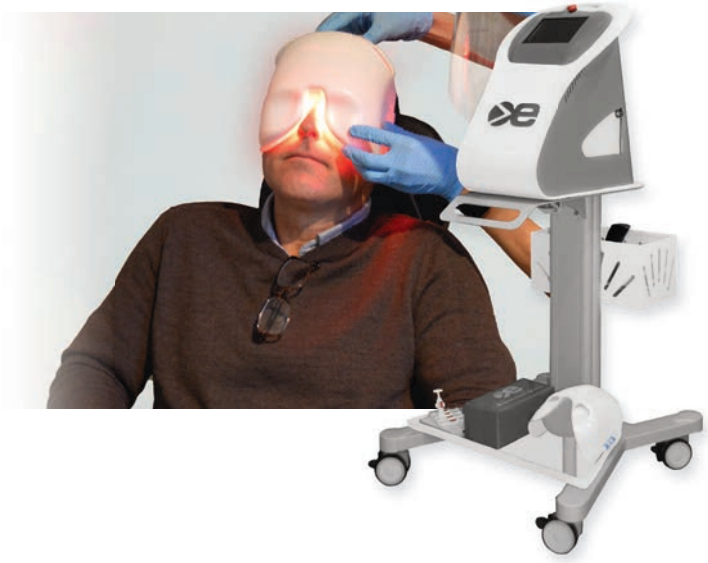
Li J, Yuan N, Chu WK, et al. Exposure to secondhand smoke in children is associated with a thinner retinal nerve fiber layer: The Hong Kong Children Eye Study. Am J Ophthalmol 2021;223:91-99.

(Continued on p. 22)

The Latest Dry Eye Technology

Exclusively from Marco

Become a Dry Eye Center of Excellence with innovative technology from Marco. Effectively diagnose and treat dry eye in your patients and **generate additional revenue streams** for your practice.



Equinox Low Level Light Therapy

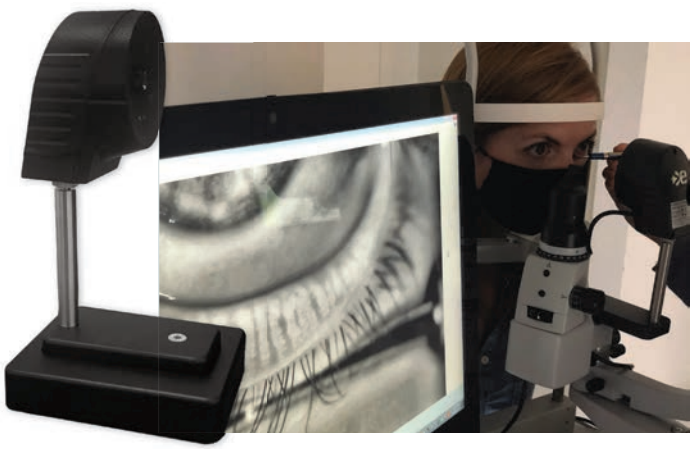
Effectively treat the root cause of MGD using red light to stimulate ATP production, leading to increased cellular function and enhanced cell vitality.

Phoenix Dry Eye Workstation with Topography

The Phoenix Meibography Workstation with Topography gives a dynamic view of non-invasive tear film break-up time with tear meniscus height imaging and measurement.

Me-Check Meibomian Gland Imaging

Capture high-quality meibomian gland images in your exam room with ME-CHECK. Simply mount it on your slit lamp, align, click, and easily save to your EMR or imaging database.



Let us show you what's possible. Contact Marco First.

904.997.4131 | MARCO.COM/FIND-YOUR-AREA-MANAGER

REVIEW of OPHTHALMOLOGY

Clinical advice you can trust

CONTRIBUTORS

ADVISORY BOARD

BUSINESS OFFICES
19 CAMPUS BOULEVARD, SUITE 101
NEWTOWN SQUARE, PA 19073
SUBSCRIPTION INQUIRIES (877) 529-1746
(USA ONLY); OUTSIDE USA, CALL (847) 763-9630

BUSINESS STAFF
PUBLISHER
MICHAEL HOSTER
(610) 492-1028 MHOSTER@JOBSON.COM

EXECUTIVE DIRECTOR
JAMES HENNE
(610) 492-1017 JHENNE@JOBSON.COM

REGIONAL SALES MANAGER
MICHELE BARRETT
(610) 492-1014 MBARRETT@JOBSON.COM

REGIONAL SALES MANAGER
JONATHAN DARDINE
(610) 492-1030 JDARDINE@JOBSON.COM

CLASSIFIED ADVERTISING
(888)-498-1460

PRODUCTION MANAGER
FARRAH APONTE
212-274-7057 FAPONTE@JOBSON.COM

PRODUCTION MANAGER
KAREN LALLONE
(610) 492-1010 KLALLONE@JOBSON.COM

SUBSCRIPTIONS
$63 A YEAR, $99 (U.S.) IN CANADA,
$158 (U.S.) IN ALL OTHER COUNTRIES.
SUBSCRIPTIONS E-MAIL:
REVOPHTHALMOLOGY@CAMBEYWEST.COM

CIRCULATION
PO BOX 71, CONGERS, NY 10920-0071
(877) 529-1746
OUTSIDE USA: (845) 267-3065

SENIOR CIRCULATION MANAGER
HAMILTON MAHER
(212) 219-7870 hmaher@jhihealth.com

CEO, INFORMATION GROUP SERVICES
MARC FERRARA

SENIOR VICE PRESIDENT, OPERATIONS
JEFF LEVITZ

VICE PRESIDENT, HUMAN RESOURCES
TAMMY GARCIA

VICE PRESIDENT, CREATIVE SERVICES & PRODUCTION
MONICA TETTAMANZI

CORPORATE PRODUCTION DIRECTOR
JOHN ANTHONY CAGGIANO

VICE PRESIDENT, CIRCULATION
JARED SONNERS

395 Hudson Street, 3rd Floor,
New York, NY 10014

REVIEW OF OPHTHALMOLOGY (ISSN 1081-0226; USPS No. 0012-345) is published monthly, 12 times per year by Jobson Medical Information. 395 Hudson Street, 3rd Floor, New York, NY 10014. Periodicals postage paid at New York, NY and additional mailing offices. Postmaster: Send address changes to Review of Ophthalmology, PO Box 71, Congers, NY 10929-0071. Subscription Prices: US One Year $63.00, US Two Year $112.00, Canada One Year $99.00, Canada Two Year $181.00, Int'l One Year $158.00, Int'l Two Year $274.00. For subscription information call (877) 529-1746 (USA only); outside USA, call (845-267-3065. Or email us at revophthalmology@cambeywest.com. Canada Post: Publications Mail Agreement #40612608. Canada Returns to be sent to Bleuchip International, P.O. Box 25542, London, ON N6C 6B2.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use LOTEMAX® SM safely and effectively. See full prescribing information for LOTEMAX® SM.

LOTEMAX® SM (loteprednol etabonate ophthalmic gel) 0.38%

For topical ophthalmic use
Initial U.S. Approval: 1998

INDICATIONS AND USAGE

LOTEMAX® SM is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.

DOSAGE AND ADMINISTRATION

Invert closed bottle and shake once to fill tip before instilling drops. Apply one drop of LOTEMAX® SM into the conjunctival sac of the affected eye three times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

Delayed Healing: The 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: Employment 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: 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.

Contact Lens Wear: Contact lenses should not be worn when the eyes are inflamed.

ADVERSE REACTIONS

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. 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. There were no treatment-emergent adverse drug reactions that occurred in more than 1% of subjects in the three times daily group compared to vehicle.

USE IN SPECIAL POPULATIONS

Pregnancy: Risk Summary: There are no adequate and well controlled studies with loteprednol etabonate in pregnant women. Loteprednol etabonate produced teratogenicity at clinically relevant doses in the rabbit and rat when administered orally during pregnancy. Loteprednol etabonate produced malformations when administered orally to pregnant rabbits at doses 4.2 times the recommended human ophthalmic dose (RHOD) and to pregnant rats at doses 106 times the RHOD. In pregnant rats receiving oral doses of loteprednol etabonate during the period equivalent to the last trimester of pregnancy through lactation in humans, survival of offspring was reduced at doses 10.6 times the RHOD. Maternal toxicity was observed in rats at doses 1066 times the RHOD, and a maternal no observed adverse effect level (NOAEL) was established at 106 times the RHOD. The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies. Data: *Animal Data*. Embryofetal studies were conducted in pregnant rabbits administered loteprednol etabonate by oral gavage on gestation days 6 to 18, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations at 0.1 mg/kg (4.2 times the recommended human ophthalmic dose (RHOD) based on body surface area, assuming 100% absorption). Spina bifida (including meningocele) was observed at 0.1 mg/kg, and exencephaly and craniofacial malformations were observed at 0.4 mg/kg (17 times the RHOD). At 3 mg/kg (128 times the RHOD), loteprednol etabonate was associated with increased incidences of abnormal left common carotid artery, limb flexures, umbilical hernia, scoliosis, and delayed ossification. Abortion and embryofetal lethality (resorption) occurred at 6 mg/kg (256 times the RHOD). A NOAEL for developmental toxicity was not established in this study. The NOAEL for maternal toxicity in rabbits was 3 mg/kg/day. Embryofetal studies were conducted in pregnant rats administered loteprednol etabonate by oral gavage on gestation days 6 to 15, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations, including absent innominate artery at 5 mg/kg (106 times the RHOD); and cleft palate, agnathia, cardiovascular defects, umbilical hernia, decreased fetal body weight and decreased skeletal ossification at 50 mg/kg (1066 times the RHOD). Embryofetal lethality (resorption) was observed at 100 mg/kg (2133 times the RHOD). The NOAEL for developmental toxicity in rats was 0.5 mg/kg (10.6 times the RHOD). Loteprednol etabonate was maternally toxic (reduced body weight gain) at 50 mg/kg/day. The NOAEL for maternal toxicity was 5 mg/kg. A peri-/postnatal study was conducted in rats administered loteprednol etabonate by oral gavage from gestation day 15 (start of fetal period) to postnatal day 21 (the end of lactation period). At 0.5 mg/kg (10.6 times the clinical dose), reduced survival was observed in live-born offspring. Doses ≥ 5 mg/kg (106 times the RHOD) caused umbilical hernia/incomplete gastrointestinal tract. Doses ≥ 50 mg/kg (1066 times the RHOD) produced maternal toxicity (reduced body weight gain, death), decreased number of live-born offspring, decreased birth weight, and delays in postnatal development. A developmental NOAEL was not established in this study. The NOAEL for maternal toxicity was 5 mg/kg.

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

Pediatric Use: Safety and effectiveness of LOTEMAX® SM in pediatric patients have not been established.

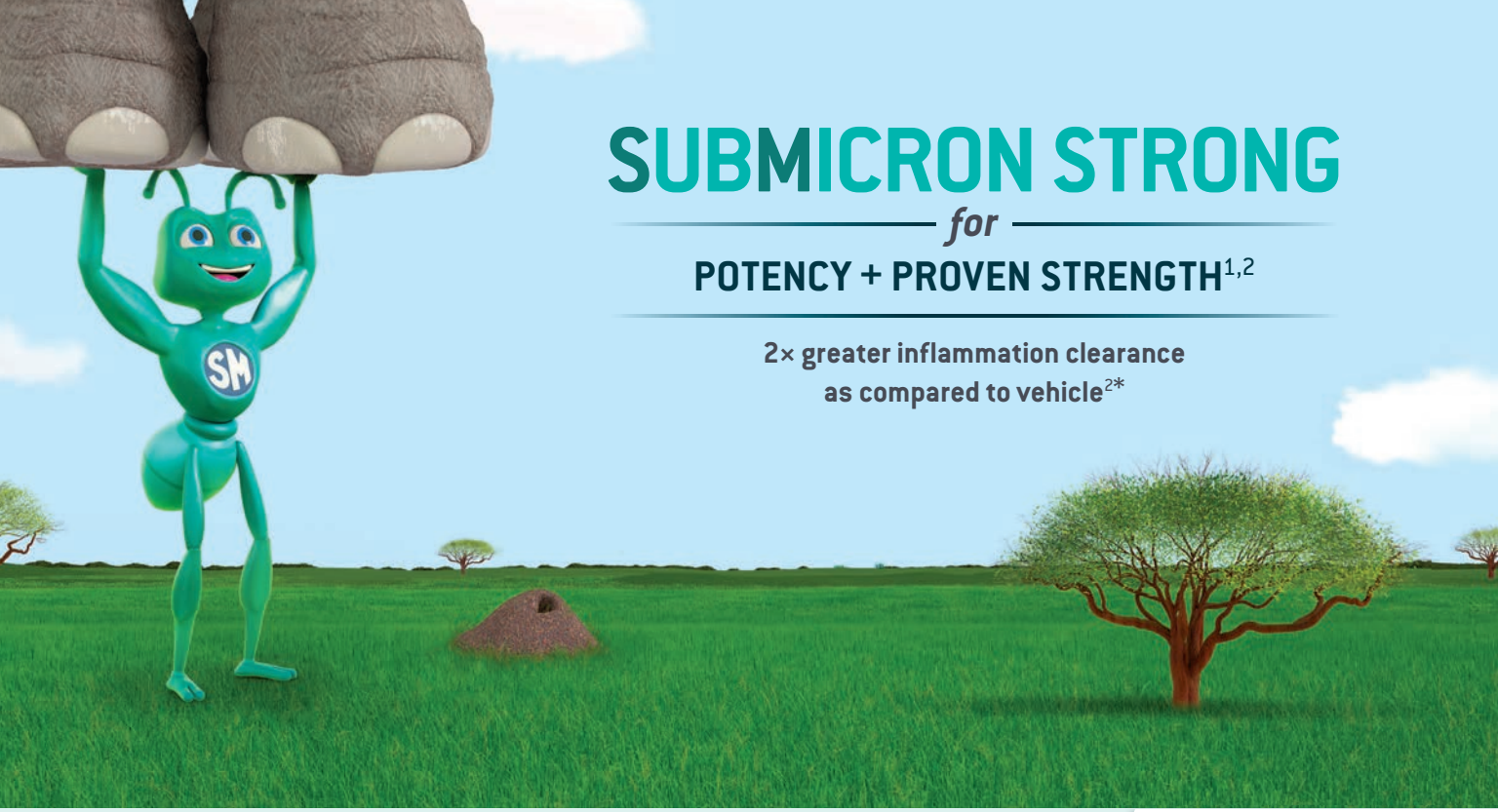
Geriatric Use: No overall differences in safety and effectiveness have been observed between elderly and younger patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma tk assay, or in the chromosomal aberration test in human lymphocytes, or *in vivo* in the mouse micronucleus assay. Treatment of male and female rats with 25 mg/kg/day of loteprednol etabonate (533 times the RHOD based on body surface area, assuming 100% absorption) prior to and during mating caused preimplantation loss and decreased the number of live fetuses/live births. The NOAEL for fertility in rats was 5 mg/kg/day (106 times the RHOD).

Distributed by: Bausch + Lomb, a division of
Bausch Health US, LLC, Bridgewater, NJ 08807 USA
Manufactured by: Bausch & Lomb Incorporated, Tampa, FL 33637 USA
U.S. Patent Number: 10,596,107

Based on 9669601 (Folded) 9669701 (Flat) Revised: 4/2020
LSM.0032.USA.21 Issued: 2/2021



SUBMICRON STRONG

for

POTENCY + PROVEN STRENGTH[1,2]

2× greater inflammation clearance as compared to vehicle[2]*

SM TECHNOLOGY™

- **Engineered with SM Technology™ for efficient penetration at a low BAK level (0.003%)[1,3]**
- **~2× greater penetration** to the aqueous humor than LOTEMAX® GEL (loteprednol etabonate ophthalmic gel) 0.5%[3]

Clinical significance of these preclinical data has not been established.

LOTEMAX® SM
(loteprednol etabonate ophthalmic gel) 0.38%

SMALL & MIGHTY
SUBMICRON PARTICLES

*PROVEN STRENGTH

- **30% of LOTEMAX® SM patients had complete ACC resolution** vs vehicle (15%) at Day 8 (N=371, *P*<0.0001)[1,2†]
- **74% of LOTEMAX® SM patients were completely pain-free** vs vehicle (49%) at Day 8 (N=371, *P*<0.0001)[1,2‡]

†Pooled analysis of Phase 3 clinical studies. **Study 1:** 29% LOTEMAX® SM (N=171) vs 9% vehicle (N=172). **Study 2:** 31% LOTEMAX® SM (N=200) vs 20% vehicle (N=199); *P*<0.05 for all.

‡Pooled analysis of Phase 3 clinical studies. **Study 1:** 73% LOTEMAX® SM (N=171) vs 48% vehicle (N=172). **Study 2:** 76% LOTEMAX® SM (N=200) vs 50% vehicle (N=199); *P*<0.05 for all.

Indication

LOTEMAX® SM (loteprednol etabonate ophthalmic gel) 0.38% is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.

Important Safety Information

- LOTEMAX® SM, as with other ophthalmic corticosteroids, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.
- Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. If LOTEMAX® SM is used for 10 days or longer, IOP should be monitored.
- Use of corticosteroids may result in posterior subcapsular cataract formation.

Important Safety Information (cont.)

- The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those with 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 infections.
- Employment 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. Fungal cultures should be taken when appropriate.
- Contact lenses should not be worn when the eyes are inflamed.
- There were no treatment-emergent adverse drug reactions that occurred in more than 1% of subjects in the three times daily group compared to vehicle.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit **www.fda.gov/medwatch** or call **1-800-FDA-1088**.

Please see brief summary of Prescribing Information on adjacent page.

References: 1. LOTEMAX SM Prescribing Information. Bausch & Lomb Incorporated. **2.** Data on file. Bausch & Lomb Incorporated. **3.** Cavet ME, Glogowski S, Lowe ER, Phillips E. Rheological properties, dissolution kinetics, and ocular pharmacokinetics of loteprednol etabonate (submicron) ophthalmic gel 0.38%. *J Ocul Pharmacol Ther.* 2019. doi: 10.1089/jop.2019;35(5):291-300.

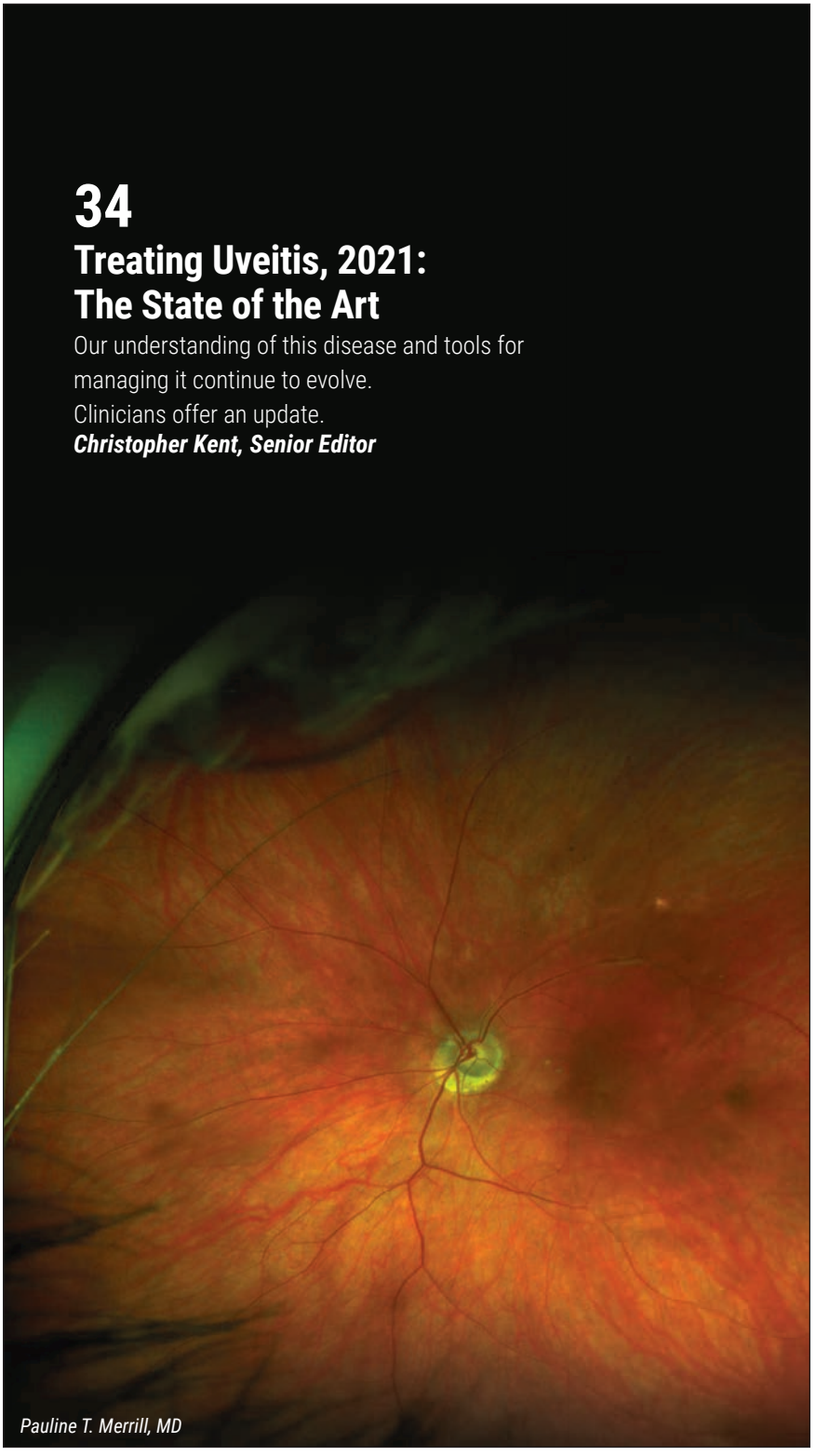
BAUSCH+LOMB

Discover more at
www.LOTEMAXSM.com

LOTEMAX® SM
(loteprednol etabonate ophthalmic gel) 0.38%

FEATURES

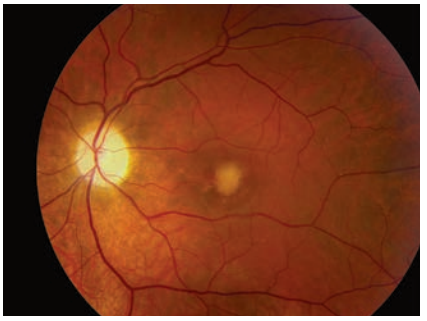
Vol. 28, No. 5 • MAY 2021



34
Treating Uveitis, 2021: The State of the Art
Our understanding of this disease and tools for managing it continue to evolve. Clinicians offer an update.
Christopher Kent, Senior Editor

Pauline T. Merrill, MD

46
Sunny Side Up: Vitelliform Dystrophy
This condition is often misdiagnosed as AMD. Find out how to differentiate it from AMD, with insights from retinal specialists.
Christine Leonard, Associate Editor



54
The Quest for Perfect Vision
How to use precise patient profiling, ocular surface management, state-of-the-art diagnostics and today's IOLs to provide patients with excellent vision.
Sean McKinney, Senior Editor

62
An Update on Therapies For Ocular Allergies
A stepwise approach that starts with over-the-counter medications and then progresses to steroids in severe cases.
Michelle Stephenson, Contributing Editor

DEPARTMENTS

MAY 2021

5
News

18
Editor's Page
Knowing When to Take a Time Out
Walter C. Bethke, Editor in Chief

20
TECHNOLOGY UPDATE
Acuity Testing at Home: Ready for Clinical Use?
Thanks to the pandemic, methods for assessing visual acuity away from the clinic are finally starting to get real.
Christopher Kent, Senior Editor

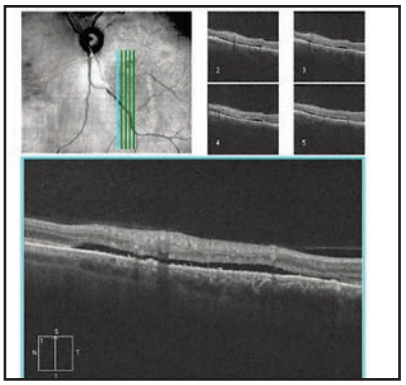
25
THE FORUM
All for One And One for All
Mark H. Blecher, MD
Chief Medical Editor

29
REFRACTIVE/CATARACT RUNDOWN
Screening Refractive Surgery Patients
How to use personality profiling and counseling to select patients.
Rohit Shetty, DNB, FRCS, PhD
Pooja Khamar, MS, FCRS, PhD
Sneha Sengupta, MS, DNB

66
CORNEA/ANTERIOR SEGMENT
Conjunctivochalasis Surgical Techniques
Though it shares symptoms with dry eye, don't confuse the two conditions.
Samantha Marek, MD, and Stephen Orlin, MD

72
RETINAL INSIDER
Going the Distance for Underserved Patients
The rewards—and challenges—of bringing vitreoretinal care to Kenya.
Benjamin Roberts, MD

75
AD INDEX



76
GLAUCOMA MANAGEMENT
Evaluating Glaucoma With Retinal Disease
How to determine the condition of the eye and the cause of any changes.
Yao Liu, MD, MS

84
PRODUCT NEWS

85
WILLS EYE RESIDENT CASE SERIES
Mysterious Swelling Brings a Woman to Wills
Bonnie Sklar, MD, Mary Stefanyszyn, MD, Ralph C. Eagle Jr., MD, Tatyana Milman, MD

89
CLASSIFIEDS

90
RESEARCH REVIEW

VISIT US ON SOCIAL MEDIA

Facebook **www.facebook.com/RevOphth**

Twitter **twitter.com/RevOphth**


Frank Bucci

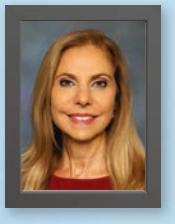

Eric Donnenfeld


John Hovanesian


Mitch Jackson


Richard Lindstrom


James Loden

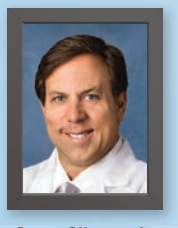

Cynthia Matossian


Cathleen McCabe


Bob Osher


Sheri Rowen


John Sheppard


Steve Silverstein


Inder Paul Singh


Denise Visco


Keith Walter

Your name here

These cataract surgeons use OMIDRIA® (phenylephrine and ketorolac intraocular solution) 1% / 0.3% for **less stress, pure success** in their O.R. day[1]

What about you?

OMIDRIA helps your cataract surgery by inhibiting prostaglandin release to block inflammation and maintain iris tone, preventing miosis and reducing postoperative pain for your patients.[2,3] Experience less stress in your O.R. day with OMIDRIA.[1]

INDICATIONS AND USAGE

OMIDRIA® (phenylephrine and ketorolac intraocular solution) 1% / 0.3% is added to ophthalmic irrigating solution used during cataract surgery or intraocular lens replacement and is indicated for maintaining pupil size by preventing intraoperative miosis and reducing postoperative ocular pain.

IMPORTANT SAFETY INFORMATION

OMIDRIA must be added to irrigating solution prior to intraocular use.

OMIDRIA is contraindicated in patients with a known hypersensitivity to any of its ingredients.

Systemic exposure of phenylephrine may cause elevations in blood pressure.

Use OMIDRIA with caution in individuals who have previously exhibited sensitivities to acetylsalicylic acid, phenylacetic acid derivatives, and other nonsteroidal anti-inflammatory drugs (NSAIDs), or have a past medical history of asthma.

The most commonly reported adverse reactions at ≥ 2% are eye irritation, posterior capsule opacification, increased intraocular pressure, and anterior chamber inflammation.

Please see the Full Prescribing Information for OMIDRIA at www.omidria.com/prescribinginformation.

You are encouraged to report Suspected Adverse Reactions to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

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.

The healthcare professionals portrayed in this advertisement are consultants of Omeros Corporation.

OMEROS

OMIDRIA®
(phenylephrine and ketorolac intraocular solution)
1% / 0.3%

REVIEW of OPHTHALMOLOGY

WALTER C. BETHKE, EDITOR IN CHIEF

EDITOR'S PAGE

Knowing When to Take a Time Out

Cataract surgeons and their staff will often take a surgery "time out" in which the entire OR staff pauses and confirms such things as the patient's identity, the correct eye to be operated on and if the procedure that's about to be performed is, in fact, the procedure the patient was scheduled to have. This simple break in the action can avoid horrendous errors and their knock-on effects, and has proven very useful for ophthalmic practices.

It turns out these time outs work for other things too, like leaving for a flight: One time, when packing for an ASCRS meeting, I took a time out before closing my suitcase and discovered I hadn't packed any belts!

Or family trips: We drove two hours to an amusement park only to realize we'd left the tickets at home. (I didn't say I always took time outs, just that they work.) The six hours I spent on the road that day were almost as painful as having my wrong eye operated on.

And now, thanks to an interesting study in the April issue of *JAMA Ophthalmology*, it appears that taking a step back and evaluating how ophthalmologists perform cost/utility analyses can pay dividends as well.

In the study, Gary Brown, MD, of the Center for Value-Based Medicine, and his co-authors queried 309 non-ophthalmic-patient subjects and 505 ophthalmic patients regarding the perceived utility of cataract surgery and intravitreal ranibizumab for wet age-related macular degeneration. They also looked at the responses with and without the application of "systemic comorbidity" limits (a theory of cost-utility analysis that says the utility of an ophthalmic intervention will be capped, in a sense, by the co-existing negative effects of diseases the patient already has).

The researchers found that using non-patients to quantify the quality-of-life benefits of interventions and the systemic comorbidity utility level "cap" resulted in large decreases in calculated patient value in terms of quality-of-life years as well as in cost-effectiveness, and potentially discriminated against disabled, elderly and African-American patients. It turns out that, if you want to get an accurate picture of how a surgery or other treatment will impact a patient, you probably should ask a patient with the disease, rather than an objective source. The authors say that identifying this negative potential bias can help avoid the denial of beneficial interventions for patients, the loss of research funding, the slowing of advances in treatment and the potential decrease in reimbursements for treatments.

It's refreshing to see that something as simple as taking a time out to stand back and evaluate a process and make sure nothing's been missed can be as effective in the complex world of medical cost-utility analysis as it can in the simple task of packing belts in your suitcase.

In both instances, you make sure that you don't miss anything important and, in the end, you don't get caught with your pants down.

— *Walter Bethke*
Editor in Chief


Custom Pak®
SURGICAL PROCEDURE PACK
Alcon
CUSTOM PAK®
SURGICAL PROCEDURE PACK
YOUR PROCEDURE. OUR PRIORITY.
ALWAYS THERE. ALWAYS READY.
BECAUSE YOU DESIGNED IT THAT WAY.
Alcon prioritizes the thing you don't need to worry about, equipping you with complete surgical packs, customized for each surgeon. Alcon Custom Pak® ensures that you are ready for every procedure, every time.
Your focus is on patients. We make sure it stays that way.
SEE HOW WE DO IT AT
www.myalcon.com/custompak
Alcon
©2021 Alcon Inc. 03/21 US-CPP-2100007

Acuity Testing at Home: Ready for Clinical Use?

Thanks to the pandemic, methods for assessing visual acuity away from the office are finally starting to get real.

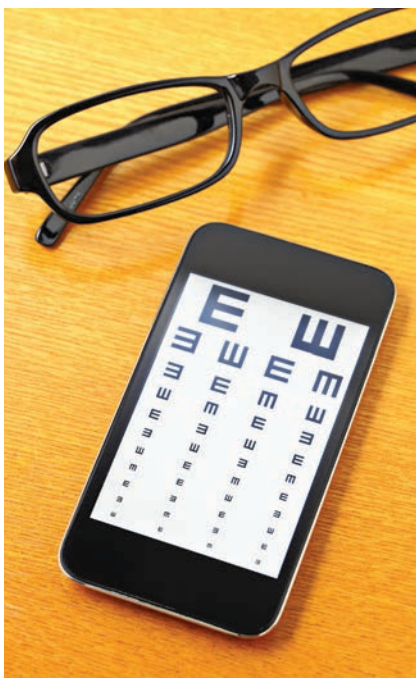
BY CHRISTOPHER KENT
SENIOR EDITOR

Being able to examine and measure a patient's eyes remotely has taken on increasing importance, thanks to the current pandemic. For obvious reasons, this isn't an easy task, even though some basic parts of an exam (examining the front of the eye, for example) can be done via telemedicine without too much difficulty.

One type of remote testing that sounds plausible is visual acuity testing; yet getting patients to accomplish this with any level of accuracy at home has been a challenge. Many companies and software developers have created apps purportedly designed to do this for one basic reason: This measurement ties into the fairly common need to be measured for a new pair of spectacles. However, these apps don't have to meet any legal or medical standards. The resulting plethora of options has been something resembling the Wild West.

Given the pandemic, however, ophthalmologists and optometrists have become interested in finding a medically useful way to effectively measure visual acuity at home. As a result, studies of the accuracy of different apps and other remote testing options have recently begun to appear in the literature.

According to one survey,[1] as of March 2020 at least 130 apps could be identified that related to eye-care functions, such as checking visual acuity, that could be considered relevant for ophthalmic practice but didn't require special equipment (about half available on iPhone and half on Android phones.) Forty-one were intended for eye-care professionals. Only six of those were claimed (by the developers) to have validation. A 2021 survey of mobile apps purportedly designed to test visual acuity found that none of the apps examined by the study authors were, in their opinion, suitable for telemedicine use.[2]



The technical challenges associated with visual acuity testing at home are not insurmountable. Some systems are showing merit in clinical testing.

Mohammad Rafieetary, OD, FAAO, who practices at the Charles Retina Institute in Germantown, Tennessee, sees home visual acuity measuring as a mixed bag. "Remote testing and home monitoring of medical parameters isn't a new idea," he notes. "For example, think about the history of the thermometer for detecting fever, or home monitoring devices for checking blood sugar levels. This phenomenon is just one way in which the field of eye care is expanding."

Dr. Rafieetary notes, however, that some of the proliferating methods for "measuring your vision at home" may not be designed with the health of the user in mind. "A few of these apps are designed to help people who have vision issues realize that they need to see a doctor," he says. "However, others are simply a way to bypass having a professional eye care provider re-examine your eyes when you need new prescription eyeglasses. They promote the idea of doing your refraction at home, picking your frame, measuring your pupillary distance and ordering your glasses without coming in to an office. They imply that you don't need an eye doctor. The idea that you should only 'see your eye doctor when you can't see' is a prescription for trouble—undetected glaucoma, undetected retinal disease and a long list of other problems.

"These tools, when clinically tested and applied appropriately, can

This article has no commercial sponsorship.

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

be aids for overall health care," he concludes. "But whether the majority of home vision-testing apps fall into that category is another question."

An accurate, easy-to-use home visual acuity test would clearly be useful, not only during the current pandemic but in the future as remote medical care becomes more common. With that in mind, here are profiles of three current options for home visual acuity testing that have some clinical trial data supporting their validity as a medical tool.

• ***The Home Acuity Test.*** The Home Acuity Test, or HAT (available at homeacuitytest.org) is an open-source visual acuity screening test designed at Moorfields Eye Hospital in London that can be downloaded from the internet free of charge and printed out by patients. A silhouette of a credit card is included on the printout to help patients confirm that the size of the image is correct. Each downloaded eye chart is unique, to prevent memorization of correct responses. (The software is designed to produce billions of unique charts.)

The HAT chart consists of 18 randomly selected Sloan letters displayed over five lines. The letters on each line are half the size of those in the line above, with two letters on the top line and four on each line below. From a distance of 150 cm, the largest letters subtend 1.3 logMAR (3/60); the smallest letters subtend 0.1 logMAR (6/7.5).

Researchers at Moorfields tested the accuracy of the chart on 100 ophthalmology outpatients with a wide range of eye problems (two-thirds women, average age 55 years), and 50 control subjects, in May of 2020.[3] All of the outpatient group reported subjectively stable vision. Patients were sent a 150-cm length of string to use to ensure the test was conducted at the correct distance from the chart.

Two tests were conducted, using different charts, to confirm repeatability. The tests were conducted by the patient during a phone call with a clinician, who recorded the number of letters correctly read. Because of COVID-19-related restrictions, the measurements taken by the outpatients were compared to their most recent previous standard in-clinic exam rather than to a newly performed in-clinic test.

> **"Many companies have created apps puportedly designed to [measure acuity] … However, these apps don't have to meet any legal or medical standards. The resulting plethora of options has been something resembling the Wild West."**

Among the outpatients testing themselves at home, the HAT results were one line worse, on average, than the previous in-clinic measurement. Among the control subjects, the measurements were, on average, between one and two lines worse than testing done with a standard clinic chart. The data showed that the test had high repeatability; between two consecutive tests, the mean difference in measured visual acuity was 0 letters.

The researchers concluded that the HAT could be a viable means of measuring visual acuity in patients unable to visit a clinic.

• ***The Peek (Portable Eye Examination Kit) Acuity app.*** This was developed by the International Centre for Eye Health in London; it tests distance visual acuity only. The test requires two people to complete, which could be a limitation for some patients who live alone. It's free, but only available on Android devices.

The Peek Acuity test measures visual acuity using the "tumbling E" format. It includes an interactive guide for users, explaining, among other things, how to calibrate the size and brightness of the optotypes. Scores are provided in Snellen units (metric, imperial or logMAR), but the app also creates a visual representation of the results that patients can readily understand. It's been clinically shown to produce accurate and repeatable measurements of distance acuity, comparable to measurements obtained through standard testing.

The developers tested the app on 233 elderly patients in private clinics and rural settings in Kenya, and found it to be accurate and repeatable in either situation.[4] Other studies found the app to be valid as a tool for school screening,[5-8] when used by nonophthalmic staff in an emergency room,[9] and when tested on Chinese and Australian individuals.[10]

Doctors can find more information about the Peek Acuity app at: peekvision.org/assets/Documents/July2020_PeekAcuity_remote_healthcare.pdf .

• ***OdySight.*** OdySight is a clinically validated app for remote vision monitoring designed by Tilak Healthcare in France, where it's available by prescription only. (The company recently signed an agreement with Novartis Pharmaceuticals to promote the app in the United States and around the world.) The name comes from the French word "odyssee"—"odyssey" in English. The app provides a mix of puzzles and vision tests (including an Amsler grid test) to encourage patient engagement.

Once the app is accessed, it uses a proprietary algorithm to calculate the distance between the patient's eye and the screen, as well as detecting the amount of ambient lighting. Distance to the eye is calculated using the patient's interpupillary distance, the size of the camera feed and current frame, and the camera

specs for the smartphone being used to conduct the test. A tutorial shows the patient how to do a test or puzzle.

The visual acuity test uses a tumbling E optotype; users indicates the orientation of the letter by sliding their finger in the same direction. Orientation and size of the letter changes after each response. If the patient doesn't respond (indicating inability to determine the orientation) the app presents a "not sure" button the user can tap. The first time each eye is tested, a longer sequence of tests establishes a baseline visual acuity; follow-up tests are shorter. At the end of a test, the app displays the user's score (for that test only).

A loss of five or more letters between visual acuity tests causes the app to prompt the patient to redo the test the following day. If the score is still the same (plus or minus two letters), both the patient and the doctor are notified of the change, and the user is asked to schedule a visit with the doctor. Test results automatically show up on the doctor's dashboard.

A clinical study was conducted by the company in conjunction with the University of Pittsburgh School of Medicine, and the Vision Institute and Quinze-Vingts National Eye Hospital, both located in Paris.[11] The study compared the test results to the gold standard tests for each variable tested (visual acuity, contrast sensitivity and Amsler grid). The data showed statistically significant agreement with gold-standard measurements of visual acuity in the majority of the test subjects. ◀

1. Aruljyothi L, Janakiraman A, Malligarjun B, Babu BM. Smartphone applications in ophthalmology: A quantitative analysis. Indian J Ophthalmol 2021;69:548-53.
2. Steren BJ, Young B, Chow J. Visual acuity testing for telehealth using mobile applications. JAMA Ophthalmol 2021;139:3:344-347.
3. Crossland MD, Dekker trabecular meshwork, Hancox A, et al. Evaluation of a home-printable vision screening test for telemedicine. JAMA Ophthalmol 2021;139:3:271-277.
4. Bastawrous A, Rono HK, Livingstone IA, Weiss HA, Jordan S, Kuper H. Development and validation of a smartphone-based visual acuity test (peek acuity) for clinical practice and community-based fieldwork. JAMA Ophthalmol 2015;133:930–7.
5. Brady CJ, Eghrari AO, Labrique AB. Smartphone-based visual acuity measurement for screening and clinical assessment. JAMA 2015;314:2682–3.
6. Dhanesha U, Polack S, Bastawrous A, Banks LM. Prevalence and causes of visual impairment among school children in Mekelle, Ethiopia. Cogent Med 2018;5:1554832.
7. Zhao L, Stinnett SS, Prakalapakorn SG. Visual acuity assessment and vision screening using a novel smartphone application. J Pediatr 2019;213:203–10.
8. Rono HK, Bastawrous A, Macleod D, Wanjala E, Di Tanna GL, Weiss HA, et al Smartphone-based screening for visual impairment in Kenyan school children: A cluster randomized controlled trial. Lancet Glob Health 2018;6:e924–32.
9. Pathipati AS, Wood EH, Lam CK, Sáles CS, Moshfeghi DM. Visual acuity measured with a smartphone app is more accurate than Snellen testing by emergency department providers. Graefe's Arch Clin Exp Ophthalmol 2016;254:1175–80.
10. Han X, Scheetz J, Keel S, Liao C, Liu C, Jiang Y, et al Development and validation of a smartphone-based visual acuity test (vision at home). Transl Vis Sci Technol 2019;8:27.
11. Brucker J, Bhatia V, Sahel JA, et al. Odysight: A mobile medical application designed for remote monitoring—a prospective study comparison with standard clinical eye tests. Ophthalmol Ther 2019;8:461-476.

REVIEW NEWS

Blood Pressure's Effect on Anti-VEGF Injections

Like macular degeneration, hypertension is a common problem among older adults. However, because the two so often coincide, it's unclear exactly how they may be related. A new study investigating these conditions and treatment strategies for wet AMD patients affected by hypertension might have found a particular way that the two conditions are associated.

The study included 3,096 wet AMD patients (58.3 percent male; aged 50 to 96) at a single center in China from 2002 to 2019. The researchers found a significant association between the two conditions and, after adjusting for sex and age, they reported a significant association between hypertension in wet AMD and the number of injections they received. Hypertension status wasn't significantly associated with need for vitrectomy.

"The reason why wet AMD patients with hypertension need more anti-VEGF treatment than those without hypertension may be that the renin-angiotensin-aldosterone system (RAAS) not only affects critical components of the heart and cardiovascular system, but also influences blood vessels in the retina," the researchers wrote in their paper. "Angiotensin 2 (Ang 2) caused apoptosis in retinal endothelial cells, which can cross the blood-retina barrier and support the development of choroidal neovascularization. Additionally Ang 2 can reduce the blood flow to the choroid by decreasing the diameter of retinal arterioles and capillaries. Moreover, Ang 2 upregulates VEGFR-2, which contributes to the development of choroidal neovascularization by destroying the balance of antiangiogenic and angiogenic factors."

The team believes that RAAS hyperactivity, which promotes inflammation resulting in macrophage infiltration that induces CNV, may aggravate wet AMD progression, requiring greater need for those with hypertension to receive anti-VEGF treatments.

The researchers concluded that hypertension was significantly correlated with wet AMD. After a regular series of three anti-VEGF injections, wet AMD patients with hypertension were more likely to receive anti-VEGF injections than those without hypertension. "These results may facilitate prospective research on the prevention of wet AMD and contribute to the management of wet AMD patients," the researchers wrote. ◀

Wang T, Xia J, Yuan M, et al. Hypertension affects the treatment of wet age-related macular degeneration. Acta Ophthalmologica. March 31, 2021. [Epub ahead of print].

UPLIFTED

Give Ptosis Patients an EYE-OPENING Lift With a Daily Drop of Upneeq® (oxymetazoline hydrochloride ophthalmic solution), 0.1%[1]

The only FDA-approved prescription eyedrop proven to lift upper eyelids in adults with acquired blepharoptosis (low-lying lids)[1]

Learn more at Upneeq.com.

INDICATION

Upneeq® (oxymetazoline hydrochloride ophthalmic solution), 0.1% is indicated for the treatment of acquired blepharoptosis in adults.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

DRUG INTERACTIONS

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

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

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

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

RVL PHARMACEUTICALS, INC.

Distributed by: RVL Pharmaceuticals, Inc.
Bridgewater, NJ 08807
Customer Service 1-866-600-4799

PM-US-UPN-0197 01/21

Learn more at Upneeq.com

UPNEEQ®
(oxymetazoline hydrochloride ophthalmic solution), 0.1%*

*Each mL of Upneeq contains 1 mg of oxymetazoline hydrochloride, equivalent to 0.9 mg (0.09%) of oxymetazoline free base.

Eye-Opening Possibilities

UPNEEQ® (oxymetazoline hydrochloride ophthalmic solution), 0.1%,* for topical ophthalmic use

*Each mL of UPNEEQ contains 1 mg of oxymetazoline hydrochloride, equivalent to 0.9 mg (0.09%) of oxymetazoline free base.

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

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

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

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Potential Impacts on Cardiovascular Disease

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

5.2 Potentiation of Vascular Insufficiency

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

5.3 Risk of Angle Closure Glaucoma

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

5.4 Risk of Contamination

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

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

7 DRUG INTERACTIONS

7.1 Anti-hypertensives/Cardiac Glycosides

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

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

7.2 Monoamine Oxidase Inhibitors

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

Data

Animal Data

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

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

10 OVERDOSAGE

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

PATIENT COUNSELING INFORMATION

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

RVL PHARMACEUTICALS, INC.

Manufactured for: RVL Pharmaceuticals, Inc.
Bridgewater, New Jersey 08807

PM-US-UPN-0203 01/21

All for One And One for All

Musings on life, medicine and ophthalmology.

BY MARK H. BLECHER, MD
CHIEF MEDICAL EDITOR

Happy spring! Finally. For much of the country, this was a very rough winter. And I'm not just talking about the weather. As many reputable experts predicted as far back as a year ago, this past winter was the worst of the pandemic. And the cold days and long nights made it seem even more depressing. A combination of good luck, delayed arrival of more infectious variants, and widespread (but inconsistent) public health measures provided a somewhat surprising, but welcome, decline in COVID cases from the peak in January.

But where do we go from here? As a country, as a community, as a profession? Clearly the answer is vaccination, as imperfect as that may be. And by the time this issue hits your desks I'm anticipating that over half the country will have gotten at least one vaccination. We've already seen very notable drops in mortality, having first protected the elderly and infirm with vaccine. I'm hoping that our overall numbers will drop as well, since it's become pretty apparent that long-term sequalae of COVID are not infrequent, even for the young and healthy.

If vaccination is the path to 'normalcy', then how do we get everyone vaccinated? We're finally at the point where there is more than enough vaccine in the United States, but there are still sizable populations who don't want to get the shot. In March, almost half of our active military troops declined the vaccine.

There's an active antivaxxer movement that found new life in refuting the science of COVID vaccines, and a variety of demographic groups that, for a variety of reasons, are digging their heels in. So far, with exceptions, there's no requirement to get a vaccine. But should there be? And if so, for whom?

It seems clear to me that, rightly or wrongly, in the United States we won't be able to mandate the vaccine. But, as with the flu shot, are some groups/work categories so critical that they must receive it? There's a precedent for this, with the mandate that health-care workers of all stripes be vaccinated for flu, measles, etc. Can we—should we—do that for the COVID vaccine as a condition for them to keep their jobs? How about flight attendants? Restaurant workers? Things get complicated then. Legally, employers do have the right to require vaccinations as a condition of employment, but as I know first-hand from managing my practice, it can entail some unpleasant conversations.

I believe that with a combination of education, encouragement, incentives and coercion, we'll get the vaccinated percentage of our population quite high. Will it be high enough, though? And what do we do with the unvaccinated? I would like to say leave them be. Those who wish to protect themselves, can. Those who don't can take their chances. But should they be spared from the consequences of their decision, such as being fired from their jobs, being denied boarding on airplanes, or being turned away from concerts? Should we as a society subsidize their health-care costs if they fall ill?

As gratifyingly Old Testament as my response sounds, there are those pesky public-health considerations. The more COVID is still circulating, the greater the likelihood that variants will arise and the greater the risk that even the vaccinated will no longer be protected. For those espousing an individual's right to not be vaccinated, that decision has implications for all of society. In a planet as overpopulated and connected as ours, John Donne's famous quote, "No man is an island," is truer now than when he wrote it 400 years ago. ◀

This article has no commercial sponsorship.

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

WHAT COULD SHE SEE THIS YEAR?

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

Inspired by a real patient with DME.

375 MATH TESTS

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

REGENERON

EYLEA ACHIEVED RAPID, SUSTAINED OUTCOMES IN DME

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

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

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

P<0.01 vs control at Year 1.

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

INDICATIONS

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

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

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

04/2021
EYL.21.03.0211

EYLEA® (aflibercept) Injection
For Intravitreal Injection

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

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

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

4 CONTRAINDICATIONS

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

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

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

5 WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

REGENERON

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

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

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

EYL.20.09.0052

Screening Refractive Surgery Patients

How to use personality profiling and counseling to minimize unhappy postop patients in this era of COVID-19.

ROHIT SHETTY, DNB, FRCS, PHD
POOJA KHAMAR, MS, FCRS, PHD
SNEHA SENGUPTA, MS, DNB
BANGALORE, INDIA

In our daily refractive surgery practice, we often encounter patients who are unhappy after refractive surgery, despite having undergone uneventful procedures and achieved a best corrected visual acuity of 20/20. This has led us on a quest to identify a common cause of these patients' dissatisfaction. We found ourselves exploring the link between patients' responses to refractive surgery and their personalities, as has been done in other research.[1] The research question we posed was this: Is there a relationship between a patient's personality and his or her postop treatment outcomes in the post-COVID era?

In this report, we'll discuss the findings of our research, which has improved the way we preoperatively and postoperatively manage patients with different personality types. We hope you'll gain insights that will help you incorporate similar refinements in your practice.

Step One: Initial Screening

Our institution, the Narayana Nethralaya Hospital in Bangalore, India, performs 500 refractive surgery procedures each month. We have two operating surgeons and 30 other staff members. Patients come to us from all over India and other parts of the world. This study, conducted between 2018 and 2019, involved 200 patients. Here's how we set it up:

After performing a vision assessment, detailed ocular examination, corneal topography and aberrometry, we asked each preop patient in the study to complete an Eysenck Personality Inventory. The EPI is a validated 57-item (yes/no format) questionnaire designed to measure two pervasive, independent dimensions of personality—extroversion/introversion and neuroticism/stability—that account for most of the variance among people's personalities.[2] We asked patients to fill out a hard copy of the questionnaire on the day they came in for their surgeries; it took seven to eight minutes to complete. The EPI, available at simplypsychology.org/eysenck-inventory.pdf), can be directly administered online at iluguru.ee/test/eysencks-personality-inventory-epi-extroversionintroversion or it can be printed out for patients to complete with a pen or pencil.

Based on the EPI scores we gathered, we categorized patients along two axes—ranging from extroverted to introverted on one axis and from stable to unstable/neurotic on the other axis. Additionally, as presented in Figure 1 on page 33, we placed patients in one of the following subgroups:

- ***sanguine*** (optimistic), 57 patients, ranging from stable to extroverted;
- ***phlegmatic*** (stolid), 86 patients, ranging from stable to introverted;
- ***melancholic*** (pensive, sad), 44 patients; ranging from unstable/neurotic to extroverted; and
- ***choleric*** (irritable, unreliable), 13 patients, ranging from unstable/neurotic to extroverted.

The EPI also produced a so-called "falsification score" that proved valuable in evaluating the surgical readiness of patients. A score of 5 to 9 in the questionnaire results revealed patients who were likely not completely honest because they were trying to present themselves in a way that they believed would make a positive impression on the surgeons and clinical team. This falsification characteristic was identified both in patients who weren't fully aware of their deceptive communication and in those with psychological issues who were best described as mendacious (consciously falsifying information).

Step 2: Postop Evaluation

All 200 patients underwent uneventful refractive surgery, including LASIK (120 procedures), SMILE (60 procedures) and flapless, transepithelial-PRK (40 procedures). We assessed all patients at one month and six months postop and determined that their clinical findings were virtually the same during both visits. (*See Figure 2 on page 33 for an overview of patient recruitment, preop assessment and personality assessment.*)

Postop evaluation included vision assessments, detailed ocular exams, orthoptic assessments and aberrometry. All of the patients emerged from

This article has no commercial sponsorship.

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

OCULAR SYMPTOMS & MOOD DISORDER-RELATED ISSUES

Patient type	Ocular symptoms linked to pathology	Ocular complaints absent pathology	Mood disorder-related complaints
Phlegmatic (n=12)	50%	42%	8%
Sanguine (n=3)	100%	0%	0%
Melancholic (n=23)	22%	48%	30%
Chloleric (n=8)	13%	38%	50%

surgery with 20/20 Snellen vision. None had evidence of dry eye or orthoptic abnormalities, and all of the postop patients were advised to seek annual follow-up visits.

During both the one-month and six-month follow-up visits, the patients were also asked to take five minutes to complete a 20-item, Quality of Life Impact of Refractive Correction questionnaire, designed to measure the quality of life of presbyopes who require optical correction by spectacles, contact lenses or refractive surgery. The QIRC questionnaire, which has broad applicability for cross-sectional and outcomes research, was developed using Rasch analysis and has been shown to be valid and reliable.[3]

The resulting QIRC scores, determined to be statistically significant (p<0.000001), were correlated by our team with the patients' personalities to try to determine if their personalities had any effect on their QIRC scores. Discernible patterns did arise. The mean QIRC scores were as follows, with higher scores reflecting a more positive outcome:

- phlegmatic patients: 54.11 (ranging from 53.66 to 54.70);
- sanguine patients: 52.60 (ranging from 51.5 to 53.60);
- melancholic patients: 44.57 (ranging from 43.89 to 46.44); and
- choleric patients: 39.20 (ranging from 35.70 to 41.10)

We found no variation in QIRC results based on surgical modality (trans-PRK, LASIK and SMILE). The most compelling finding was that the choleric patients experienced a significantly poorer quality of life related to vision compared to the three other patient types after surgery. We also evaluated an association of mood disorder complaints and ocular symptoms in patients who presented with and without accompanying ocular pathologies. We found that:

- ***choleric*** patients reported significantly higher mood disorder complaints than melancholic, phlegmatic and sanguine patients;
- ***melancholic*** patients predominantly included those reporting ocular symptoms that weren't associated with pathology or high mood disorders; and
- ***phlegmatic*** and ***sanguine*** patients had limited ocular symptoms that were associated with some pathology.

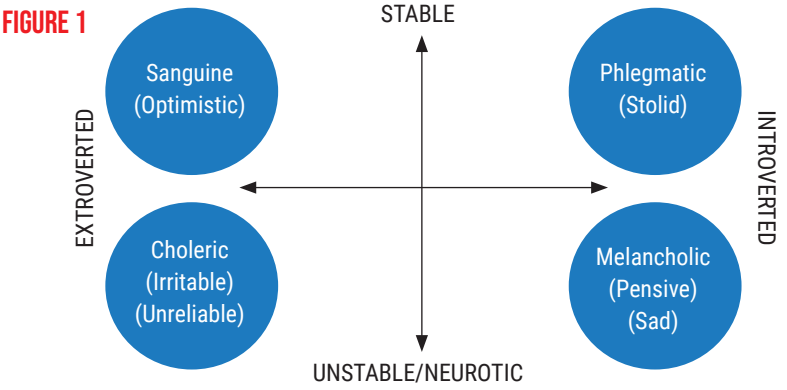
The pattern—rather than the number—of reports was notable. "*See Ocular Symptoms & Mood Disorder-Related Issues*" above.

Step 4: A New Workflow

As a result of our findings, we created a new workflow, which we've followed since late 2019. Our goal is to increase patients' satisfaction after refractive surgery. Below is the approach we now take at our hospital:

1. Patients come in to undergo a preop evaluation for refractive surgery.
2. Hospital staff members raise a "red flag" if refractive surgery candidates exhibit unusual behaviors, body language or interactions with other people. For example, the way they speak, the continuity in their thoughts, their maintenance of eye contact, their way of dressing, their interpersonal relationships and their history of recent emotional adversity may be worth noting.
3. All preop patients, including those who prompt our staff to raise "red flags," are required to complete the EPI.
4. All patients are referred with their EPI results to their primary care doctor for guidance on surgical fitness and related issues. The phlegmatic and the sanguine personality types are advised to proceed with refractive surgery. Melancholics are managed with precautions, including the administration of counseling for the patient and his or her relatives.
5. The patients who are identified as choleric are recognized as potentially having mental illness. They're required to undergo psychological assessments and thorough counseling for three months before they're considered for refractive surgery. At the time of surgery, the patients' families or significant others are kept informed about their condition and are thoroughly educated on the prognosis of the surgery.
6. The melancholics may be flagged because of abnormal behavior or communication, such as being

FIGURE 1



NO PAZEO*? NO PROBLEM!

For ocular itch associated with allergic conjunctivitis

INITIATE ZERVIATE®

Choose the topical prescription treatment that delivers the proven power of cetirizine (active ingredient in ZYRTEC*)[1]

- Provides fast-acting, long-lasting relief that lubricates with every drop[2,3]
- Covered on most commercial and Medicare Part D plans

Available by prescription only

Formulated with HYDRELLA™ for comfort.[1]
Visit **MyZERVIATE.com** for more information.

INDICATIONS AND USAGE

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

IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

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

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

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

eyevance pharmaceuticals

ZERVIATE™ (cetirizine ophthalmic solution) 0.24%

Brief Summary

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

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

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

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

ADVERSE REACTIONS

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

Data

Animal Data

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

Lactation

Risk Summary

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

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

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

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

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

Mutagenesis

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

Impairment of Fertility

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

PATIENT COUNSELING INFORMATION

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

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

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

Storage of Single-use Containers:
Instruct patients to store single-use containers in the original foil pouch until ready to use.

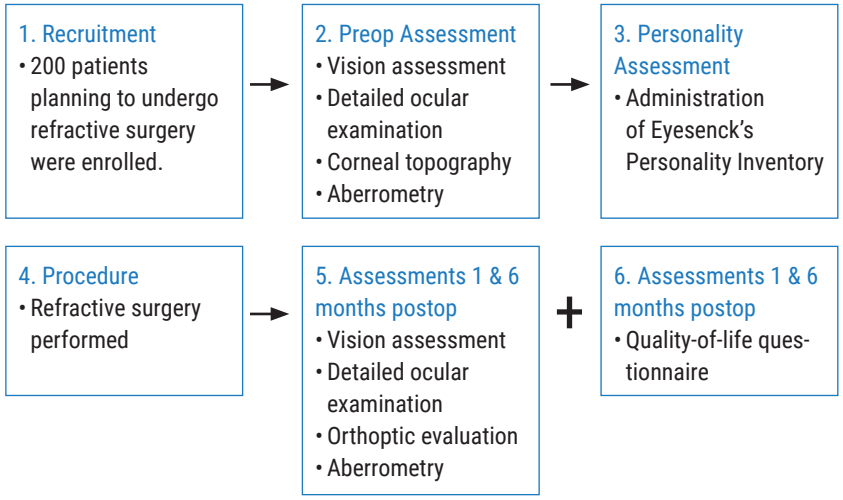
Rx Only

Distributed by: Eyevance Pharmaceuticals LLC. Fort Worth, TX 76102

eyevance® pharmaceuticals

ZER-04-20-MS-44

FIGURE 2: EVALUATING EFFECTS OF PERSONALITY ON REFRACTIVE SURGERY



introverted or depressed. Close observation may associate them with difficult behavior or negative comments and thoughts. They don't necessarily have to be referred for psychological treatment. Instead, we counsel these patients and their relatives and, if we identify potential psychological issues, we postpone the surgery for three months. Patients, relatives and possibly the patients' friends are asked to sign a consent form that confirms among all parties their shared understanding of the prognosis of patients after refractive surgery.

7. Patients who have registered a falsification score of five or more are excluded from surgery and referred to a psychologist.

Step 5: Applying Pandemic-Learned Principles

How might our research and the implementation of our new workflow relate to COVID-19? Consider this: During the COVID-19 lockdown, many individuals across the globe experienced tremendous degrees of stress of one form or another, such as loss of employment, risks to the safety of themselves and their families, fear of infection by the virus, financial instability, isolation, working alone and remotely and loss or shutdown of their businesses. These factors all have the potential to negatively affect mental health, which has already been shown to have been influenced by the pandemic.[4-7]

We're only beginning to document and understand the effects of the pandemic on mental health, including how pervasive these mental health effects may be and how long they may persist. Based on our experiences with some of the patients in our research, we believe the pandemic will likely play a role in our patients' responses to refractive surgery for the indefinite future, suggesting a need for all refractive surgeons to be aware of the potential for a pandemic-related impact on their practices. Affected patients may present to us with certain unusual, non-optical complaints which we've documented, despite ocular examination findings within normal limits.

It's because of our experience and our reflection on the current environment that we have incorporated the EPI questionnaire into the routine care we provide all of our patients, not just the ones whose behavior raises red flags.

Consistent with the effects of stress and anxiety associated with the pandemic, we've documented a greater proportion of melancholic and choleric patients who have presented with nonspecific body and eye pain, inability to concentrate and complaints related to mood disorder. Patients who have blamed these symptoms on the effects of refractive surgery have been found to be susceptible to the stress, anxiety and mood disorders that have been exacerbated by the pandemic. Both phlegmatic and sanguine patients have reported these symptoms, but the phlegmatic patients report them in a higher concentration. Ocular symptoms not related to any pathology have required appropriate management and counseling.

Many mental health centers have reached out to people with these issues. As clinicians, we feel a responsibility to do the same. The result of our efforts will be the provision of more support for patients in need, but also a protocol that'll ensure a higher percentage of our refractive surgery patients walk away from our operating room stress-free and happy. ◀

1. Kerry K, Giedd JK, Mark J, et al. Personality in keratoconus in a sample of patients derived from the internet. Cornea 2005;24:3:301-7.
2. Nada Pop-Jordanova N, Ristova J, Loleska S. The Eysenck Personality Profile in selected groups of ophthalmological patients. Pril 2019:40:2:41-49.
3. Pesudovs K, Garamendi E, Elliott DB. The Quality-of-Life Impact of Refractive Correction (QIRC) Questionnaire: Development and validation. Optom Vis Sci 2004;81:10:769-77.
4. Heitzman J. Impact of COVID-19 pandemic on mental health. Psychiatr Pol 2020:54:2:187-198.
5. Fiorillo A, Gorwood P, The consequences of the COVID-19 pandemic on mental health and implications for clinical practice. Eur Psychiatry 2020;63:1:e32.
6. Hossain MM, Samia Tasnim S, Abida Sultana A, et al. Epidemiology of mental health problems in COVID-19: A review. SF1000Res 2020;9:636.
7. Czeisler ME, Lane RI, Wiley JF, et al. Follow-up survey of US adult reports of mental health, substance use and suicidal ideation during the COVID-19 pandemic, September 2020. JAMA netw Open 2021;4:2.

ABOUT THE AUTHORS



Dr. Shetty is a clinical and translational scientist at Narayana Nethralaya, Bangalore, India, and a member of the faculty in the department of ophthalmology, University of Maastricht, Maastricht, Netherlands. **Dr. Khamar** is a clinical and translational scientist and cataract and refractive surgeon at Narayana Nethralaya. She's also a member of the faculty in the department of ophthalmology, University of Maastricht. **Dr. Sengupta,** serves in cataract and refractive services, optics and clinical research at Narayana Nethralaya. **Drs. Shetty, Khamar and Sengupta** report no relationships with companies that make products mentioned in this article.

TREATING UVEITIS, 2021: THE STATE OF THE ART

Our understanding of this disease and tools for managing it continue to evolve. Clinicians offer an update.

BY CHRISTOPHER KENT
SENIOR EDITOR

Like many ophthalmic problems, uveitis can be a challenge for clinicians. It has numerous possible etiologies that require different treatment approaches, and every patient is unique; there's currently no way to be sure how the patient seated in front of you will react to a given treatment. The practical result is that addressing uveitis requires a lot of trial and error, ruling out possible causes to avoid inappropriate treatment, and then working your way through a series of options to find the right treatment—or combination of treatments—that will bring your patient relief and preserve vision.

Here, surgeons with extensive experience managing these patients offer their advice.

Ruling Out Infection

Surgeons agree that the first step in addressing uveitis is determining the cause of the problem. "One reason that managing uveitis is challenging is that up to half of the cases are idiopathic," notes Priya Janardhana, MD, director of the uveitis service and an assistant professor of ophthalmology at the University of Massachusetts Medical School in Worcester. "However, we know that uveitis can be caused by autoimmune disease or infectious disease, so it's important to test patients for these. It's especially important to rule out infectious causes, because if there's an infection, we need to treat that before putting a patient on immunosuppressive medications.

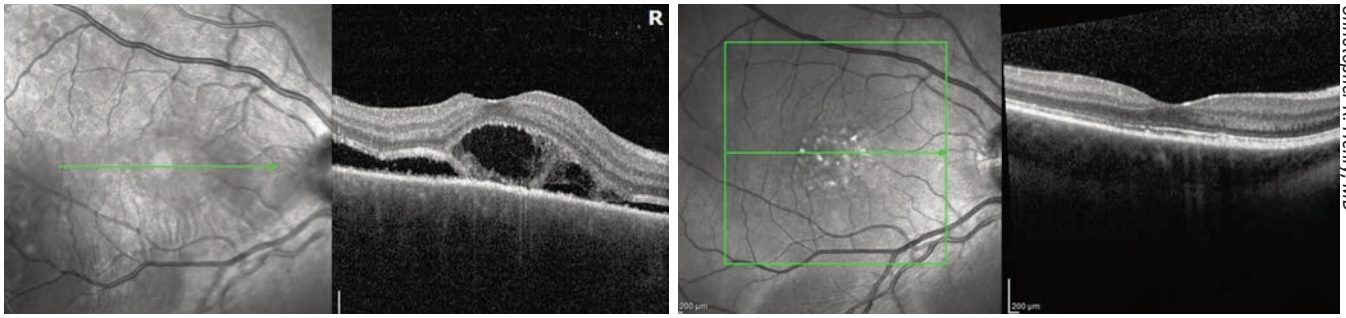
"In particular, we have to order tests to rule out sarcoidosis, tuberculosis and syphilis—the 'masqueraders of the eye'—in every patient," she says. "I order syphilis testing, both treponemal and nontreponemal testing; quantiferon—PPD is OK—to rule out TB; sarcoidosis labs, both ACE and lysozyme; and a chest X-ray. Then, I order a number of panels to look for autoimmune inflammatory markers. Which specific ones I order will depend on whether the uveitis is anterior, posterior or panuveitis." Dr. Janardhana adds that it's OK to start the patient on topical steroid drops while waiting for the lab results to come in.

Pauline T. Merrill, MD, a partner at Illinois Retina Associates and an associate professor of ophthalmology at Rush University in Chicago, agrees that the most important thing a clinician should do after discovering uveitis is make 100-percent certain that the uveitis is noninfectious. "This requires a lab workup," she says. "There's no way anyone can be certain whether or not the uveitis is infectious just by looking. As a rule of thumb, you should assume it could be syphilis or TB until proven otherwise."

Dr. Merrill notes that, in some cases, you may be able to identify viral uveitis via a thorough exam. "Always do a complete eye exam before you start thinking about treatment, and be sure to consider viral uveitis," she says. "A mild iritis in a patient with a history of herpetic infection might respond to topical treatment; but only by dilating and doing a full exam can you make sure that you're not missing retinitis that could blind the patient if not treated promptly. Clinical signs can be fairly characteristic for some viral presen-

This article has no commercial sponsorship.

Dr. Merrill is a consultant to Santen and Gilead, and has received study support from Santen, Roche, Clearside and Gilead. **Dr. Henry** is a consultant for Clearside Biomedical and Bausch + Lomb. **Dr. Janardhana** reports no financial disclosures relevant to this topic.



Christopher R. Henry, MD

Left: A 43-year-old female diagnosed with Vogt-Koyanagi-Harada disease, pretreatment. Right: After tapering a course of oral prednisone as a bridge to treatment with monthly Remicade infusions and weekly methotrexate.

tations such as acute retinal necrosis, but I still often confirm that with PCR testing—in addition to testing for syphilis, of course."

Dr. Merrill adds that another masquerader you need to consider is intraocular lymphoma, particularly in older patients. "Intraocular lymphoma is rare, but it's important to rule it out as a cause of vitritis in patients over 50," she explains.

"The point," she says, "is that although most uveitis won't turn out to be infectious or intraocular lymphoma, the few patients that do have these conditions are the patients who may go blind or worse without proper treatment. That's why you should always consider the worst possible scenario before deciding how to proceed."

Treating with Topical Steroids

"Once you're sure you're dealing with a noninfectious process, your treatment paradigm depends on three things," says Christopher R. Henry, MD, a fellowship-trained vitreoretinal surgeon and uveitis specialist who practices at Retina Consultants of Texas, and a clinical assistant professor of ophthalmology at the Houston Methodist Institute for Academic Medicine. "First is chronicity: Has this been a chronic process or an acute process? Second is severity. Is this vision-threatening, or not too severe? Third is bilaterality: Is this a one-eye or two-eye process? If it's mild, isolated acute uveitis, you can often manage that with topical or local therapy. If it's chronic, severe, bilateral uveitis you'll often have to resort to systemic therapy."

"I typically start with topical steroids while I'm waiting for the lab results," says Dr. Merrill. "This does a couple of things. First, it may help treat whatever anterior component of the uveitis is present. Durezol (difluprednate ophthalmic emulsion) can also penetrate posteriorly. Second, how the patient's IOP reacts may give you an idea of whether the patient is a steroid responder. If the pressure goes through the roof on prednisolone four times a day for a few weeks, you'll think twice before giving that patient a steroid injection."

Once infection has been ruled out, Dr. Janardhana also starts the patient on steroids. She explains that her protocol—particularly choosing oral steroids vs. topical drops—is based on numerous factors. "If I only find anterior involvement, or anterior and intermediate involvement, I typically start the patient on just a topical steroid drop such as prednisolone, plus a cycloplegic drop," she says. "Durezol is a really good medication for anterior and intermediate uveitis. It has very good penetration to the posterior part of the eye. So, for patients who have contraindications to systemic steroids, such as a brittle diabetic patient, this would be a good option. However, it's important to monitor intraocular pressure carefully and warn patients of the risk of cataract formation with long-term use."

Steroids Into the Eye

If topical drops are insufficient, most surgeons move on to either systemic steroid treatment or steroid injections into the eye. The latter can be done directly, or via an implant that will deliver a steroid slowly over an extended period.

Dr. Merrill says that what she does after steroid drops depends on the situation. "If the patient just has mild anterior uveitis, drops might be all the patient needs," she explains. "In that case, you treat intensively at first and then taper slowly. However, a lot of patients don't improve significantly with topical steroids in a short period of time, or they have more posterior involvement. Those patients will benefit from either local injections or systemic treatment."

Dr. Janardhana explains that there are several situations in which she might offer steroid injections into the eye. "I may offer the option of a short- or long-acting periocular or intravitreal steroid injection to a patient with unilateral noninfectious uveitis who hasn't been on oral steroids," she says. "However, I wouldn't inject Ozurdex or Triesence into the eye without knowing first whether the patient is a steroid responder, so before I do an injection I always start the patient on topical steroid drops, like prednisolone or Durezol. I've seen patients receive an Ozurdex injection without having used topical drops first, and then develop steroid-induced ocular hypertension, and in extreme cases need glaucoma surgery.

MANAGING INFECTIOUS FORMS OF UVEITIS

Christopher R. Henry, MD, a fellowship-trained vitreoretinal surgeon and uveitis specialist who practices at Retina Consultants of Texas, says the mainstays of treatment for infectious uveitis haven't changed. "We direct the treatment based on the infectious organism," he says. "If it's syphilis, the patient gets IV penicillin; if it's herpes or shingles, they get valacyclovir; and so on. You verify the infection with either systemic lab serology or—sometimes—direct ocular cultures. Then you tailor your treatment to the organism."

"If the uveitis is infectious, whether viral, bacterial or fungal, we treat with the appropriate antiviral, antibacterial or antifungal medication," says Priya Janardhana, MD, director of the uveitis service and an assistant professor of ophthalmology at the University of Massachusetts Medical School in Worcester. "However, even after treating with the appropriate medication you'll often still have inflammation that needs to be addressed. If there's still a lot of inflammation after 48 hours, I start the patient on oral prednisone—as long as there's good coverage with an antibiotic or antiviral. This is a balancing act; we don't want to encourage the infection by suppressing the immune system, but the body's immune system is creating all of this inflammation with its immune cells trying to fight the infection, and that's what's actually causing the damage. So we use prednisone to control that aspect of the process while the antibiotic or antiviral is controlling the infection."

"Some of the more interesting things on the horizon for infectious uveitis are in the area of diagnostics," notes Dr. Henry. "Right now it's pretty easy to run multiplex PCR to detect viruses like herpes, shingles and cytomegalovirus. But bacterial and fungal cultures traditionally have been done using standard culture plates. It's currently possible to get bacterial and fungal PCR sequencing through labs such as the University of Washington, but it can be a difficult test to order, and there can be a several-week timeframe to obtain results. In the not-too-distant future, we hope to have more easily accessible PCR tests that can do pan-bacterial and pan-fungal testing, in addition to pan-viral testing."

—CK

"Also," she adds, "if a patient is taking oral steroids, depending on the type of inflammation and uveitis the patient has, I watch to see if the inflammation comes back as I'm tapering. If it does, I tell the patient that we have to think about systemic therapy, or potentially a steroid injection into the eye."

Dr. Merrill offers an overview of the steroid-eluting implants. "Starting in 2005 we had the Retisert fluocinolone surgical implant," she says. "Today we have the Yutiq fluocinolone injectable implant and the Ozurdex dexamethasone implant. Retisert is still useful in some cases, but the patient has about a 30-percent chance of needing glaucoma surgery after a Retisert implant. The Yutiq implant releases fluocinolone at a significantly lower rate, which translates to less risk for the patient; the risk of needing glaucoma surgery at three years is around 5 percent with Yutiq. Of course, the flip side is that it's not as strong, so patients may continue to need other treatments as well, but hopefully with fewer severe flare-ups of the inflammation."

Of the implant options, Dr. Janardhana says she's used Ozurdex the most. "Ozurdex is great for patients who, for various reasons, might not want to start immunosuppressive therapy, or might have contraindications to doing so," she explains. "In my experience, the benefits of Ozurdex typically last three to six months, depending on the patient. I use it in patients with noninfectious uveitis who otherwise can't tolerate systemic therapy. I also use it as a bridge medication to help a patient with chronic uveitis who's starting systemic immunosuppressive therapy, because the systemic immunosuppressive therapy can take months to kick in. The injection helps get them through that initial period."

Dr. Henry says he also tends to use Ozurdex more often than the other options. "Sub-Tenon's Kenalog injections usually last a bit longer—six to 12 months," he notes. "I use this approach if it's worked for the patient in the past, or if I want a longer duration of action than I get with Ozurdex. Yutiq can last up to two and a half years; I typically reserve it for patients who've responded well to several Ozurdex injections. Yutiq may not be as potent as Ozurdex, but it can evoke a longer response without the need for so many injections. Retisert, the surgical implant, can last up to five years. Some doctors also use intravitreal Triesence."

Retisert, appears to have become less popular with the advent of the newer, nonsurgical options. "For the right patient, Retisert can still be an excellent choice, although I don't do very many of them," Dr. Henry notes. "The issues with Retisert are, first, that it can be difficult to get insurance to approve it because it's so expensive; and second, the patient is virtually guaranteed to end up with a cataract—assuming they haven't already had cataract surgery—and very likely to develop glaucoma. That means the patient has to be prepared for possibly needing both cataract and glaucoma surgery in the future. So if you go with Retisert, you're going with what I call the 'bionic eye' approach [treatment options that may cause changes inside the eye]."

Clinical Trial Findings

Clinical trial data has shed some light on the comparative risks and benefits of the options. "The POINT study from the MUST clinical trial group compared three current options for treating macular edema due to uveitis," says Dr. Merrill. "It was a six-month study comparing sub-Tenon's triamcinolone (Kenalog), intravitreal triamcinolone

Discover continuous calm in uveitis

YUTIQ® (fluocinolone acetonide intravitreal implant) **0.18 mg:**

- **Proven to reduce uveitis recurrence at 6 and 12 months[1]***
  [At 6 months–18% for YUTIQ and 79% for sham for study 1 and 22% for YUTIQ and 54% for sham for study 2 (*P*<.01). At 12 months–28% for YUTIQ and 86% for sham for study 1 and 33% for YUTIQ and 60% for sham for study 2.]
- **Innovative Durasert® technology is designed for a sustained release of fluocinolone acetonide for up to 36 months with just 1 YUTIQ implant[2]**

For more information, visit **YUTIQ.com**

J code: J7314

Now With a Siliconized Needle

*Study design: The efficacy of YUTIQ was assessed in 2 randomized, multicenter, sham-controlled, double-masked, phase 3 studies in adult patients (N=282) with noninfectious uveitis affecting the posterior segment of the eye. The primary endpoint in both studies was the proportion of patients who experienced recurrence of uveitis in the study eye within 6 months of follow-up; recurrence was also assessed at 12 months. Recurrence was defined as either deterioration in visual acuity, vitreous haze attributable to noninfectious uveitis, or the use of prohibited medications.[1,3]

INDICATIONS AND USAGE

YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg is indicated for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Ocular or Periocular Infections: YUTIQ is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases.

Hypersensitivity: YUTIQ is contraindicated in patients with known hypersensitivity to any components of this product.

WARNINGS AND PRECAUTIONS

Intravitreal Injection-related Effects: Intravitreal injections, including those with YUTIQ, have been associated with endophthalmitis, eye inflammation, increased or decreased intraocular pressure, and choroidal or retinal detachments. Hypotony has been observed within 24 hours of injection and has resolved within 2 weeks. Patients should be monitored following the intravitreal injection.

Steroid-related Effects: Use of corticosteroids including YUTIQ may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

Risk of Implant Migration: Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

ADVERSE REACTIONS

In controlled studies, the most common adverse reactions reported were cataract development and increases in intraocular pressure.

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

References: 1. YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg full U.S. Prescribing Information. EyePoint Pharmaceuticals, Inc. October 2018. **2.** EyePoint Pharmaceuticals Receives FDA Approval of YUTIQ™ (fluocinolone acetonide intravitreal implant) 0.18 mg. Global Newswire. https://www.globenewswire.com/news-release/2018/10/15/1621023/0/en/EyePoint-Pharmaceuticals-Receives-FDA-Approval-of-YUTIQ-fluocinolone-acetonide-intravitreal-implant-0-18-mg.html. Accessed February 7, 2020. **3.** Data on file.

EyePoint PHARMACEUTICALS

480 Pleasant Street, Suite B300, Watertown, MA 02472

02/2021
US-YUT-2100009

YUTIQ™ (fluocinolone acetonide intravitreal implant) 0.18 mg, for intravitreal injection
Initial U.S. Approval: 1963

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

1. INDICATIONS AND USAGE. YUTIQ™ (fluocinolone acetonide intravitreal implant) 0.18 mg is indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

4. CONTRAINDICATIONS. 4.1. Ocular or Periocular Infections. YUTIQ is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases. **4.2. Hypersensitivity.** YUTIQ is contraindicated in patients with known hypersensitivity to any components of this product.

5. WARNINGS AND PRECAUTIONS. 5.1. Intravitreal Injection-related Effects. Intravitreal injections, including those with YUTIQ, have been associated with endophthalmitis, eye inflammation, increased or decreased intraocular pressure, and choroidal or retinal detachments. Hypotony has been observed within 24 hours of injection and has resolved within 2 weeks. Patients should be monitored following the intravitreal injection *[see Patient Counseling Information (17) in the full prescribing information]*. **5.2. Steroid-related Effects.** Use of corticosteroids including YUTIQ may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection. **5.3. Risk of Implant Migration.** Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

6. ADVERSE REACTIONS. 6.1. Clinical Studies 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. Adverse reactions associated with ophthalmic steroids including YUTIQ include cataract formation and subsequent cataract surgery, elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. Studies 1 and 2 were multicenter, randomized, sham injection-controlled, masked trials in which patients with non-infectious uveitis affecting the posterior segment of the eye were treated once with either YUTIQ or sham injection, and then received standard care for the duration of the study. Study 3 was a multicenter, randomized, masked trial in which patients with non-infectious uveitis affecting the posterior segment of the eye were all treated once with YUTIQ, administered by one of two different applicators, and then received standard care for the duration of the study. Table 1 summarizes data available from studies 1, 2 and 3 through 12 months for study eyes treated with YUTIQ (n=226) or sham injection (n=94). The most common ocular (study eye) and non-ocular adverse reactions are shown in Table 1 and Table 2.

Table 1: Ocular Adverse Reactions Reported in ≥ 1% of Subject Eyes and Non-Ocular Adverse Reactions Reported in ≥ 2% of Patients

Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Cataract[1]	63/113 (56%)	13/56 (23%)
Visual Acuity Reduced	33 (15%)	11 (12%)
Macular Edema	25 (11%)	33 (35%)
Uveitis	22 (10%)	33 (35%)
Conjunctival Hemorrhage	17 (8%)	5 (5%)
Eye Pain	17 (8%)	12 (13%)
Hypotony Of Eye	16 (7%)	1 (1%)
Anterior Chamber Inflammation	12 (5%)	6 (6%)
Dry Eye	10 (4%)	3 (3%)
Vitreous Opacities	9 (4%)	8 (9%)
Conjunctivitis	9 (4%)	5 (5%)
Posterior Capsule Opacification	8 (4%)	3 (3%)
Ocular Hyperemia	8 (4%)	7 (7%)
Vitreous Haze	7 (3%)	4 (4%)
Foreign Body Sensation In Eyes	7 (3%)	2 (2%)
Vitritis	6 (3%)	8 (9%)
Vitreous Floaters	6 (3%)	5 (5%)
Eye Pruritus	6 (3%)	5 (5%)
Conjunctival Hyperemia	5 (2%)	2 (2%)
Ocular Discomfort	5 (2%)	1 (1%)
Macular Fibrosis	5 (2%)	2 (2%)
Glaucoma	4 (2%)	1 (1%)
Photopsia	4 (2%)	2 (2%)

(continued)

Table 1: Ocular Adverse Reactions Reported in ≥ 1% of Subject Eyes and Non-Ocular Adverse Reactions Reported in ≥ 2% of Patients

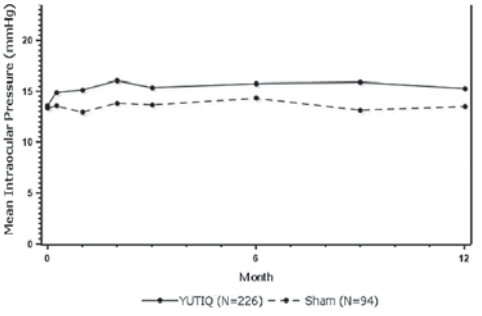
Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Vitreous Hemorrhage	4 (2%)	0
Iridocyclitis	3 (1%)	7 (7%)
Eye Inflammation	3 (1%)	2 (2%)
Choroiditis	3 (1%)	1 (1%)
Eye Irritation	3 (1%)	1 (1%)
Visual Field Defect	3 (1%)	0
Lacrimation Increased	3 (1%)	0
Non-ocular		
ADVERSE REACTIONS	**YUTIQ (N=214 Patients) n (%)**	**Sham Injection (N=94 Patients) n (%)**
Nasopharyngitis	10 (5%)	5 (5%)
Hypertension	6 (3%)	1 (1%)
Arthralgia	5 (2%)	1 (1%)

1. Includes cataract, cataract subcapsular and lenticular opacities in study eyes that were phakic at baseline. 113 of the 226 YUTIQ study eyes were phakic at baseline; 56 of 94 sham-controlled study eyes were phakic at baseline.

Table 2: Summary of Elevated IOP Related Adverse Reactions

ADVERSE REACTIONS	YUTIQ (N=226 Eyes) n (%)	Sham (N=94 Eyes) n (%)
IOP elevation ≥ 10 mmHg from Baseline	50 (22%)	11 (12%)
IOP elevation > 30 mmHg	28 (12%)	3 (3%)
Any IOP-lowering medication	98 (43%)	39 (41%)
Any surgical intervention for elevated IOP	5 (2%)	2 (2%)

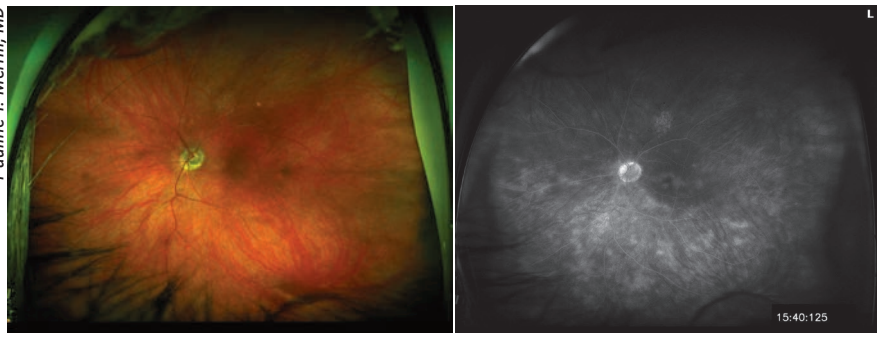
Figure 1: Mean IOP During the Studies



8. USE IN SPECIFIC POPULATIONS. 8.1 Pregnancy. Risk Summary. Adequate and well-controlled studies with YUTIQ have not been conducted in pregnant women to inform drug associated risk. Animal reproduction studies have not been conducted with YUTIQ. It is not known whether YUTIQ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. YUTIQ should be given to a pregnant woman only if the potential benefit justifies the potential risk to the fetus. All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. **8.2 Lactation.** Risk Summary. Systemically administered corticosteroids are present in human milk and can suppress growth, interfere with endogenous corticosteroid production. Clinical or nonclinical lactation studies have not been conducted with YUTIQ. It is not known whether intravitreal treatment with YUTIQ could result in sufficient systemic absorption to produce detectable quantities of fluocinolone acetonide in human milk, or affect breastfed infants or milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for YUTIQ and any potential adverse effects on the breastfed child from YUTIQ. **8.4 Pediatric Use.** Safety and effectiveness of YUTIQ in pediatric patients have not been established. **8.5 Geriatric Use.** No overall differences in safety or effectiveness have been observed between elderly and younger patients.

Manufactured by:
EyePoint Pharmaceuticals US, Inc., 480 Pleasant Street, Watertown, MA 02472 USA
Patented.

Pauline T. Merrill, MD



Chronic birdshot chorioretinitis. Left: Optos color photo showing birdshot spots and vascular sheathing. Right: Fluorescein angiogram showing CME and vasculitis. Shadows of Retisert struts are faintly visible superonasally and inferotemporally.

(Triesence), and an intravitreal dexamethasone implant (Ozurdex). The data suggests that both intravitreal treatments controlled the macular edema faster, but the sub-Tenon's injection started to catch up by six months.

"The POINT trial found that Ozurdex may have some advantages over periocular or sub-Tenon's injections in terms of treating uveitic macular edema," Dr. Henry notes. "I think this data has pushed some uveitis specialists more toward using Ozurdex and perhaps slightly away from peri-ocular steroid injections."

Dr. Merrill adds that another key finding was that there was less IOP elevation in the sub-Tenon's group than in the two intravitreal groups. "So, if you're not worried about your patient's IOP and you want a fast response, Triesence or Ozurdex are great approaches," she says. "If you're more concerned about a pressure increase and have more time, the sub-Tenon's injection may still be a reasonable option."

Dr. Merrill says she doesn't believe implants will ever totally replace simple injections. "There are some situations where you don't want to do an implant, such as in a patient who is aphakic or has a capsular tear," she explains. "The implant could end up in the anterior chamber and cause corneal edema. In that case a triamcinolone injection may be preferable. It may be a shorter-term treatment, but you have to weigh the risks and benefits of each option."

Systemic Steroids

Oral steroids—sometimes with the eventual addition of an immunomodulating drug—are another approach many patients require. Dr. Merrill says that if a patient has a bilateral panuveitis, she'll usually think about systemic options. "We want something that will treat both eyes," she explains. "Also, if it's pretty severe, the treatment will probably be longer-term, making systemic treatment helpful. The initial treatment would be oral steroids, usually 60 mg per day until the eye is quiet, but for no more than a month. After that, I taper down slowly over the following months to 7.5 mg per day or less.

"Meanwhile, as soon as I start the patient on oral steroids, I talk to them about starting a steroid-sparing immunosuppressant such as methotrexate, mycophenolate mofetil (CellCept), or adalimumab (Humira). The idea is to achieve quick control with steroids while starting something that will be better tolerated over the long term."

In terms of contraindications for oral steroids, Dr. Merrill says you want to carefully consider the systemic side effects. "For instance, if the patient is diabetic, we work closely with the patient's primary physician to monitor the patient's blood sugar," she says. "And, we talk with the patient about all of the systemic side effects that can occur, from short-term mood changes, sleeplessness and weight gain, to longer-term effects ranging from changes in blood pressure to osteoporosis. Fortunately, most people can tolerate steroids in the short term, which is all you should use them for in any case."

"If the patient has intermediate uveitis, panuveitis or posterior uveitis with retinal involvement—especially if it's bilateral—I start the patient on oral prednisone," says Dr. Janardhana. "I typically start with 1 mg per kg, which for most patients ends up being 60 mg. Then I do a taper of about 10 mg per week. If the patient has a relative contraindication to oral prednisone, such as being diabetic or having severe cardiomyopathy, I always correspond with the endocrinologist, cardiologist or primary care doctor prior to starting the patient on oral prednisone to make sure it's safe."

Dr. Henry notes that sometimes systemic and local therapy need to be combined. "It depends, among other things, on the anatomic location of the uveitis," he explains. "If the patient has isolated anterior uveitis, we can typically quiet that down with topical drops and dilation drops. But if someone has a serious intermediate uveitis, posterior uveitis or panuveitis, that patient will probably need systemic therapy—corticosteroids, with or without a bridge to longer-term immune suppression—although a few of them can be managed with local steroid injections. Many of those patients will need topical drops, too."

"Every patient with uveitis is unique," he adds. "You have to tailor your treatment to their disease and their personal preferences for management. When a patient has chronic, noninfectious severe uveitis, I frequently discuss whether they want to do the systemic therapy approach, or what I call the 'bionic eye' approach. In most cases, if

someone has autoimmune, bilateral severe disease, I'll direct them toward systemic therapy. However, some patients are just not interested in systemic therapy; they may choose to undergo chronic steroid injection or local therapy. It's my job to make sure those patients are aware that they're at risk for cataract and glaucoma. They may end up with an IOL and a tube shunt, and they have to understand that."

Antimetabolites

Patients can't remain on high-dose systemic steroids indefinitely, so if tapering leads to a resumption of the inflammation, surgeons frequently add an antimetabolite or biologic.

"Most patients with chronic, vision-threatening intermediate uveitis, posterior uveitis or panuveitis will do best if you get them over to steroid-sparing therapy," notes Dr. Henry. "In cases where someone has had an ongoing uveitis and the process appears to be a long-term threat to their vision, I'll typically start with a course of oral steroids first. If it's severe disease, I'll prescribe oral prednisone, as high as 60 mg/day, for two weeks. After two weeks I'll taper by 5 mg per week over an eight-to-10-week period. If it's chronic disease, I'll transition to longer-term immune suppression during that time."

Dr. Janardhana explains that she considers moving to other options when a patient is being weaned off of oral steroid therapy and the disease begins to reactivate. "Typically we can keep a patient on prednisone up to 10 mg/day after tapering," she notes. "But if the patient needs more than that to keep the eye quiet, we have to try something else. That might mean a series of short-term peri-ocular or intravitreal steroid injections, or a longer-lasting injection such as Ozurdex or Yutiq, or systemic immunosuppressive therapy. The choice of therapy often depends on chronicity, bilaterality, duration, contraindications to medications, and whether there's an associated systemic disease. I prefer systemic immunosuppressive therapy for patients who have chronic noninfectious uveitis—especially if it's bilateral, and of course for those who have an associated systemic disease.

"I typically start the patient on an antimetabolite, either methotrexate (dose ranges from 7.5 to 25 mg, oral, intramuscular or subcutaneously, weekly) or mycophenolate mofetil, a.k.a. CellCept (dose range 750 to 1,500 mg by mouth twice a day)," Dr. Janardhana continues. Common side effects of methotrexate are nausea, vomiting and fatigue; more severe side effects include liver toxicity, cytopenia and even kidney dysfunction in high doses. Hence, methotrexate isn't a good choice for patients who drink alcohol, because liver toxicity can occur. Methotrexate might be OK for patients who only drink alcohol once in a while, but if they drink alcohol more than a few times a month I give them mycophenolate mofetil. CellCept can cause similar side effects, but it's less likely to cause liver toxicity, so it's OK to use in patients who drink alcohol. Also, it's important to give folate with methotrexate to minimize any gastrointestinal side effects. And, it's important to let patients know that with time, side effects such as nausea, vomiting and fatigue should decrease.

"Both of these medications take three to six months to work," she adds. "For that reason, I either have the patient on topical steroid drops, give a steroid injection or prescribe oral prednisone to serve as a bridge until the antimetabolite takes full therapeutic effect."

Dr. Merrill points out that one of the holy grails for treating uveitis would be a nonsteroidal injectable medication. "The hope is that we could control inflammation without so much concern about steroid-response glaucoma," she notes. "We currently sometimes use intravitreal methotrexate off-label; that's being looked at in the MERIT study of the MUST trial group, which is comparing Ozurdex, methotrexate and Lucentis for uveitic macular edema in otherwise quiet eyes."

Biologics

"Some patients with severe non-

COMING SOON? A SUPRACHOROIDAL STEROID INJECTION

Another approach to getting a steroid into the eye is injecting it into the suprachoroidal space. Surgeons note that this has some potential advantages over the other options.

"The basic science data suggests that the steroid concentrates in the suprachoroidal space and the adjacent retina and choroid, with very little getting into the anterior chamber or angle," explains Christopher R. Henry, MD, a fellowship-trained vitreoretinal surgeon and uveitis specialist who practices at Retina Consultants of Texas. That's a theoretical advantage over intravitreal or periocular steroids, because we may be able to get a robust therapeutic response with a lower risk of cataract and glaucoma. The jury is still out, but the clinical trial data has been very promising, in terms of improving vision, reducing macular edema and limiting ocular side effects."

Dr. Henry says his practice participated in the PEACHTREE, MAGNOLIA and AZALEA clinical trials. "The new technique for performing suprachoroidal injections is fun," he notes. "These injections are not as difficult to perform as they may sound. The technique is quite intuitive, and the patients I had in the open-label AZALEA trial did extremely well."

Pauline T. Merrill, MD, a partner at Illinois Retina Associates and an associate professor of ophthalmology at Rush University in Chicago, says she hopes that suprachoroidal injection of a steroid will be approved soon. "The studies of that approach found rapid control of macular edema with possibly fewer IOP concerns than we have with intravitreal injections," she notes.

—CK

US OPHTHALMIC®

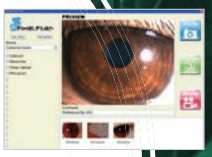
A VISION THAT INSPIRES YOURS

IMPRESS YOUR PATIENT WITH AN EMERALD

Light Source Options
LED & Halogen

EMERALD-26

Pixel Filer
Image Filing System



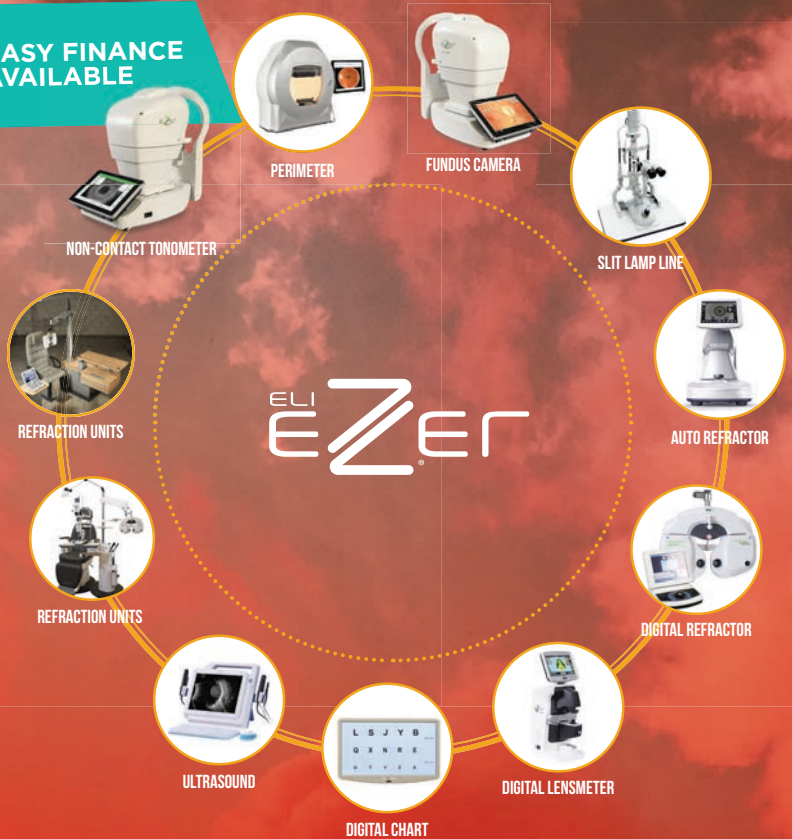
High-End Camera
SONY CCD

A TEAM BY YOUR SIDE

SATISFACTION GUARANTEED >>>>>>>>>> FROM ONE INDEPENDENT OWNER TO ANOTHER

WE CARE FOR OUR COMMUNITY

$ EASY FINANCE AVAILABLE



EZER OPHTHALMIC LINE

The Ezer Way of Life

CONTACT US FOR INFORMATION

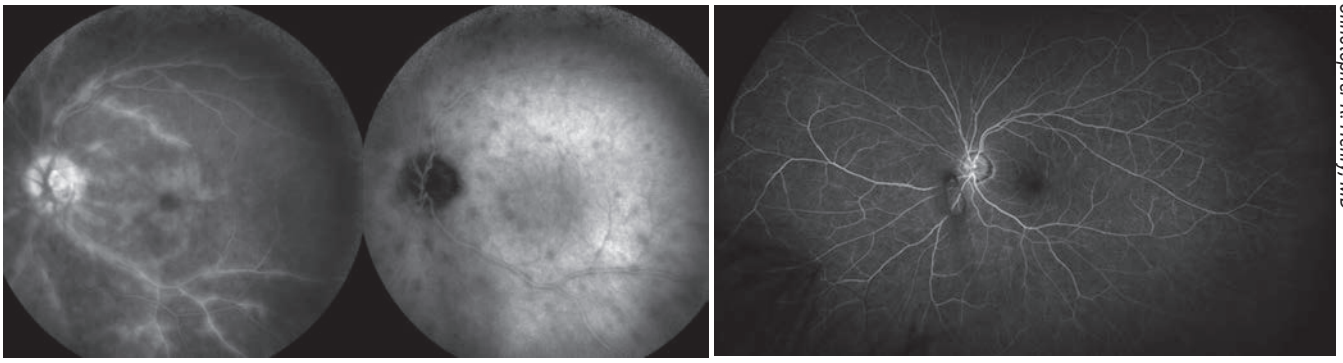
WWW.USOPHTHALMIC.COM | PH: 1.888.881.1122
INFO@USOPHTHALMIC.COM

*Follow Our Social Media Channels @**USOPHTHALMIC***

9990 NW 14th Street, Unit #105, Doral, FL 33172 | USA

SCAN TO SEE MORE!
Read all the features and benefits this item has to offer by connecting to our page.

*While you're there, don't forget to **Request A Virtual Demo Online!***



Christopher R. Henry, MD

Fluorescein angiograms of a 56-year-old female diagnosed with birdshot retinochoroiditis. Left: Before treatment. She was treated with adalimumab and mycophenolate mofetil, with Ozurdex implant supplementation as needed. Right: After two years of treatment.

infectious uveitis won't respond sufficiently to antimetabolites," Dr. Janardhana points out. "If patients are failing despite the optimal dosage of antimetabolites, then I go to the next step: TNF inhibitors—biologics. The biologics include adalimumab (Humira) and infliximab (Remicade), which is an infusion. Adalimumab is a 40-mg subcutaneous injection given every other week, and patients can self-inject it at home, which is very convenient. It typically works well for my patients, so if the patient is failing antimetabolites, starting a medication like Humira would be my next step."

"Antimetabolites such as methotrexate and mycophenolate mofetil (CellCept) are still very much in use," notes Dr. Merrill. "They tend to be the less-expensive systemic medications—especially methotrexate. The T-cell inhibitors, cyclosporine and tacrolimus, are still around, as are the alkylating agents. *[See below.]* However, I use the cytotoxics much less now that we have options like the biologics, especially Humira. Humira is FDA-approved for uveitis, so that's been a huge advance."

Dr. Henry says he starts the majority of patients needing immune suppression on an antimetabolite or a biologic. "Whether I opt for an antimetabolite or a biologic depends in part on the severity of the disease and how aggressive it is, and partly on the specific diagnosis," he notes. "For a less-aggressive, chronic, but still vision-threatening uveitis I'll sometimes lean towards methotrexate or mycophenolate first. Some patients do very well on this regimen. But if inflammation persists despite a sufficient course of one of these, then I'll add a biologic such as adalimumab."

Dr. Janardhana notes that some uveitis patients may end up on both antimetabolites and biologics. "If the patient is already on an antimetabolite like methotrexate or CellCept, I usually keep them on a low dose of the antimetabolite and add the adalimumab to that," she explains. "The justification for this has been to prevent antibodies against the adalimumab from forming. However, it's becoming less clear how much the immune system really does form antibodies in this situation, so if patients do well on adalimumab, I may taper them off the antimetabolite."

She adds that even adalimumab may not be sufficient to improve the uveitis in some patients. "Some patients don't respond sufficiently to it, while others are stable on it for years and then it stops working," she notes. "If that happens, my next step is to switch within this class of drugs to infliximab (Remicade), which is an infusion."

Dr. Henry agrees that patients with the most aggressive and vision-threatening processes may need biologic infusions. "Biologic infusions would include infliximab or golimumab (Simponi Aria), which can work well for certain patients," he says. "These are typically given in a rheumatologist's office. If a patient has extremely severe disease such as lupus-associated occlusive retinal vasculitis or ANCA-related disease, I usually favor aggressive treatment with rituximab."

"Of note, socioeconomic factors also sometimes play a role in picking an appropriate treatment plan," Dr. Janardhana says. "It's important for patients to remain compliant with appointments and for us to monitor labs and symptoms frequently while on these medications. I typically monitor patients' labs every three months—in particular white cell count and liver and kidney function tests. Also, before starting any of these immunosuppressive labs, it's important to check patients' white cell count and kidney and liver function tests, as well as ruling out infections such as tuberculosis, syphilis and hepatitis. In particular, it's important to rule out tuberculosis prior to starting TNF inhibitors."

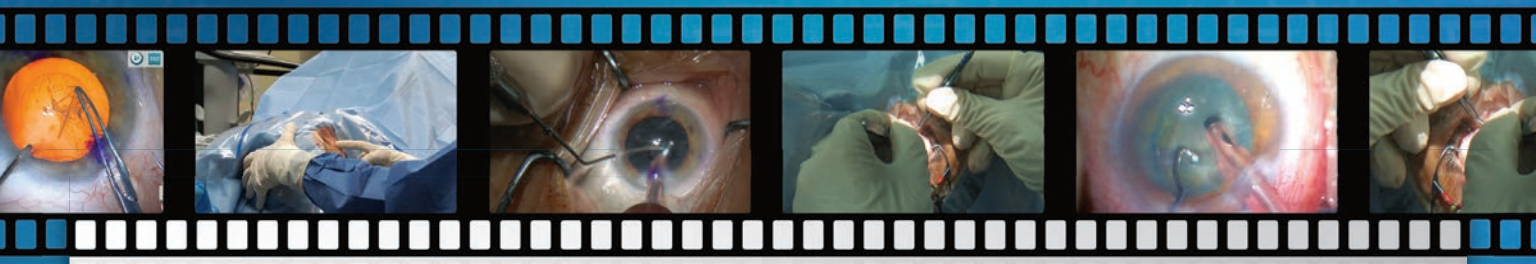
Other Options

Of course, some patients may fail even on those options. "In that case there are other medications we can try, including CD-20+ B cell monoclonal antibody inhibitors, like rituximab," says Dr. Janardhana. "This is used in severe refractory noninfectious uveitis and scleritis."

Monthly

MACKOOL ONLINE CME

CME SERIES | SURGICAL VIDEOS



To view CME video
go to:
www.MackoolOnlineCME.com

Episode 65:
"Corneal Coma and Diffractive Multifocal IOLs"

Surgical Video by:
Richard J. Mackool, MD

Video Overview:
A patient with a potentially problematic degree of corneal coma undergoes cataract–implant surgery with insertion of a diffractive multifocal IOL. Strategies to reduce possible postoperative glare/halo are presented and discussed.

MackoolOnlineCME.com MONTHLY Video Series

Richard J. Mackool, MD

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

As before, one new surgical video will be released monthly, and physicians may earn CME credits or just observe the case. New viewers are able to obtain additional CME credit by reviewing previous videos that are located in our archives.

I thank the many surgeons who have told us that they have found our CME program to be interesting and instructive; I appreciate your comments, suggestions and questions. Thanks again for joining us on Mackool Online CME.

CME Accredited Surgical Training Videos Now Available Online: www.MackoolOnlineCME.com

Richard Mackool, MD, a world renowned anterior segment ophthalmic microsurgeon, has assembled a web-based video collection of surgical cases that encompass both routine and challenging cases, demonstrating both familiar and potentially unfamiliar surgical techniques using a variety of instrumentation and settings.

This educational activity aims to present a series of Dr. Mackool's surgical videos, carefully selected to address the specific learning objectives of this activity, with the goal of making surgical training available as needed online for surgeons motivated to improve or expand their surgical repertoire.

Learning Objective

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

- recognize corneal coma and apply strategies to reduce the risk of postoperative glare/halo after diffractive multifocal IOL implantation.

Satisfactory Completion - Learners must pass a post-test and complete an evaluation form to receive a certificate of completion. You must listen to/view the entire video as partial credit is not available. If you are seeking continuing education credit for a specialty not listed below, it is your responsibility to contact your licensing/certification board to determine course eligibility for your licensing/certification requirement.

JOINTLY ACCREDITED PROVIDER™ INTERPROFESSIONAL CONTINUING EDUCATION

Physicians - In support of improving patient care, this activity has been planned and implemented by Amedco LLC and Review Education Group. Amedco LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team

Credit Designation Statement - Amedco designates this enduring material activity for a maximum of .25 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Jointly provided by: AMEDCO, REVIEW EDUCATION GROUP

Supported by an unrestricted independent medical educational grant from: **Alcon**

Additionally Supported by: **Glaukos**, **MST**, **Crestpoint Management**

In Kind Support: **Sony Healthcare Solutions**

Video and Web Production by: **JR Snowdon, Inc**

Other options include:

• ***IL-6 antibodies.*** "Tocilizumab (Actemra) is relatively new," says Dr. Henry. "It's FDA-approved for treating giant cell arteritis. In those patients it's helped to minimize the long-term side effects of oral steroids, but it also works very well for patients with uveitis. I've had good luck using it in patients with refractory scleritis, and I've switched some more aggressive uveitis patients who were on antimetabolites or a biologic such as adalimumab to tocilizumab. They've done well. For example, I have one patient with aggressive Blau-syndrome-related uveitis who's done very well since switching to tocilizumab. So I'm a big fan. I think it has a lot of promise."

"Many initial studies are looking at tocilizumab for treating noninfectious uveitis and the data looks promising," agrees Dr. Janardhana. "I've seen patients respond very well to it. In fact, my patients who are on this medication usually also have systemic disease, and it's worked well to control both.

"I think the lack of extensive data is the reason tocilizumab is still not a 'go to' medication," she adds. "The other medications, like the antimetabolites and biologics, have been well-studied for both uveitis and rheumatology, so we lean more towards those when choosing our treatments. But if the data continues to be promising, I think more doctors will start using drugs like tocilizumab to treat uveitis."

Dr. Merrill says other studies looking at intravitreal sirolimus and an intravitreal IL-6 inhibitor are currently under way. "One arm of the DOVETAIL study is looking at an IL-6 inhibitor for uveitic macular edema," she says. "Then there's the ongoing LUMINA study of intravitreal sirolimus from Santen. The previous studies of intravitreal sirolimus were promising; hopefully LUMINA will provide the data needed for FDA approval. And, in the not-too-distant future, we may have even more sustainable treatment options. A number of companies are investigating new methods of drug delivery, as well as approaches using gene therapy."

• ***T-cell inhibitors.*** Dr. Henry says he almost never recommends a T-cell inhibitor like cyclosporine or tacrolimus anymore. "I have a few patients with birdshot chorioretinopathy who are on cyclosporine, and some patients who've had organ transplants who are taking tacrolimus," he says. "But I almost never recommend them, because they require careful monitoring of factors such as blood pressure, and there are issues concerning tolerability. On the other hand, biologics work very well and are well-tolerated. So I typically go to a biologic before considering a T-cell inhibitor."

Dr. Janardhana agrees. "I tend to shy away from T-cell inhibitors/calcineurin inhibitors such as cyclosporine and tacrolimus, and alkylating agents such as cyclophosphamide and chlorambucil," she says, "given the severe side effect profile of these medications."

• ***Alkylating agents.*** Dr. Henry also says he very rarely uses alkylating agents. "They're very toxic," he points out. "For the majority of patients, biologics can do the job. For me to consider using an alkylating agent, a patient would have to have extremely aggressive, refractory disease."

Dr. Janardhana notes that studies of other options are ongoing. "Studies are being conducted for the treatment of noninfectious uveitis using other biologics such as golimumab and secukinumab (Cosentyx, an IL-17 inhibitor)," she says, "as well as T-cell inhibitors such as abatacept (Orencia). Ophthalmologists might see these medications being used for other systemic diseases such as inflammatory bowel disease or rheumatological disorders.

"We're still awaiting studies to see how efficacious these medications are against noninfectious uveitis," she says, "but if patients are already on these medications for systemic disease and have a history of uveitis, I don't immediately change medications, unless the patient has a recurrent uveitis flare or persistent chronic uveitis."

Managing Patient Expectations

Of course, no matter how effective your treatment may be, patient expectations are a huge factor in how the patient will perceive your efforts over the long run.

Dr. Janardhana says that she tells her new uveitis patients that uveitis is a complex disease with no quick remedy. "I explain that uveitis is kind of a blanket term," she says. "It can be caused by autoimmune diseases or an infection, and we can't identify the cause in half of the uveitis cases we see. In addition, uveitis—especially noninfectious uveitis—is often a chronic disease, and every patient is different. Some medications work for one patient but not the next, and we don't know why.

"The progress of uveitis is also somewhat unpredictable," she continues. "We don't always know why one person's disease is more aggressive than another's. Sometimes chronic uveitis will be quiet for years, and suddenly it becomes active, for reasons we can't determine. We do believe that factors like stress, illness and even traveling can act as triggers to reactivate the disease and cause a flare-up, but there's no way to predict exactly what's going to happen, or when.

"Most of all, patients need to understand that treating uveitis is a long process," she concludes. "We have to try different medications in a stepwise approach, and it can take several months just to find the right medication to get their disease to quiet down. So, this is a marathon, not a sprint. But no matter what it takes, I make sure they know that I'm there to work with them and help them get better." ◀

See the retina from a **Safe Distance.**

- 200° single-capture
- Multi-mode
- Easy to clean

Optos helps you see and document the retina with no face-to-face interaction. **opto**map® single capture UWF imaging has been shown to increase practice flow and patient engagement.

Keep your staff and patients safer with **opto**map

Contact us today to put the power, efficiency and safety of **opto**map in your practice

800-854-3039 www.optos.com

Nikon

optos®

SUNNY SIDE UP: VITELLIFORM DYSTROPHY

This condition is often misdiagnosed as AMD. Find out how to differentiate the two, with insights from retinal specialists.

BY CHRISTINE LEONARD
ASSOCIATE EDITOR

Adult-onset foveomacular vitelliform dystrophy goes by a few different names, but its "egg yolk" presentation remains a consistent finding in affected eyes. Depending on the disease stage, most patients have few symptoms and only mild visual impairment. However, AOFMVD is a progressive disease with no treatment, and in the atrophic stages, central vision loss is common. Because of relatively mild vision symptoms during most stages and its resemblance to age-related macular degeneration, this condition is often misdiagnosed. Here, retinal specialists discuss how to identify AOFMVD and differentiate it from macular degeneration.

Consequences of a Misdiagnosis

Vitelliform dystrophy may have phenotypic presentations similar to AMD but it has different underlying genotypes. "The term 'adult-onset foveomacular vitelliform dystrophy' is a completely descriptive term and it's a clinical diagnosis," explains Ian C. Han, MD, an assistant professor of ophthalmology and visual sciences at University of Iowa Health Care, Carver College of Medicine. "There are differences between the traditional clinical diagnosis and this era of advanced imaging and molecular genetic diagnoses. If you're in a high-volume clinical practice and see a lot of macular degeneration, it's likely that quite a few patients have something that's more vitelliform, if you will, but is simply being labeled as AMD because the patient's vision is pretty decent—and they're older, so it's fine to call it AMD. What's most clinically relevant right now is that if something looks a bit off from typical AMD, you can consider it an AMD masquerader."

It's important to catch a misdiagnosis as soon as possible, experts say. In addition to causing undue worry and distress about losing vision, a misdiagnosis of AMD may mean that the patient has been undergoing unnecessary injections, says Jay Chhablani, MD, a vitreoretinal specialist and an associate professor of ophthalmology at the University of Pittsburgh Eye Center. "It's essential to rule out this disease and understand that injections won't benefit the patient at all, unless there's CNV involved," he says.

Injections come with a financial burden and certain risks. "Every time you do an injection, not only do patients experience discomfort during and after, but there's also the psychological toll of getting these injections and the risk of endophthalmitis," says Jason Hsu, MD, an associate professor of ophthalmology at the Sidney Kimmel Medical College of Thomas Jefferson University and faculty member of the Retina Service at Wills Eye Hospital in Philadelphia. "There's limited data on using anti-VEGF for AOFMVD, and nothing so far indicates it has any effect—good or bad—on the disease. Additionally, many patients have been started on AREDS vitamins for macular degeneration, which can be quite expensive."

Shared Mechanisms, Mysteries

AMD and its mimickers, such as AOFMVD, Best's disease and other pattern dystrophies, share a malfunction at the level of the RPE and choroid. "Vitelliform lesions of

This article has no commercial sponsorship.

Dr. Hsu, **Dr. Han** and **Dr. Chhablani** have no relevant financial disclosures.

AOFMVD have high levels of lipofuscin," notes Dr. Hsu. "It's believed to be the result of accumulation of photoreceptor outer segments that failed to be digested by the underlying RPE cells, leading to buildup in the subretinal space. However, the reason for this malfunction isn't wholly understood yet."

Disease Stages

Disease stages correspond to the breaking up of the lesion, from the vitelliform stage to the pseudohypopyon stage and on to the vitelliruptive and atrophic stages. "We aren't currently aware of the mechanism behind the breaking up of the lesion, but we do know that there's an established genetic association," Dr. Chhablani says. "The staging is similar to what we sometimes see in Best's disease."

Dr. Hsu explains that any of these stages may be misdiagnosed as AMD, especially the vitelliruptive ("scrambled egg" stage) and pseudohypopyon stages, which may be taken as wet AMD with fluid; or the earlier vitelliform stage which may look like dry AMD. The atrophic stage may masquerade as advanced dry AMD with geographic atrophy. "The area of atrophy tends to be very circular in the center of both eyes, rather than a more irregular shape that you'll sometimes see with typical geographic atrophy from AMD," he notes.

Vitelliform stage. "In my practice, the most common stage at which patients present is usually the vitelliform stage, which has an egg-yolk-like lesion under the fovea," Dr. Hsu continues.

Pseudohypopyon stage. "The next stage sort of mirrors what we hear about with Best's disease," he says. "In my experience, it's been rare to see an adult-onset foveomacular dystrophy having a pseudohypopyon stage, in which there's a layering of heavier proteinaceous material inferiorly, due to gravity. The superior portion of the lesion looks more clear and fluid-filled.

"When you do an OCT scan through this pseudohypopyon, you'll see the appearance of the sedimented deposit has a hyperreflective signal on OCT, whereas the superior portion with fluid will look dark, or hyporeflective," he says. "I'd say this pseudohypopyon stage is when even retinal specialists may think there's an underlying CNV membrane and start doing injections. That's one thing to look out for."

Vitelliruptive stage. "As the disease progresses, we come to the vitelliruptive stage, which resembles scrambled eggs," Dr. Hsu says. "It no longer has a uniform grey/yellow appearance. Now there's some atrophy developing due to resorption of this vitelliform material. Essentially, it shrinks down."

Atrophic stage. "In the atrophic stage, the material is completely resolved but there's still loss of the RPE and some of the outer retina," he says.

Paradoxically, as the lipofuscin resorbs, vision usually worsens. The resorption mechanism in the atrophic stage is unknown, but one theory suggests it may be due to photoreceptor death and the subsequent decrease in production of the outer segments. "With fewer outer segments to eliminate, the RPE may catch up and elim-

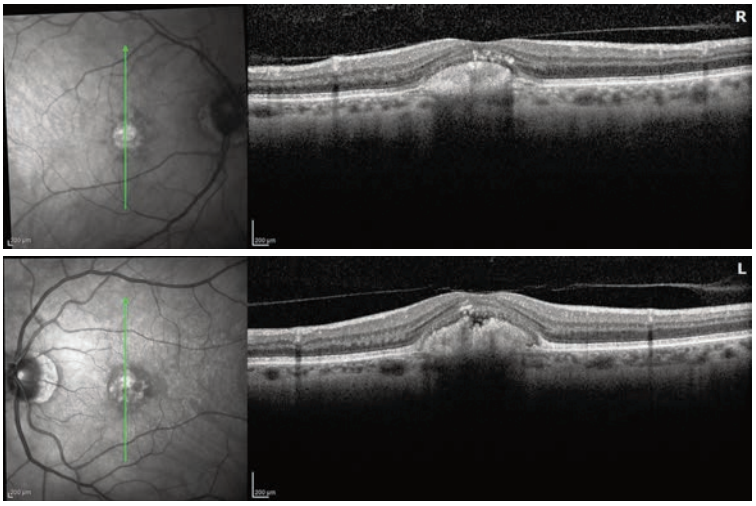
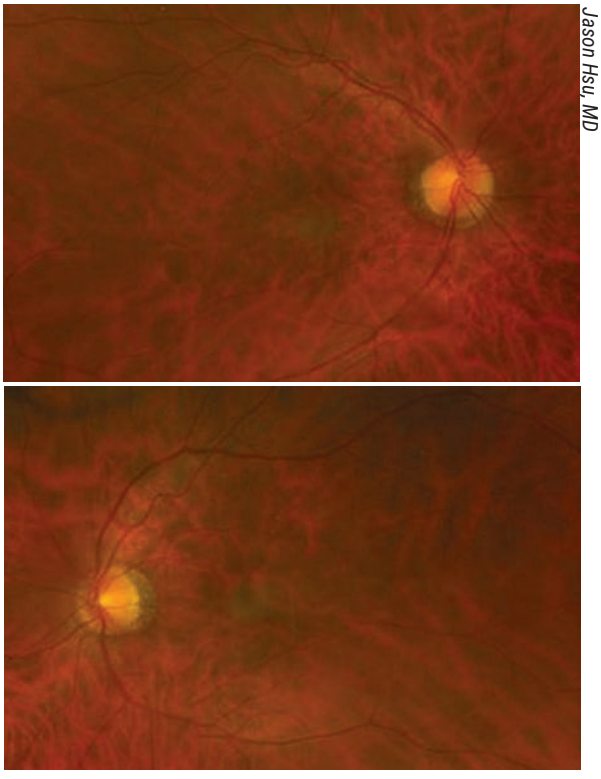
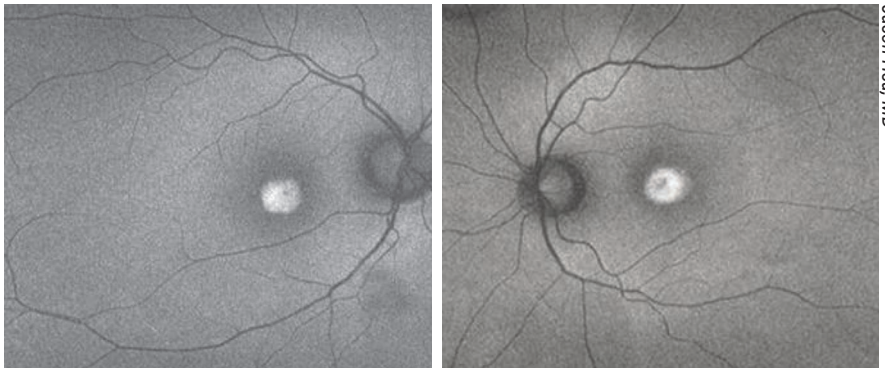


Figure 1. (Above) Spectral domain optical coherence tomography shows predominantly hyperreflective lesions in the subretinal space, located in the foveal center. The OS image shows some mild areas of hyporeflectivity which isn't uncommon but can sometimes be mistaken for evidence of fluid due to choroidal neovascularization.



Jason Hsu, MD

Figure 2. (Right) Color fundus images show symmetric, round, grey-yellowish lesions in the foveal center of each eye. Some mild pigment clumping is noted within the lesion OD.



Jason Hsu, MD

Figure 3. Fundus autofluorescence of the same patient in Figures 1 and 2 reveals classic, circular, solitary central hyperautofluorescent lesions in each eye.

inate the waste," Dr. Hsu says. "I've had patients who haven't lost vision or even showed improvement, so some patients do continue to see well after the material resorbs. Most, however, experience worsening of vision."

Lesions

Both AMD and vitelliform dystrophies, whether juvenile- or adult-onset, have yellowish deposits. Clinically, the main difference between the AMD and adult-onset foveomacular vitelliform dystrophy is the color and distribution of these deposits, explains Dr. Han.

"When you look on imaging and histology for traditional AMD, the deposits aren't just subretinal but predominantly sub-RPE," Dr. Han says. "They're more discrete and round: classic drusen. They may or may not be located subfoveally and can also be distributed throughout the macula. Some have softer borders and can be confluent, but are typically discrete.

"Clinically, vitelliform deposits can look similar to AMD early on," he continues. "However, when you see a vitelliform deposit that's classically subfoveal, larger, isolated, rounder and more yellow than your typical drusen or soft drusen, that's when a clinician may start to think of AOFMVD. Drusen tend to be a bit clumpy, but the vitelliform lesion, as the name suggests, looks more like an egg yolk with a characteristic yellow color."

"Unlike the sister diagnosis of Best's disease, whose lesions are very large in the central macula, AOFMVD lesions tend to be about 500 microns in diameter and are usually very round or oval in shape," adds Dr. Hsu. "Often, they'll have a pigmented spot in the center as well.

"There's also something called subretinal drusenoid deposits that have been described with AMD as well, so not all AMD drusen is sub-RPE," he cautions. "However, vitelliform dystrophy will have much more prominent and a greater accumulation of subretinal hyperreflective material."

Differential Diagnosis

There's a reason this disease is often mistaken for AMD, Dr. Hsu says. "For one, it's not terribly common, and for another, many of these patients have only central lesions in their macula, while others will have associated drusen around the lesions, or RPE changes," he says. "Some dystrophies are clear-cut, but the spectrum of this disease may be very similar to the spectrum of macular degeneration."

Dr. Hsu says it's easiest to diagnose patients when they come in with their disease in the vitelliform stages, when it resembles a single egg yolk in each eye. "Sometimes I'll see some surrounding drusen, but usually the drusen are much less prominent and this one lesion is very prominent. That's my usual clue that this is more of a vitelliform than an AMD eye. It becomes more difficult to differentiate as it advances."

"I think the most important thing to keep in mind when differentiating AOFMVD from AMD is that AOFMVD is primarily a bilateral, symmetrical disease, and unassociated with surrounding atrophy and AMD-associated signs which you'll see in the acquired vitelliform lesions associated with AMD," says Dr. Chhablani. "If patients present to you with bilateral, symmetrical deposits in the center with no drusen around them, then you should be thinking: Probably not AMD."

Though it typically presents bilaterally and symmetrically, this isn't always the case, notes Dr. Hsu. "I've seen it present very asymmetrically, where one eye will have a very prominent lesion and the other eye will have a much smaller, less noticeable lesion that I'd have almost glossed over if I hadn't seen the lesion in the other eye," he says.

"Age of onset is another important question for any potentially genetic vision condition," says Dr. Han. "Typical AMD is defined as occurring at greater than age 50. Most patients come in in their 60s, 70s or 80s. If you have someone with 'adult-onset' FMVD, they might be 30 or 40 years old with their earliest symptoms starting then. If you notice earlier onset, ask about family history. That yellow egg-yolk-like deposit that doesn't look like typical drusen is a trigger to think about for referral and when you look at structural OCT. The location of these deposits are important clues: They're typically subfoveal and subretinal."

With many patients referred for macular degeneration, what leads a clinician to suspect that there's been an incorrect diagnosis? "This falls under the category of differentials for non-responders," Dr. Chhablani says. "If you're seeing that your patient has subretinal fluid or hyporeflective space on OCT that's not flattening, and you're considering this to be subretinal fluid and possible CNV, that's the time to go back and look at your imaging, such as autofluorescence, or do a detailed examination of past OCTs. If you did fluorescein

IN THE BATTLEGROUND OF DRY EYE...

When Dry Eye Flares strike, fight back first with fast.*

- EYSUVIS is ***THE FIRST AND ONLY FDA APPROVED SHORT TERM (up to two weeks) RX TREATMENT*** for the signs and symptoms of Dry Eye Disease
- EYSUVIS ***RAPIDLY REDUCED**** Dry Eye signs and symptoms in the largest clinical development program in Dry Eye (N=2871)[1]
- EYSUVIS ***TARGETS OCULAR SURFACE INFLAMMATION***, an underlying pathology of Dry Eye
- EYSUVIS is formulated with AMPPLIFY® Drug Delivery Technology, designed to ***ENHANCE OCULAR SURFACE TISSUE DISTRIBUTION AND PENETRATION***[2,3]
- EYSUVIS had a ***LOW INCIDENCE OF INTRAOCULAR PRESSURE ELEVATION*** (similar to vehicle) and was well-tolerated in clinical trials[4] —Please see Warning on Intraocular Pressure Increase below

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

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

INDICATION

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

IMPORTANT SAFETY INFORMATION

Contraindication:

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

Warnings and Precautions:

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

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

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

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

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

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

Adverse Reactions:

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

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

References: 1. Holland E, Nichols K, Foulks G, et al. Safety and efficacy of KPI-121 ophthalmic suspension 0.25% for dry eye disease in four randomized controlled trials. Presented at: AAO 2020: November 13-15, 2020; virtual meeting. **2.** Schopf L, Enlow E, Popov A, et al. Ocular pharmacokinetics of a novel loteprednol etabonate 0.4% ophthalmic formulation. *Ophthalmol Ther*. 2014;3(1-2):63-72. **3.** Popov A. Mucus-penetrating particles and the role of ocular mucus as a barrier to micro- and nanosuspensions. *J Ocul Pharmacol Ther*. 2020;36(6): 366-375. **4**. Korenfeld M, Nichols KK, Goldberg D, et al. Safety of KPI-121 ophthalmic suspension 0.25% in patients with dry eye disease: a pooled analysis of 4 multicenter, randomized, vehicle-controlled studies. *Cornea*. 2020. In press.

kala PHARMACEUTICALS

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

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

The most common adverse reaction observed in clinical trials with EYSUVIS was instillation site pain, which was reported in 5% of patients.

USE IN SPECIFIC POPULATIONS

Pregnancy—Risk Summary: There are no adequate and well controlled studies with loteprednol etabonate in pregnant women. Loteprednol etabonate produced teratogenicity at clinically relevant doses in the rabbit and rat when administered orally during pregnancy. Loteprednol etabonate produced malformations when administered orally to pregnant rabbits at doses 1.4 times the recommended human ophthalmic dose (RHOD) and to pregnant rats at doses 34 times the RHOD. In pregnant rats receiving oral doses of loteprednol etabonate during the period equivalent to the last trimester of pregnancy through lactation in humans, survival of offspring was reduced at doses 3.4 times the RHOD. Maternal toxicity was observed in rats at doses 347 times the RHOD, and a maternal no observed adverse effect level (NOAEL) was established at 34 times the RHOD.

The background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies.

Data—*Animal Data:* Embryofetal studies were conducted in pregnant rabbits administered loteprednol etabonate by oral gavage on gestation days 6 to 18, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations at 0.1 mg/kg (1.4 times the recommended human ophthalmic dose (RHOD) based on body surface area, assuming 100% absorption). Spina bifida (including meningocele) was observed at 0.1 mg/kg, and exencephaly and craniofacial malformations were observed at 0.4 mg/kg (5.6 times the RHOD). At 3 mg/kg (41 times the RHOD), loteprednol etabonate was associated with increased incidences of abnormal left common carotid artery, limb flexures, umbilical hernia, scoliosis, and delayed ossification. Abortion and embryofetal lethality (resorption) occurred at 6 mg/kg (83 times the RHOD). A NOAEL for developmental toxicity was not established in this study. The NOAEL for maternal toxicity in rabbits was 3 mg/kg/day.

Embryofetal studies were conducted in pregnant rats administered loteprednol etabonate by oral gavage on gestation days 6 to 15, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations, including absent innominate artery at 5 mg/kg (34 times the RHOD); and cleft palate, agnathia, cardiovascular defects, umbilical hernia, decreased fetal body weight and decreased skeletal ossification at 50 mg/kg (347 times the RHOD). Embryofetal lethality (resorption) was observed at 100 mg/kg (695 times the RHOD). The NOAEL for developmental toxicity in rats was 0.5 mg/kg (3.4 times the RHOD). Loteprednol etabonate was maternally toxic (reduced body weight gain) at 50 mg/kg/day. The NOAEL for maternal toxicity was 5 mg/kg.

A peri-/postnatal study was conducted in rats administered loteprednol etabonate by oral gavage from gestation day 15 (start of fetal period) to postnatal day 21 (the end of lactation period). At 0.5 mg/kg (3.4 times the clinical dose), reduced survival was observed in live-born offspring. Doses ≥ 5 mg/kg (34 times the RHOD) caused umbilical hernia/incomplete gastrointestinal tract. Doses ≥ 50 mg/kg (347 times the RHOD) produced maternal toxicity (reduced body weight gain, death), decreased number of live-born offspring, decreased birth weight, and delays in postnatal development. A developmental NOAEL was not established in this study. The NOAEL for maternal toxicity was 5 mg/kg.

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

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

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

NONCLINICAL TOXICOLOGY

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

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

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

Part # 2026R02

October 2020
Kala®

US-EYS-2000115

angiography, then check those again. OCTA also allows us to rule out the vascular network, which you see in wet AMD but not in AOFMVD."

Imaging Modalities

Experts agree that OCT is probably the most useful imaging modality for detecting AOFMVD. When AMD and AOFMVD deposits look similar on clinical examination, OCT can help you make the final call by checking where the material is accumulating. "If you look carefully at cross-sectional imaging, the vitelliform deposits tend to be truly subretinal, in the sense that they're between the neurosensory retina and above the level of the RPE," Dr. Han says. "It's accumulating above the level of a brighter band on OCT of the RPE and can sometimes be seen associated with elongation of the photoreceptors, along with some hyporeflective space. We tend to use the term neurosensory detachment because it's probably some light thinning of the photoreceptors where the retina's actually separating from the RPE."

"If vision is good and your OCT shows a nice, uniform, hyperreflective lesion that's clearly in the subretinal space, you'll see preservation in areas such as the outer retina, ellipsoid zone and external limiting membrane," adds Dr. Hsu. "That's the easiest time to diagnose this condition."

Dr. Chhablani's advice is to look carefully. "If you do an OCT and see hyporeflective space, don't assume it's subretinal fluid," he points out. "When we see hyporeflective areas and think subretinal fluid, we think of anti-VEGF injections, but in the case of AOFMVD we don't want to do that. When I've had patients who've been injected before, I ask them to bring their previous OCTs. It's important to examine their previous OCTs and see their treatment history and treatment response. If their response wasn't good, start thinking that this might not be AMD but AOFMVD. Start investigating. Seeing hyporeflective space and initiating injections in a very conventional way isn't a great idea.

"If you suspect choroidal neovascularization, look carefully at the whole volume OCT scan," he continues. "Scroll up and down again and again. Be sure to look for a type-1 component, and look for RPE breach if you suspect type-2 CNV membrane. If you can't make out anything, observing the patient for two more weeks won't hurt, or you can inject and see if there's no response. Hold off on the second injection and see if it worsens. If there's a very subtle, slow leakage, you can wait for a week and see how the disease worsens."

While fluorescein angiography is helpful for identifying CNV in AMD, it's not particularly useful for visualizing a potential CNV net in vitelliform conditions, including Best's disease. This is because the dye leaks into the lesions, making it difficult to tell whether there's abnormal CNV leakage or the usual leakage associated with vitelliform lesions. Dr. Hsu explains, "The lipofuscin blocks the underlying fluorescein dye. Then, there's often a rim of hyperfluorescence surrounding that lesion due to some RPE changes. If you do FA in an atrophic stage, it'll just be a window defect in the center."

Dr. Han says that OCTA is more helpful for visualizing a CNV net in vitelliform diseases, even though it doesn't show leakage. "OCTA is basically motion-capture of blood cells going through blood vessels," he explains, "but for vitelliform diseases, it's advantageous because the leakage obscures everything when you look on FA. With OCTA, you can actually see through the vitelliform lesion to a potential CNV membrane under the retina."

For cases of AOFMVD without CNV, Dr. Chhablani says you'll see a shadow artifact on OCTA from the vitelliform deposit. "If you were suspecting subretinal fluid due to CNV, and OCTA turns up no vascular network, then that rules out the diagnosis of wet AMD, which is helpful."

A clinical exam and OCT are usually all you need to diagnose AOFVMD, but if you're still unsure, experts say fundus autofluorescence is a good ancillary test. "Typically you'll see a hyperautofluorescent lesion corresponding to the yellow spot we see in both eyes," says Dr. Hsu. "The pattern of the autofluorescence is key. If you perform autofluorescence on an AMD eye, you'll often see patchy areas of hyperautofluorescence where some drusen are located and other areas where there's pigment clumping, which will appear as hypoautofluorescence. AMD has a very heterogeneous pattern, whereas vitelliform dystrophy is mostly homogeneous. You'll see a bright, central spot where the lesions are located and everything around it will look fairly normal and intact.

Genetic Etiology

Further genetic studies may reveal more about the etiologies of these diseases. "AMD has a trend toward genetic characterization, and many of its masqueraders such as AOFVMD likely have a genetic cause or the patient has a genetic predisposition," Dr. Han says. "Symmetry between the two eyes is usually a clue to macular dystrophies that have a genetic predisposition, as opposed to AMD, which usually has bilateral involvement but is asymmetric. There's probably a broad spectrum of age-related accumulation of debris in the retina with a genetic background."

AOFMVD hasn't been attributed solely to a genetic etiology, but there are several genes potentially implicated in the condition, including BEST1 and interphotoreceptor matrix proteoglycan or pattern dystrophy genes such as IMPG1, IMPG2 and RDS, also known as PRPH2. Best's disease, or juvenile-onset FMVD, is linked to the BEST1 gene but doesn't always show up in childhood, despite its name. It's often clinically diagnosed as adult-onset FMVD, in

the absence of genetic testing.

"One of the classic genetic features of autosomal-dominant diseases is what we call incomplete penetrance, which means that not everyone will express the full strength of the mutation," says Dr. Han, explaining these late manifestations. "Variable expressivity and incomplete penetrance may manifest in a wide spectrum across family members. Some patients fit cleanly into one box of clinical diagnosis and others don't. We tend to label patients as having Best's disease of late onset when they have a BEST1 mutation. Because of variable expressivity and incomplete penetrance, we're not surprised if someone with a BEST1 genetic variant has a later onset of disease, even though it's clinically diagnosed as a juvenile macular dystrophy. It's helpful to examine other family members, even if they're allegedly asymptomatic."

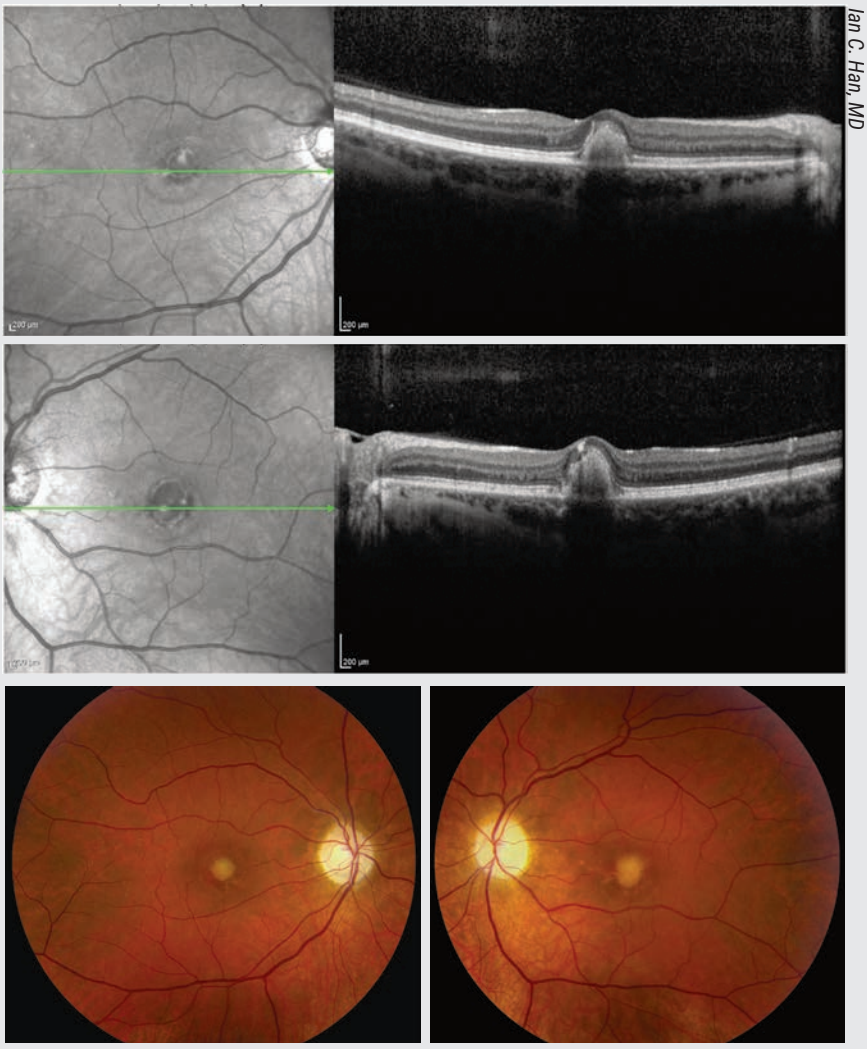
Genetic testing

Genetic testing is more often reserved for severe or systemic disease or diseases with wide-ranging implications that may affect multiple generations. Most clinicians don't offer genetic testing for AMD or AOFMVD because the results won't change much about disease management, even when distinguishing between the two.

Dr. Chhablani says you can rule out Best's disease without resorting to genetic testing by doing an electrooculogram. "Best's disease will have a subnormal or reduced Arden ratio," he says. "If I don't see any changes on EOG, then I don't usually ask for a genetic test."

Dr. Han says he offers genetic testing for patients with AOFVMD. At the Carver College of Medicine, he has easy access to the Carver Non-Profit Genetic Testing Laboratory, which has one of the largest collections of genetic testing for eyes in the world.

"In your daily clinics of AMD patients, it's highly likely that some have a genetic predisposition to macular disease that may currently or in the future be determined to be something other than AMD," Dr. Han says. "Adult-onset foveomacular vitelliform dystrophy is a clinical diagnosis. The terms 'adult onset' and 'vitelliform' are very instructive. We're moving into the era of genetics and advanced imaging, so we're seeing that some of these AOFMVD patients turn out to have late-onset Best's disease. Others probably just have some level of anatomical dysfunction in the photoreceptor-RPE-choriocapillaris unit that's shared with the pathophysiologic mechanisms of multiple diseases. Depending on how that abnormal clearance of debris manifests, it can look similar on clinical examination but may have a different underlying genetic basis." ◀



Ian C. Han, MD

Example Case

This is a 44-year-old woman who presented with mild distortion in both eyes. Visual acuity was 20/25 in both eyes, and the fundus examination was remarkable for central vitelliform lesions. The OCT line scans demonstrate subretinal hyperreflective material above the level of the RPE-Bruch's membrane.

The small, discrete yellow dots temporally in both eyes (more apparent in the right eye) resemble more typical age-related drusen.

She had no family history. Genetic testing was unrevealing for any pathologic variants in BEST1, IMPG1, IMPG2, and RDS.

RayOne EMV

A new fully preloaded non-diffractive IOL solution

"I collaborated with Rayner on bringing to market RayOne EMV, an exciting new product for all surgeons."

Prof. Graham Barrett

RayOne EMV and TECNIS Eyhance Comparative Clinical Defocus Curve[1]

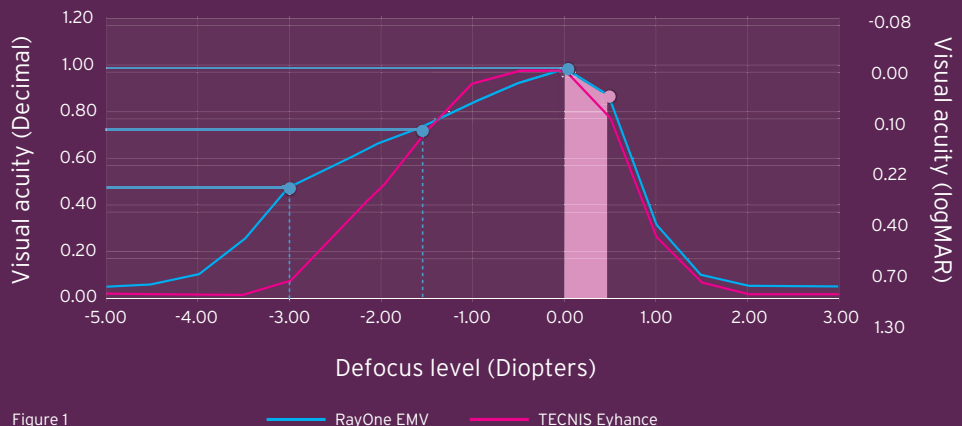


Figure 1

Compatible with

RayPRO

rayner.com/RayPRO

Three years' free patient outcomes data on visual outcomes, patient satisfaction, spectacle independence, and more

Contact USMarketing@rayner.com for more information **rayner.com/EMV**

Rayner
Your Skill.
Our Vision

RayPRO IOLs

MADE IN UK

Rayner

1. Royo, M. RayOne EMV and TECNIS Eyhance: A Comparative Clinical Defocus Curve. Data on file. 2021.

Not all Rayner products are approved for sale in every country. Please contact your local Rayner distributor for details of which products are available in your area.

THE QUEST FOR PERFECT VISION

How to use precise patient profiling, ocular surface management, state-of-the-art diagnostics and today's IOLs to provide patients excellent vision.

BY SEAN MCKINNEY
SENIOR EDITOR

Preoperative steps	Optimize ocular surface	Use corneal higher order aberrations	Manage expectations
Intraoperative steps	Center capsulotomy on visual axis	Ensure optic has 360 degrees of capsular overlap	Polish the capsule
Postoperative steps	YAG capsulotomy for PCO	Laser fine-tune cornea for residual refractive error	Manage the ocular surface

Brian Shafer, MD

Suggestions on how to optimize vision with cataract surgery.

How many times have you heard a 20/20 postop cataract patient say his vision is disappointing? Or a 20/40 who tells you she can see perfectly? If you can remember such a case, or can think of similar ones, you're not alone. Increasingly, cataract surgeons report that one of their biggest challenges today is ensuring that the quality of patients' postop vision is as good or better than their acuity.

Sometimes that means hitting 20/20 Snellen, sometimes not.

Part of the challenge is matching patients' varied visual needs with the individualized solutions made possible by a growing assortment of advanced intraocular lenses. Another part of the challenge is the need to respond to the once-overlooked nuances on the cornea and inside the eye that are now recognizable because of the growing sophistication of today's diagnostic technologies. Finally, the availability of increased ocular surface treatments ups the ante in many of these cases. Here, surgeons explain how they avoid patient unhappiness and maximize positive outcomes by following new approaches preoperatively, intraoperatively and postoperatively.

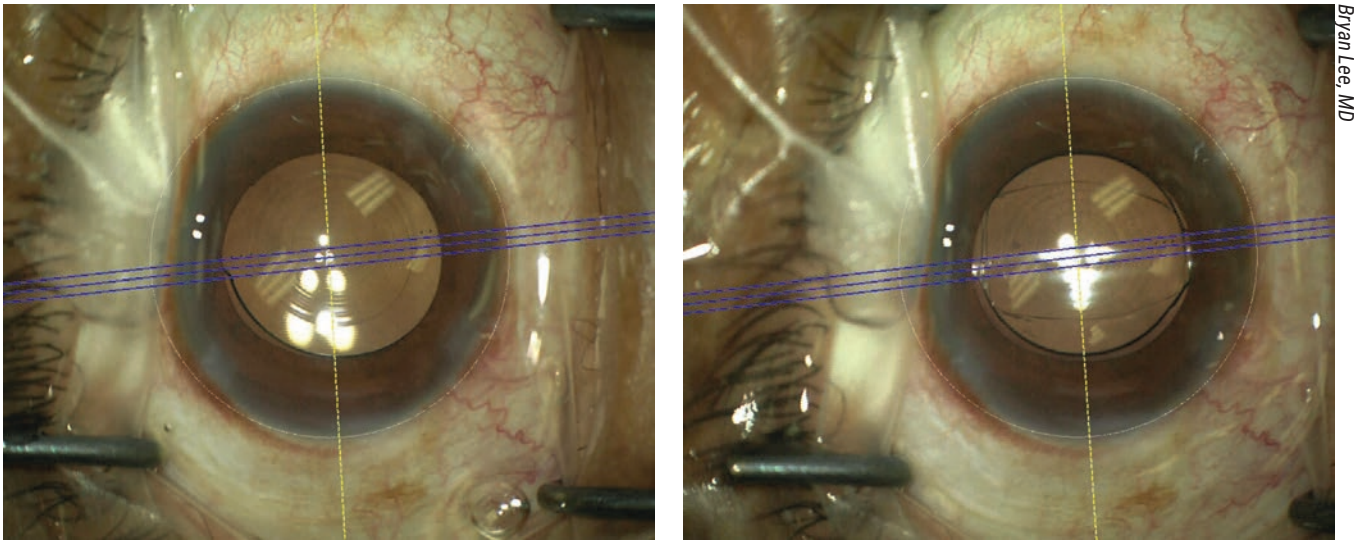
Why Now?

Y. Ralph Chu, MD, Founder, CEO and Medical Director of Chu Vision Institute and Chu Surgery Center in Bloomington, Minnesota, puts the issue of vision quality into simple terms: "We've learned over the past 20 years that Snellen acuity doesn't define the quality of a patient's vision," he says. "For example, in many situations, including clinical trials, we've seen loss of contrast sensitivity compromise aspects of functional living, such as the ability to drive at night for patients who have shown acceptable results on the Snellen chart. Some patients can actually have very good visual acuity, even in the presence of dim lighting conditions. But as soon as a source of glare hits their eyes, the quality of their vision decreases dramatically."

Dr. Chu says wavefront aberrometery and other diagnostics available today enable you to evaluate a patient's entire optical system, including the cornea and ocular structures, for potential sources of suboptimal vision. "We shouldn't focus on just the pathology—a cataract in this case," he says. "Remember that something as simple as an epiretinal membrane can also affect

This article has no commercial sponsorship.

Dr. Hatch is a consultant for Johnson & Johnson Vision and Kala Pharmaceuticals. **Drs. Shafer, Lee, Chu and McKee** report no relevant financial disclosures.



Bryan Lee, MD

This patient was experiencing persistent and intolerable negative dysphotopsias after cataract surgery (left). A reverse optic capture eliminated the troublesome symptoms (right).

the patient's vision."

Bryan Lee, MD, JD, who's in private practice at Altos Eye Physicians in Los Altos, California, agrees with this notion, saying the clinical measures used for clinical trials and related purposes are difficult to quantify. "We all see patients whose vision doesn't necessarily reflect a measurement on the Snellen chart," says Dr. Lee, who is also an adjunct clinical assistant professor of ophthalmology at Stanford University. "When it comes to defining success, I think we still have to figure out better measures as a profession. Right now, it's highly subjective. A lot depends on what the patient tells you, which is fair because the need for cataract surgery should be based on visual functioning and the patient's quality of life."

At the same time, Dr. Lee continues, "when I'm determining how patients are doing postop—despite what I've just said—I have to admit that I'd prefer my evaluation to also be based on at least some objective measures that I can consider. We have to know what the patient sees. In our practice, we try to get at that by doing a lot of testing, such as reducing contrast on the Snellen chart by 50 percent."

Yuri McKee, MD, MS, a corneal and refractive surgeon at East Valley Ophthalmology in Mesa, Arizona, says the key measure of success he seeks to achieve when striving to optimize vision is, quite simply, patient happiness. "I want to know if they feel they've met their goals." he asks. "I want to know if they would recommend a friend or family member to see me for surgery. Measured visual acuity is important, but happy patients are the best indicator of success."

Dr. McKee says his practice spends a lot time on patient surveys to profile happy and unhappy patients. "We take all reviews, good and bad, very seriously," he says. "Sometimes, patients complain about things I can't change, like an epiretinal membrane, but even this reminds me to spend more time counseling patients about pre-existing pathology. Sometimes patients give us great feedback that reflects well on our practice processes and staff. If a patient has a negative comment, we scrutinize the related process to see how we can improve the patient experience."

First Things First

Asking patients a lot of incisive preop questions remains one of the most effective methods of determining your potential for maximizing their vision quality, according to Brian Shafer, MD, a cornea, refractive, glaucoma and anterior segment fellow at Vance Thompson Vision in Sioux Falls, South Dakota. For example, how do patients feel when they're driving? Can they read all of the signs in front of them? How about when they're driving at night? Can they read the stop signs or the license plate on the car in front of them? How much glare do they see when a car is approaching them from another direction? Is it significant enough to make them avert their eyes?

"Taking this approach moves us to the forefront of the refractive surgery mindset," says Dr. Shafer. "For a number of years, as my mentors and colleagues are quick to point out, patients measuring 20/20 after refractive procedures have still been troubled by glare and other issues, such as problems driving at night. Now, these issues are surfacing in the IOL space. We're learning a lot more about how to maximize vision quality in what has evolved into what we call refractive-cataract surgery."

Dr. Lee likes to remind colleagues that patients' visual needs vary more than was fully appreci-

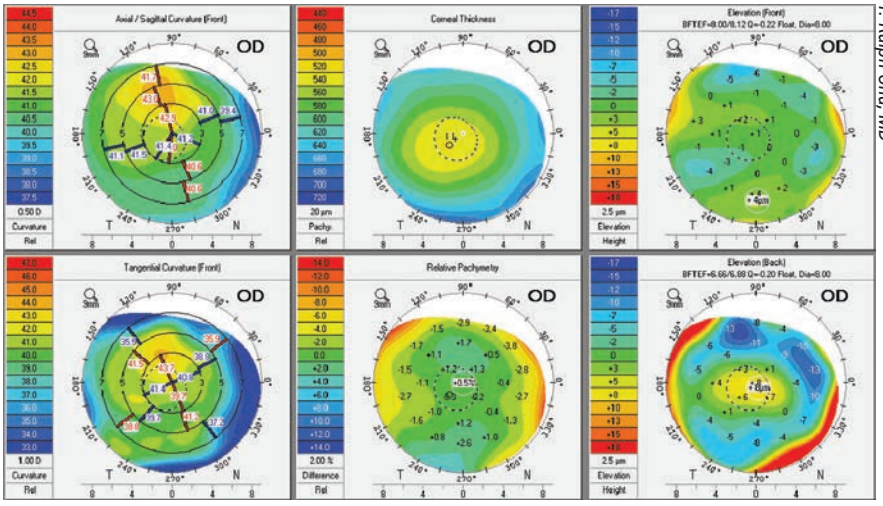
ated in the past. For example, patients may spend most of their time reading from desktop computers, laptops, tablets, cell phones and printed text—or combinations of these formats.

"Patients may also be reading at different distances that we need to identify," he points out. "There's no ideal number for us to hit when measuring the vision a patient has while reading. But we pay close attention to the quality, speed and ease of how the patient reads. We're constantly striving to measure quantitative and qualitative aspects of their vision."

Ultimately, he admits, achieving optimal vision—or going beyond the clinical definition of perfect—is a "huge" challenge when caring for some patients.

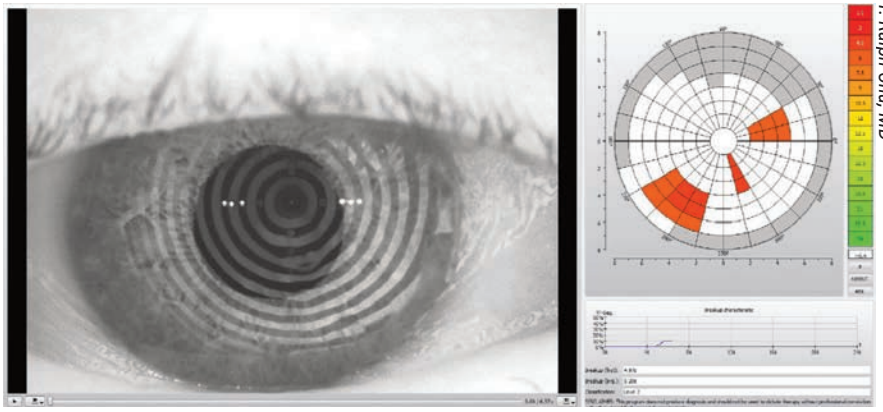
"The outcomes of cataract surgery are very good these days," he notes. "If patients are healthy, their acuity is going to be really high. As far as assessing their happiness, that's really hard because patient satisfaction varies so much. One person's definition of success applies to only that one person. I don't think we'll ever have a perfect system that will tell us exactly what we want to know."

Beyond the use of questionnaires—always critical before surgery—Dr. Lee uses extensive preop conversations with patients to shed light on their goals and personalities, which are also critical to know. "For example, a patient might say, 'I'm here because I can't see my golf ball,'" he says. "Obviously, the goal will be to help the patient achieve good outdoor distance vision, slightly different than good indoor distance vision. These conversations are an ongoing challenge because there are so many lens options to choose from. We need to talk through the pros and cons and help narrow the choices for them."



Y. Ralph Chu, MD

Corneal topography of this patient's right postop eye reveals irregular astigmatism secondary to a dry ocular surface.



Y. Ralph Chu, MD

Non-invasive testing of this patient's right eye shows a decreased tear break-up time, potentially affecting postop quality of vision.

Premium Considerations

Kathryn M. Hatch, MD, director of the refractive surgery service at Massachusetts Eye & Ear and an assistant professor of ophthalmology at Harvard Medical School, assesses a patient's suitability for premium IOLs by first focusing on preop symptoms not related to her patient's mature cataracts.

"Patients may have starbursts because of pupil size, for example," she says. "Or their preoperative symptoms could just be related to their anatomy. If they have these symptoms before surgery, you have to keep in mind that they'll likely still have these symptoms after surgery."

She relies on wavefront aberrometry to identify pre-existing issues, such as higher-order aberrations or alpha and kappa angles that suggest the pupil isn't the center of the visual axis. "If you see a very large angle, you may want to avoid a multifocal because it could mean the patient won't be happy looking through the center of the IOL, especially if it's an IOL with a diffractive optic," she says.

Dr. Shafer focuses preoperatively on "corneal-only" higher-level aberrations, quantifying how much light is being scattered by the corneal shape. These effects are distinctly different from internal higher-order aberrations associated with the dysfunctional lens that he's preparing to remove.

"Although I don't follow any hard and fast rules on this, I generally consider corneal higher order aberrations greater than 0.3 RMS

AN INVESTMENT THAT GETS SMARTER ALL THE TIME.

LENSTAR 900. IOL calculation powered by artificial intelligence.

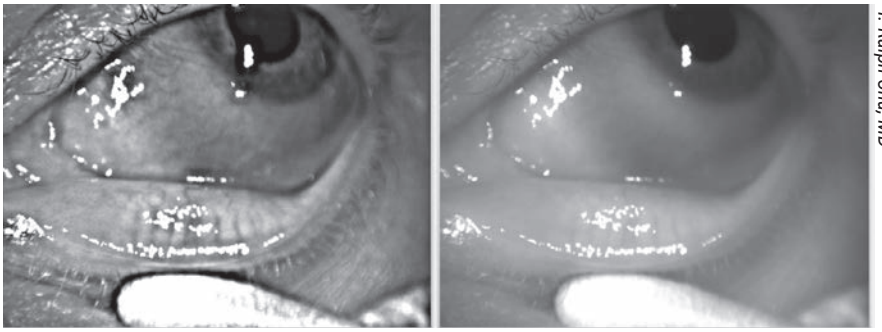
Hill-RBF 3.0, exclusively integrated into the Lenstar 900, has been updated with a greatly expanded and refined artificial intelligence model. This not only improves the accuracy for normal eyes, but is also more accurate for eyes with unusual anterior segments, as well as the high axial myope and hyperope. Also, the number of out-of-bounds indications for most cataract surgery patients has been dramatically reduced due to the incorporation of lens thickness, WTW, CCT, and patient gender.

Enjoy improved accuracy with the ever-increasing predictive power of AI.
Learn more at mylenstar.com

Current Lenstar customers: Ask us how to add EyeSuite Myopia to your existing Lenstar 900.

mylenstar.com

HAAG-STREIT USA



Y. Ralph Chu, MD

Preoperative imaging of the meibomian gland shows truncated glands corresponding to a lipid deficiency in the tear film of this patient. This is just one more condition to consider when identifying and addressing factors that can prevent you from achieving the best possible cataract surgery outcomes.

a risk factor for decreased postop visual quality," he says. "For these patients, I tend to avoid implanting a diffractive multifocal lens, which will split light in bothersome ways for any patient who already has the propensity for developing positive dysphotopsias, such as glare and halos. I find this approach can lead to improved outcomes and optimized vision quality."

When patients are considering premium lenses in her practice, Dr. Hatch pays close attention to how they react when she tells them that they may experience postop halos and glare.

"If they have a strong reaction to that possibility, I know that these lenses might not be a good idea for them," she notes. "In some ways, I'm letting patients weed themselves out. A patient might say, 'Oh, I'm fine wearing reading glasses.' Then I'll get the patient who says, 'I'll do anything I can to get out of my glasses!' Being ready to do anything, of course, must include a willingness to pay the extra cost of a premium IOL that's not covered by insurance. At that point, I start looking at what lens might be best for that type of patient."

Dr. Lee also relies heavily on high-order aberrometry to screen for risks of positive dysphotopsias, most importantly if patients choose multifocal, extended depth-of-focus or trifocal lenses.

"We try to avoid premium lenses when we think hitting plano will be very difficult," he says. "We're also factoring in the personality types that we've observed or documented to determine if we think we're going to be able to satisfy the patient."

For some of these cases, Dr. Lee and his colleagues recommend the use of a monofocal IOL.

"When we implant a monofocal as the first lens or as a replacement for a premium lens in an unhappy patient, we make sure we appropriately manage the patient's expectations about the need to wear glasses," he says. "As a result, I don't usually see many patients with monofocal lenses who are dissatisfied with their vision."

Dr. Chu recommends widening your diagnostic approach. "In many cataract patients, we need to remember that the overall quality of their vision is declining because of the aging of their eyes," he says. "We see cataracts, but their problems could also be due to degradation of the tear film. We have also learned that dry eye or the broader category of ocular surface disease, can be a significant source of poor vision quality."

Ocular Surface Management

Surgeons say that all efforts should be made to ensure a pristine ocular surface to optimize postop vision, since a disrupted ocular surface can negatively affect visual acuity. "If a patient has an abnormal tear film or epithelial basement membrane dystrophy," says Dr. Shafer, "that patient may have what we call epithelial blur. The patient's postop vision may refract to 20/20, but he or she will experience a blur from a disrupted ocular surface."

For these patients, Dr. Shafer places a gas permeable contact lens over the patient's eye before surgery, bypassing the epithelium/tear-film interface. A sudden development of crisp vision can confirm that the reduced visual quality is secondary to tear film or epithelial issues, according to Dr. Shafer.

"We then know we need to address the surface of the eye, including the possibilities of aqueous deficiency, requiring us to use punctal plugs to boost the tear film; or meibomian gland dysfunction, calling for treatment of the glands with such devices as Lipiflow, TearCare, or warm compresses for manual expression," says Dr. Shafer. "If there's an inflammatory component to the patient's dry eye, we treat the inflammatory condition. Completing this treatment generally takes six weeks before the patient is ready for surgery."

Dr. Shafer rules out EBMD with what he calls the "loose carpet" test. "The epithelium in these patients is, in fact, like a loose carpet," he notes. "I rub the epithelium with a cotton swab, and if the epithelium moves, I know it's sick and has to be removed." For EBMD, he performs a superficial keratectomy, polishes the corneal surface with a diamond burr and finishes with a gentle phototherapeutic keratectomy, applying excimer laser pulses to the periphery and center of the cornea. He says he typically follows with cataract surgery three months after this procedure.

Intraoperative Techniques

During surgery, Dr. Shafer confirms that the capsulotomy is centered on the visual axis. He then creates

WIDELY AVAILABLE

Sustained Delivery with DuraSite® Technology

AKORN | EYE CARE

MyAkornEyeCare.com
for office resources

a 5.2- or 5.3-mm capsulorhexis to ensure there's adequate capsular overlap on the optic. "If there's 360 degrees of overlap of the IOL, that lens will be rock-solid stable," he says. "If the capsulotomy is centered on the visual axis, the central portion of the optic will be right at the visual axis. That will allow it to function optimally."

Dr. Shafer also polishes the posterior capsule to minimize the possibility of posterior capsule opacification from developing. "When appropriate, a YAG capsulotomy is also reasonable to do, typically three months postop, to help improve visual quality if there's any PCO at all," he says. "But it's somewhat optional if there's a lot of cortex on the posterior capsule."

For premium lens patients, Dr. Shafer says he routinely performs PRK or LASIK as a final "tune-up" to ensure the patient benefits from the best vision possible. "We price our premium offering so that the premium cataract surgery patient pays for this enhancement up front, after we explain how it works," he explains.

Meanwhile, before performing a YAG capsulotomy, Dr. Hatch recommends making sure the lens itself isn't the issue affecting vision. "You wouldn't want to do a YAG and then find out that you have to do a lens replacement, even in a rare situation," she says.

Dr. Lee also uses the YAG laser after implanting premium IOLs, but only in patients who were initially happy with the lens before glare and halos developed at night. "If a patient isn't initially happy with the quality of vision the lens provides, it's a clue that the optics of the lens aren't working for the patient. I won't perform a YAG capsulotomy because we may need to do a lens replacement."

Postop Measures

The biggest challenges typically facing Dr. Lee and his patients are positive dysphotopsias at night, especially when the patients have received premium IOLs.

> **You can have patients whose cataract surgery outcomes are excellent, but remember that they can still have poor vision quality because of meibomian gland disease, aqueous-deficient dry eye and related issues.**
>
> **— Y. *Ralph Chu, MD***

"A lot of these patients are functionally doing very well without glasses," he notes. "I'll tell them to keep a pair of glasses in the car and put them on when they're driving at night. Other times, when necessary, we may prescribe brimonidine or even pilocarpine to try to shrink the pupil and reduce some of the nighttime positive dysphotopsias. For extreme cases of positive dysphotopsias, meanwhile, we can usually help a patient by doing a lens exchange. I do a high number of lens exchanges in my practice. Most of these patients do very well."

Negative dysphotopsias present a different challenge, creating unexpected shadows or dark crescents, almost always in the postop patient's temporal vision, according to Dr. Lee.

"These manifestations are unpredictable, sometimes occurring in patients who have apparently good outcomes," he says. "Some patients may even have the same lens in both eyes and have symptoms in one eye but not the other. The good news, however, is that negative dysphotopsias almost always go away with time. If they persist and the patient comes back to me with the same complaints in three months, we can try to do a reverse optic capture, surgically elevating the optic out of the capsule and into the sulcus and leaving the haptics in the bag. Doing this changes the position of the lens edge or the overlap of the capsule and lens edge in most patients, reducing negative dysphotopsias. (*See the figure on page 55.*) If that doesn't work, the next step would be to put a replacement lens in the sulcus and suture the lens to the iris."

To spare postop patients negative dysphotopsias, Dr. McKee tries to avoid the use of square-edged IOLs, which he finds to be more frequently associated with these disturbances.

"A smooth, rounded anterior optic doesn't seem to result in as many negative dysphotopsias," he says. "I polish the anterior rims of all capsules, which I think helps. It certainly reduces scarring and makes IOL repositioning or lens exchanges easier in the future, if indicated. I follow these patients closely. I have seen self-referred patients who felt like their surgeons didn't believe they were experiencing these effects."

Rewards of Vigilance

Like his colleagues, Dr. Chu recommends vigilance when evaluating vision quality throughout the postop period.

"You can have patients whose cataract surgery outcomes are excellent, but remember that they can still have poor vision quality because of meibomian gland disease, aqueous-deficient dry eye and related issues," he says. "Identifying all potential issues from the front of the eye to the back of the eye—possibly involving the tear film, cornea, lens, capsule, retina and even the vitreous—is always important to ensure the highest quality of vision. Yes, even a vitreous floater can significantly degrade quality of vision. So every medium of the eye is important when you're assessing patient satisfaction and the definition of vision that has the

DATA THAT **EMPOWERS**

HEIDELBERG
EYE EXPLORER

Welcome to the next generation platform for image management and device integration. Built to optimize eye care workflow, simplify data exchange, and increase security; HEYEX 2 delivers the future today.

Experience the power of HEYEX 2. Call 800-931-2230 or visit www.heidelberg-eye-explorer.com

- **DICOM Standard**
- **Dynamic Visualization**
- **PACS Technology**

HEIDELBERG ENGINEERING

30 YEARS EMPOWERING YOU

AN UPDATE ON THERAPIES FOR OCULAR ALLERGIES

A stepwise approach that starts with over-the-counter medications and then progresses to steroids in severe cases.

BY MICHELLE STEPHENSON
CONTRIBUTING EDITOR

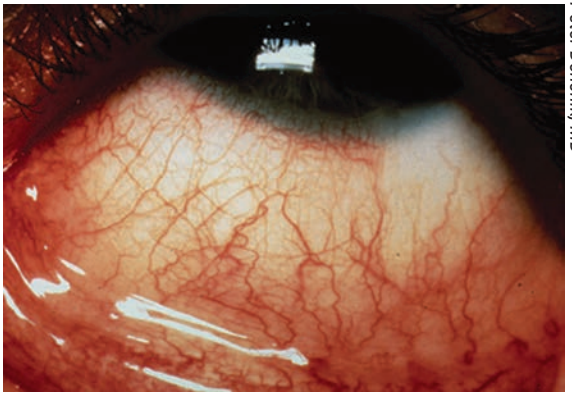
Because the eye is in constant contact with the environment, it is vulnerable to irritants. Allergic conjunctivitis affects approximately 40 percent of the population,[1] and treatment involves a comprehensive, stepwise approach, according to experts. Here's a look at how clinicians approach allergy patients with today's modalities.

First-line Approaches

Seasonal allergic conjunctivitis and perennial allergic conjunctivitis are the most common ocular allergies, affecting 15 to 25 percent of the population.[1] Atopic keratoconjunctivitis, vernal keratoconjunctivitis and giant papillary conjunctivitis are more severe conditions and more challenging to treat.

Treatment typically begins with nonpharmacological agents, such as cold compresses, and progresses to a variety of topical and oral medications. Of the pharmaceutical agents available, antihistamines, mast cell stabilizers, and dual-action agents are the most common.

Tears are often the initial treatment to rinse allergens from the eye. "When a patient presents to my office with ocular allergy symptoms, I first use refrigerated, preservative-free tears, specifically a watery, non-viscous variety like Refresh Plus," says Robert Latkany, MD, who is in practice in New York City. "Patients can refrigerate the tears and rinse the eyes with them a few times a day. Patients like the cold drops, and they tolerate them well because they are preservative-free. Any watery, non-viscous, preservative-free drop will work well."



Peter Donshik, MD

Working with an allergist can help root out the source of the problem, clinicians note.

Antihistamines and Mast Cell Stabilizers

To treat the source of the allergy, however, clinicians usually reach for an antihistamine or a mast cell stabilizer.

Cetirizine ophthalmic solution 0.24% (Zerviate, Eyevance) is the most recent addition to the topical antihistamine armamentarium, having been launched for allergic conjunctivitis last year.[2] It's been approved for b.i.d. dosing.

Single-center and multicenter, double-masked, randomized, vehicle-controlled, parallel group conjunctival allergen challenge studies were conducted over approximately five weeks and four study visits. Approximately 100 people were randomized in each study. Primary endpoints were ocular itching and conjunctival redness 15 minutes and eight hours post-treatment, post-

This article has no commercial sponsorship.

Dr. Mah is a consultant for Novartis, Allergan/Abbvie, Bausch + Lomb, Sun, Kala and Eyevance. **Dr. Latkany** has no financial interest in any of the products discussed.

conjunctival allergen challenge.

In the study, cetirizine administered 15 minutes or eight hours prior to conjunctival allergen challenge resulted in significantly lower ocular itching scores compared to vehicle at all time points post-conjunctival allergen challenge. Investigators measured conjunctival redness and found that it was significantly lower after cetirizine treatment compared to vehicle at seven minutes post-conjunctival allergen challenge at both 15 minutes and eight hours post-treatment in both studies. Cetirizine also resulted in significant improvement in chemosis, eyelid swelling, tearing, ciliary redness, and episcleral redness, as well as nasal symptoms after conjunctival allergen challenge. No safety concerns were identified.

According to Francis Mah, MD, who's in practice in San Diego, some of the more popular medications in this category now have generic and over-the-counter options. "Alcon has made the decision to put Patanol (0.1% olopatadine), Pataday (0.2% olopatadine) and then Pazeo all over-the-counter under the Pataday name," he says. "That's significant because those were the most popular prescriptions that we were writing in eye care, and now they're all OTC. The other medication that ophthalmologists are writing for is Zerviate, so that's kind of the last man standing for prescription medications."

Dr. Latkany agrees. "My favorite of the group is the Pataday Once Daily. "Patients seem to tolerate it well, and there is very little stinging," he says. "It used to be a popular drop when it was a prescription, but it was often not covered by insurance. Another medication in that category is Bepreve. Others include over-the-counter Zaditor and Lastacaft. Cetirizine is now just a straight antihistamine drop, and some people use cromolyn sodium, which is a nice cheap drop."

Dr. Mah notes that these topical agents can get the majority of seasonal allergy patients under control. "More than 90 percent of patients can be controlled with artificial tears, avoidance of the allergen, and then using topical antihistamines or mast cell stabilizers," he says.

If the patient has allergy symptoms that extend beyond the eye, such as rhinitis, post-nasal drip or asthma, Dr. Mah recommends using a systemic medication. "You want to start simple," he advises. "Allegra is a really good one because it has few systemic side effects, like drowsiness. Zyrtec and Claritin are also great. If a patient has lots of nasal symptoms, Flonase can be added, and you can also add a decongestant. Generally, for me, I tend to go to either Zerviate, which is a prescription, or topical Pazeo, which is OTC. Then, I add Flonase if the patient has a nasal component."

Steroids

Steroids can be added if the eye is very inflamed or if there are significant ocular issues. "I'm not afraid to give a little steroid now that we have low concentrations of loteprednol," Dr. Latkany says. "Because loteprednol is not a super-strong steroid, there are fewer side effects. Giving it to the patient for a couple of weeks seems to work better than just going to an antihistamine or mast cell stabilizer combo. If a patient has severe allergies, I might start off with the steroid and switch him or her to an antihistamine/mast cell stabilizer. Other products that I use off-label are in the NSAID category to help with some of the secondary inflammation. Some favorites in that category include Prolensa, BromSite, and Nevanac. I'm not a big fan of any of the generics in that category, but I have had some success with them."

Patients who have severe cases of atopic keratoconjunctivitis may require a stronger steroid. "I might

MEDICATIONS TO TREAT OCULAR ALLERGY

Generic	Brand
ketorolac tromethamine 0.4%	Acular LS
ketotifen fumarate 0.035%	Alaway
loteprednol etabonate 0.2%	Alrex
bepotastine besilate 1.5%	Bepreve
epinastine HCl 0.05%	Elestat
emedastine difumarate 0.05%	Emadine
alcaftadine 0.25%	Lastacaft
azelastine hydrochloride 0.05%	Optivar
olopatadine hydrochloride 0.2%	Pataday
olopatadine hydrochloride 0.1%	Patanol
olopatadine hydrochloride 0.7%	Pazeo
ketotifen fumarate 0.035%	Zaditor
cetirizine 0.24%	Zerviate
nedocromil sodium 2%	Alocril
lodoxamide tromethamine 0.1%	Alomide
cromolyn sodium 4%	Crolom

start off with a stronger steroid, such as prednisolone, and possibly Durezol, if the eye is very inflamed," Dr. Latkany adds. "Once the eye has been quieted over a few days, I can convert to a less potent drug. In addition to drops, we can also use oral antihistamines for these patients." Physicians' steroid regimens usually consist of an initial high dose and then a quick taper.

Involve an Allergist

It's important to determine the source of the allergy, so it can be helpful to involve an allergist. "Some ophthalmologists do their own testing in their offices to detect what allergens are the source of the patient's symptoms," Dr. Latkany explains. "I perform a prick test followed by an intradermal test, if necessary, to detect the specific triggers. If we can determine the source, patients can make lifestyle modifications, such as not allowing the dog or cat in their bed if they are allergic. Or, if a patient is allergic to pollen, he or she could shower before bed to remove any pollen. It's nice to detect the exact allergen."

When treating ocular allergy, Dr. Latkany takes a comprehensive approach. "I like to hit the allergy from many angles: cold compresses; cold tears; Pataday; include an allergist; identify the allergen," he says. "Then, once you know the specific allergen, start with anti-allergy environmental changes, and then consider immunotherapy shots. Some people are even doing sublingual therapy, which includes tricking the immune system into thinking that the patient is not being exposed to something he or she is allergic to."

Besides environmental allergens, patients can be allergic to products they use on their faces, such as certain moisturizers and cosmetics. "It's important for patients to bring all face and eye products to an allergist," says Dr. Latkany. "The allergist can do a patch test on the patient's back. If the patient is allergic to a product, we want to know that rather than just giving him or her Pataday and a steroid, while they keep using the product. Identifying product sensitivities helps us treat them."

> **Take a comprehensive approach and attack the source of the problem rather than the symptom.**
>
> ***—Robert Latkany, MD***

Patients can also be allergic to medications they're taking. "Patients can also be allergic to the preservatives in glaucoma drops or be allergic to the medication itself," notes Dr. Latkany. "It's important to identify this rather than treating the allergy with medication. In these cases, call the glaucoma doctor and ask if you can switch medications for a week to see if the allergy symptoms get any better. Lastly, contact lenses can cause allergy symptoms. The contact lens or the contact lens solution may be triggering an allergic or chemical sensitivity."

Dr. Latkany adds that treatment will be much more successful once the source of symptoms is identified. "Take a comprehensive approach and attack the source of the problem rather than the symptom," he advises.

The Future

Aldeyra has developed an anti-inflammatory drug called reproxalap that has been quite successful in reducing allergic conjunctivitis symptoms. The company announced positive results from a Phase III trial of 0.25% and 0.5% reproxalap topical ophthalmic solution in patients with allergic conjunctivitis. The clinical trial met the primary endpoint and the key secondary endpoint for both concentrations of reproxalap.[3]

The Phase III trial was a double-masked, randomized, vehicle-controlled, multicenter, parallel-group conjunctival allergen challenge that assessed the efficacy and safety of 0.25% and 0.5% concentrations of reproxalap topical ophthalmic solutions compared to vehicle in 318 patients with seasonal allergic conjunctivitis.

Compared to patients treated with vehicle, patients treated with 0.25% and 0.5% reproxalap experienced a statistically significant reduction in ocular itching. The investigators found that both concentrations of the drug exhibited an anti-inflammatory profile that's distinct from standard-of-care antihistamine therapy and supports a differentiated mechanism of action for the treatment of allergic conjunctivitis.[3]

"I think the coolest line of potential topical drugs are the biologics," says Dr. Mah. "They're obviously strong anti-inflammatories. Because allergy is an inflammatory condition, I think that would be interesting. However, they haven't even entered Phase II trials, so it'll be a while before they are available. Everything else in the pipeline is either a topical antihistamine, a topical antihistamine/mast cell stabilizer, or a topical mast cell stabilizer, and we've had these medications for decades."

While topical ophthalmic solutions are the most convenient treatment, the eye's anatomy and physiology lead to decreased bioavailability of the drugs. Ocular drug-delivery systems are also being studied to overcome this limitation. ◀

1. Kimchi N, Bielory L. The allergic eye: Recommendations about pharmacotherapy and recent therapeutic agents. Current Opinion in Allergy and Clinical Immunology 2020;20:4:414-420.
2. Meier EJ, Torkildsen GL, Bomes PJ, Jasek MC. Phase III trials examining the efficacy of cetirizine ophthalmic solution 0.24% compared to vehicle for the treatment of allergic conjunctivitis in the conjunctival allergen challenge model. Clinical Ophthalmology 2018:12:2617-2628.
3. Aldeyra trial news. https://ir.aldeyra.com/news-releases/news-release-details/aldeyra-therapeutics-announces-positive-top-line-results-phase-3.

ACELLFX™

ACELLULAR AMNIOTIC MEMBRANE

ACCELERATE with ACELLFX.

The *BEST* choice for your patients, *NATURALLY*.

- Improve Visual and Surgical Outcomes
- Promote Healthy Epithelial Cells and Thick Tear Film
- **NEVER** any Cryopreservants, Antibiotics, Cross Linkers or Ethanol

Exclusively Distributed by

Blythe Medical

706.654.3209

SCAN ME

ACELLFX™

acellfx.com

JOIN US for a free webinar.

Conjunctivochalasis Surgical Techniques

Though it shares symptoms with dry eye, don't mistake the two conditions.

BY SAMANTHA MAREK, MD, AND STEPHEN ORLIN, MD
PHILADELPHIA

Conjunctivochalasis is often overlooked in older individuals because its symptoms are very similar to those of dry-eye disease. The loose, redundant, nonedematous conjunctiva that characterizes the condition frequently disrupts tear production. It was first described in 1908 by Anton Elschnig,[1] but the term conjunctivochalasis was coined in 1942 by Wendell Holmes, MD.[2] Here, we'll review the clinical findings, pathogenesis and management of this condition.

Clinical Findings

Conjunctivochalasis is characterized by loose, redundant, non-edematous conjunctiva. It's typically found on the inferior globe (*Figures 1 and 2*)[3,4,5,6] but sometimes occurs superiorly. The redundancy may be localized to one portion of the globe—either nasally, temporally or centrally—or span the entire inferior portion of the globe. When the loose conjunctiva folds over the lower lid margin, it's easily seen and diagnosed.

The condition typically affects elderly patients, but can also be seen in younger patients. Women are more commonly and more severely affected than men. Bilateral presentation is most common, but it may also be asymmetrical and even unilateral.

Symptoms often include mild irritation, foreign body sensation, localized pain, tearing, blurred vision, burning, mucus discharge and nocturnal lagophthalmos. In the case of inferiorly located redundancies, the folded configuration of the conjunctiva at the inferior lid margin may cause disruption of the tear meniscus, reducing the spread of tears on the ocular surface and resulting in tearing. Epiphora may also occur secondary to redundant conjunctiva overriding the puncta, leading to punctal occlusion.

It's important to note, however, that some patients may be completely asymptomatic. In these cases, it's not unusual for mild conjunctivochalasis to be misidentified as a normal variant of dry eye and a result of the aging process. Dry-eye disease and conjunctivochalasis may also occur concomitantly, making it difficult to determine which condition to attribute the symptoms to. However, if the pain is worsened in downgaze or with blinking, conjunctivochalasis is the likely culprit. Additionally, the clinician can reproduce the pain of conjunctivochalasis by applying pressure on the lids over the area of the redundancy while the patient looks in the opposite direction.[7]

Besides the hallmark redundant conjunctiva, other examination findings include subconjunctival hemorrhage due to mechanical trauma from friction with blinking, unstable tear film, conjunctival injection from inflammation and lagophthalmos. The cornea may be clear or have punctate staining, as well as dellen formation adjacent to the redundant conjunctiva, or marginal ulcers.

Pathogenesis

The exact mechanism for conjunctivochalasis development isn't known, but the literature suggests that it's multifactorial.[5,6] One thing we do know is that this condition is associated with pterygia and pingueculae. While older age plays a role in both pingueculae and conjunctivochalasis,[8] the condition's link to pterygia is thought to be related to dry eye and a shared association with inflammatory cytokines.[9]

Histopathologic studies are conflicting: Some have shown normal conjunctiva on microscopic evaluation[10] and others have demonstrated degeneration of elastic fibers and chronic inflammation.[11] Elastic fiber degeneration is seen in pingueculae, pterygia and photoaged skin, which suggests that conjunctivochalasis is induced, in part, by ultraviolet radiation.[8,12]

Also like pterygia, the conjunctivochalasis tissue itself has been shown to have increased levels of matrix metalloproteinases,[13,14,15] which are enzymes that degrade matrix proteins. The tissue has also been shown to have increased reactive oxygen species that lead to oxidative stress.[16] Why these

This article has no commercial sponsorship.

Dr. John is a clinical associate professor at Loyola University at Chicago and is in private practice in Oak Brook, Tinley Park and Oak Lawn, Illinois. He has a small equity interest in, is consultant/advisor to, and has received lecture fees and grant support from Bio-Tissue and Tissue Tech. He can be reached at 708-429-2223; email: tjconference@gmail.com.

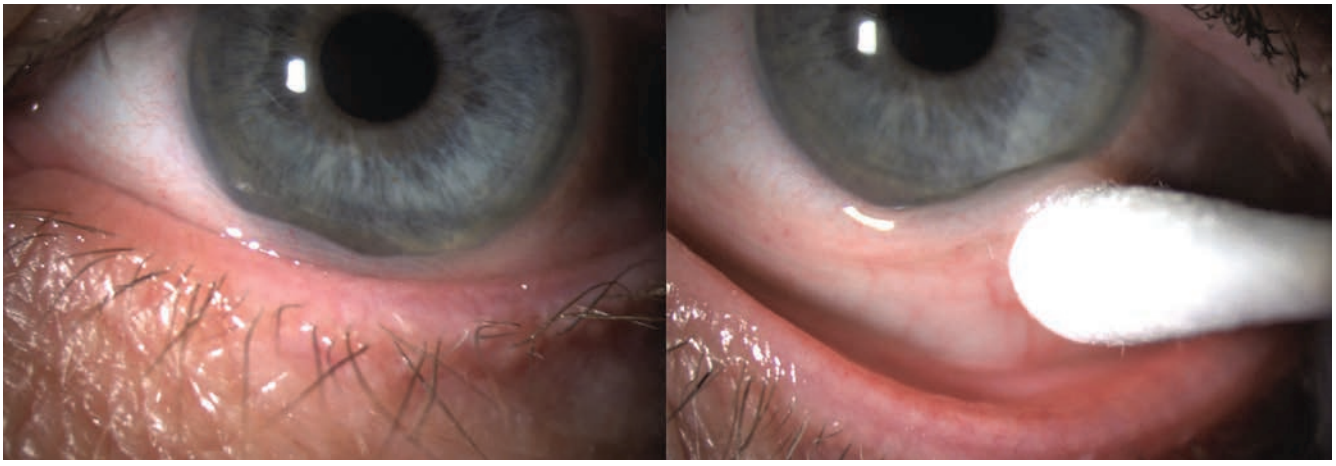


Figure 1. Conjunctivochalasis of the inferior bulbar conjunctiva.

develop is still unknown, but one hypothesis suggests that mechanical friction and dryness kick off an inflammatory reaction. The conjunctivochalasis tissue disrupts the tear film, which can cause tear pooling, either by disruption of the film or by punctal occlusion, which in turn provides a reservoir that prolongs the amount of time the inflammatory reaction is in contact with the ocular surface.[5,6]

Considering all of these factors, one can imagine conjunctivochalasis as a cycle that feeds upon itself, leading to the progression of the condition. Senile eyelid laxity may lead to dryness and friction that then induces an inflammatory cascade, including metalloproteinases and reactive oxygen species that damage the extracellular matrix proteins that ensure the conjunctiva adheres to the sclera. This leads to the conjunctiva hanging loosely and folding in on itself. In doing so, it creates more surface to undergo mechanical trauma with blinking, and that feeds back to create more inflammatory reactions. The resulting inflammatory reaction may also contribute to the symptoms associated with conjunctivochalasis.

Management

Asymptomatic patients don't require treatment, but symptomatic patients should be trialed first on conservative medical management before considering surgical options.[5,6,17] The goals of treatment are to smooth the ocular surface; restore the tear meniscus in order to improve tear-film stability; and reduce surface irritation and inflammation.

These conservative measures primarily include ocular lubrication with artificial tears and lubricating ointments. If these treatments alone are insufficient to bring symptomatic relief, autologous serum tear drops, topical steroids, NSAIDs and antihistamines may also provide relief. Patients experiencing nocturnal lagophthalmos may benefit from nighttime lubricating ointment and patching to protect the ocular surface.

Coexisting ocular surface disease such as meibomian gland dysfunction, blepharitis and dry eye should also be treated accordingly. If other surface issues are left untreated, patients may remain symptomatic.

Surgical management can be considered for patients who haven't responded to the above regimen. Numerous surgical methods have been described, and they can be broken into three main categories: shrinkage of redundant tissue; excision of redundant tissue; and improved adhesion of conjunctiva to sclera. These methods create a smoother ocular surface by eliminating or reducing the redundant tissue folds. With surgical procedures, the risk of cicatricial changes, symblepharon formation and shortening of the fornix are important risks to consider, as they can lead to worsening symptoms. Here are the options for surgical management:

Shrinkage of redundant tissue. Conjunctival cauterization is used to shrink the redundant tissue;[18,21] it can also improve conjunctiva-sclera adhesion through coagulation. Conjunctival cauterization has been very successful in improving both symptoms and clinical findings related to conjunctivochalasis. After the procedure, patients may experience mild irritation, foreign body sensation, hyperemia, chemosis and subconjunctival hemorrhage—all of which are self-limited.

Some of the benefits of this procedure are that it can be performed with topical or local anesthesia, it doesn't require sutures and it has a lower risk of infection, scar formation and restricted postop motility. Risks include symblepharon formation, cicatricial entropion and shortening of the fornix.

Shrinkage and coagulation of tissue can also be achieved with argon laser photocoagulation and radiowave electrosurgery.[19] These have risks and benefits similar to cauterization and achieve similar results. Radiowave electrosurgery

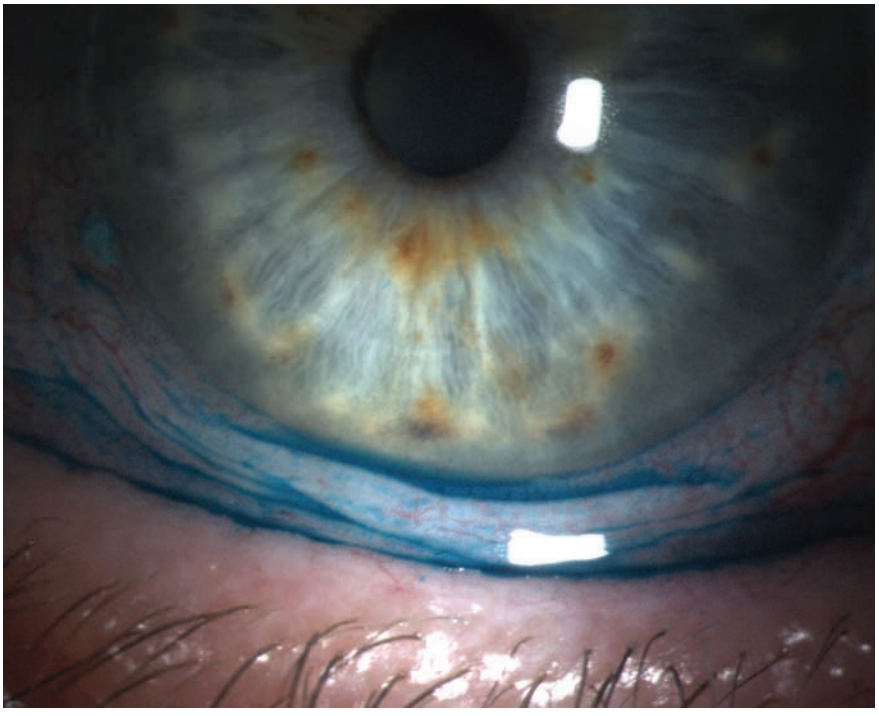


Figure 2. Conjunctivochalasis of inferior bulbar conjunctiva with lissamine green staining.

induces intracellular water boiling to shrink and coagulate the redundant conjunctiva and avoid charring of the tissue. This reduces the risk of scarring and enhances healing since there's less thermal damage to tissues.

Tissue excision. The second surgical approach category is removal of the excess conjunctival tissue. This involves excision of the redundant conjunctiva.[20] The tissue removed can be either localized to the area with the most clinical change or it can be done along the entire inferior bulbar conjunctiva.

Once tissue is removed, the wound can be managed in a number of different ways, including primary healing, suturing or gluing, and amniotic membrane grafting. Primary healing[21] typically has a prolonged recovery time compared to other closure methods. It also has a high reported recurrence rate—24 percent—whereas recurrence rates with other surgical methods are reported to be zero percent.

With direct closure using absorbable sutures[21,26] it can be difficult to determine how much conjunctiva to remove. If too much tissue is taken, the fornix may be shortened and cicatricial changes are likely to become more problematic. If not enough tissue is removed, the procedure may be non-therapeutic. The required sutures can prolong healing time, cause irritation postoperatively and lead to abscess or pyogenic granuloma formation.

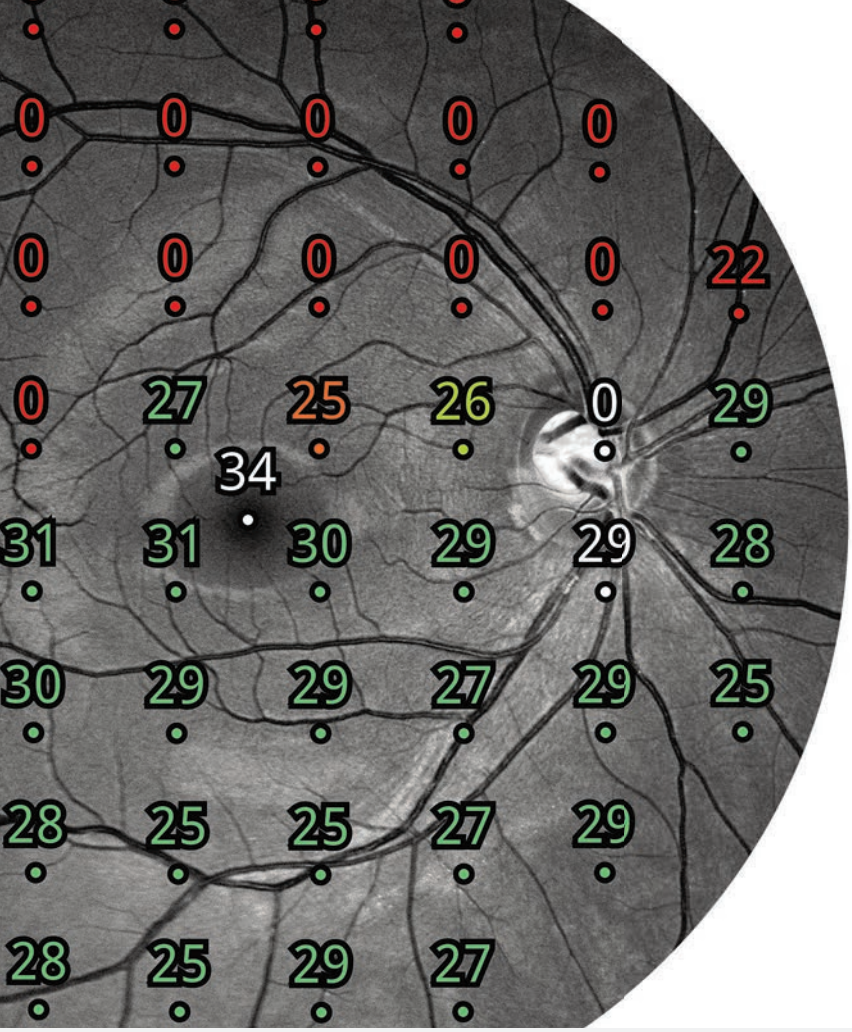
Fibrin glue[22] has been used in place of sutures. This reduces the risks of suturing and causes less postoperative discomfort. Another technique is to make a conjunctival incision, inject the fibrin glue, and then pinch and lift the conjunctiva to allow glue polymerization to occur. The surgeon then excises the elevated conjunctiva after the glue has set. Both methods have been shown to be successful.

Finally, an amniotic membrane graft can be used to cover bare sclera.[23,24] The graft can be secured with fibrin glue or sutures to cover the bare sclera. Fibrin glue is associated with more postoperative comfort than sutures and reduces the infectious and inflammatory risks associated with sutures. Use of amniotic membrane grafting reduces risks of fornix shortening and limitations of ocular motility.

Conjunctival ligation is another option for removing the redundant tissue.[25] This method involves drawing up the redundant tissue into a drip tube. Then, a suture is placed at the base of the conjunctiva and the tied-off tissue is excised. This method may lead to less postoperative discomfort than conjunctival resection with direct closure using sutures.

Improving adhesion. The last category of surgical methods aims to improve conjunctival adhesion to the underlying sclera. It includes scleral fixation with sutures or cauterization and amniotic membrane used to reinforce Tenon's capsule.[26] No conjunctiva is excised with these methods. Scleral fixation involves straightforward attachment of the redundant conjunctiva to the underlying sclera. For Tenon's reinforcement, an incision is made in the conjunctiva and loose Tenon's capsule is excised. The amniotic membrane is placed over the sclera and conjunctiva is closed over top. These methods reduce the risk of fornix shortening and ocular motility limitation.

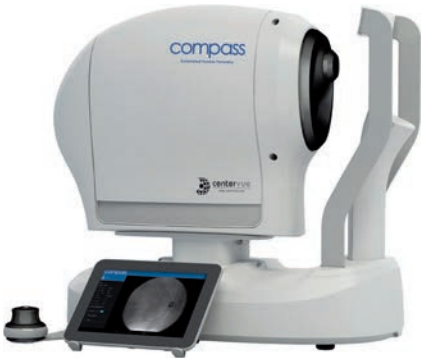
In summary, conjunctivochalasis is a condition characterized by loose, non-edematous, redundant conjunctiva. The mechanism for pathogenesis is unknown, but is likely multifactorial and related to UV damage, mechanical friction and inflammatory reaction that leads to loss of tissue elasticity. Symptoms of this condition range from none to tearing, irritation and pain. Asymptomatic patients don't require treatment. For symptomatic patients, conservative treatment is initially targeted at lubrication of the ocular surface. If conservative measures



iCare COMPASS

Fundus automated **perimetry**

+ Real-time retinal tracking
+ Imaging & Perimetry in one device
+ TrueColor confocal retinal imaging
+ No trial lens required
+ Significantly less variable than Standard Perimetry



iCare IC200

200 degrees of **tonometry**

+ Supine, elevated & seated operation
+ No corneal disruptions
+ Suitable for every patient
+ Single use probes to exceed infection control guidelines

For more information, scan, call 888.422.7313, or email infoUSA@icare-world.com
www.icare-world.com/USA

For better perception **icare**

fail, surgical options include shrinkage of redundant tissue, removal of redundant tissue and increased adhesion between conjunctiva and sclera. ◀

1. Elschnig A. Beitrag zur aetiologie und therapie der chronischen konjunktivitis. Dtsch Med Wochenschr 1908;34:1133-1155.
2. Hughes WL. Conjunctivochalasis. Am J Ophthalmol 1942;25:48-51.
3. Di Pascuale MA, Espana EM, Kawakita T, Tseng SCG. Clinical characteristics of conjunctivochalasis with or without aqueous tear deficiency. Br J Ophthalmol 2004;88:388-391.
4. Balci O. Clinical characteristics of patients with conjunctivochalasis. Clinical Ophthalmology 2014;8:1655-1660.
5. Meller, D, Tseng SC. Conjunctivochalasis: Literature review and possible pathophysiology. Survey of Ophthalmology 1998;43:3:225-232.
6. Marmalidou A, Kheirkhah A, Dana R. Conjunctivochalasis: A systematic review. Survey of Ophthalmology 2018;3:554-564.
7. Mimura T, Yamagami S, Usui T, et al. Changes of conjunctivochalasis with age in a hospital-based study. Am J Ophthalmol 2009;147:1:171-77.
8. Mimura T, Mori M, Obata H, et al. Conjunctivochalasis: Associations with pinguecula in a hospital-based study. Acta Ophthalmol 90:8:773-82.
9. Tong L, Lan W, Sim HS. Conjunctivochalasis is the precursor to pterygium. Med Hypotheses 2013;81:5:927-30.
10. Watanabe A, Yokoi N, Kinoshita S, Hino Y, Tsuchihashi Y. Clinicopathologic study of conjunctivochalasis. Cornea 2004;23:3:294-298.
11. Francis IC, Chan DG, Kim P, Wilcsek G, Filipic M, Yong J, Coroneo MT. Case-controlled clinical and histopathologic study of conjunctivochalasis. Br J Ophthalmol 2005;89:302-305.
12. Tong L, Lan W, Sim HS, Hou A. Conjunctivochalasis is the precursor to pterygium. Medical Hypotheses 2013;81:927-930.
13. Li D, Meller D, Liu Y, Tseng SCG. Overexpression of MMP-1 and MMP-3 by cultured conjunctivochalasis fibroblasts. IOVS 2000;41:2:404-410.
14. Acera A, Vecino E, Duran JA. Tear MMP-9 levels as a marker of ocular surface inflammation in conjunctivochalasis. IOVs 2013;54:13:8285-8291.
15. Guo P, Xhang S, He H, Zhu Y, Tseng SCG. TSG-6 controls transcription and activation of matrix metalloproteinase 1 in conjunctivochalasis. IOVS 2012;53:3:1372-1380.
16. Ward SK, Wakamatsu TH, Dogru M, Ibrahim OMA, Kaido M, Ogawa Y, Matsumoto Y, Igarashi A, Ishida R, Shimazaki J, Schnider C, Negishi K, Katakami C, Tsubota K. The role of oxidative stress and inflammation in conjunctivochalasis. IOVS 2010;51:4:1994-2002.
17. Mamalidou A, Palioura A, Dana R, Kheirkhah A. Medical and surgical management of conjunctivochalasis. The Ocular Surface 2019;17:393-399.
18. Haefliger IO, Vysniauskiene I, Figueiredo AR, Piffaretti JM. Superficial conjunctiva cauterization to reduce moderate conjunctivochalasis. Klin Monatsbl Augenheilkd 2007;224:237-239.
19. Trivle A, Dalianias G, Terzidou C. A quick surgical treatment of conjunctivochalasis using radiofrequencies. Healthcare 2018;6:14:1-5.
20. Petris CK, Holds JB. Medial conjunctival resection for tearing associated with conjunctivochalasis. Ophthalmic Plast Reconstr Surg 2013;29:304–7.
21. Liu D. Conjunctivochalasis: A cause of tearing and its management. Ophthalmic Plastic and Reconstructive Surgery 1986;21:25-28.
22. Brodbaker E, Bahar I, Slomovic AR. Novel use of fibrin glue in the treatment of conjunctivochalasis. Cornea 2008;27:950-2.
23. Georgiadia NS, Terzidou CD. Epiphora caused by conjunctivochalasis: Treatment with transplantation of preserved human amniotic membrane. Cornea 2001;20:6:619-621.
24. Meller D, Maskin SL, Pired RTF, Tseng SCG. Amniotic membrane transplantation for symptomatic conjunctivochalasis refractory to medical treatments. Cornea 2000;19:6:796-803.
25. Nakasato H, Uemoto R, Meguro A, et al. Treatment of symptomatic inferior conjunctivochalasis by ligation. Acta Ophthalmol 2014;92:e411-2.
26. Otaka I, Kyu N. A new surgical technique for management of conjunctivochalasis. Brief Reports 1999;129:3:385-387.

DISCLOSURES

Samantha Marek, MD, is a resident at the University of Pennsylvania Department of Ophthalmology.
Stephen Orlin, MD, is the director of the Cornea Department, chair of the Cornea Service, co-director of the Refractive Surgery Service and an associate professor of ophthalmology at the Penn Presbyterian Medical Center of Philadelphia. They report no related financial disclosures.

eyes on EYECARE

Find the best talent for your practice

Accelerate your hiring process with Eyes On Eyecare's industry-leading solutions. We've helped hundreds of private practices and large organizations find qualified optometrists, techs, opticians, and ophthalmologists.

Post a job on eyecare's #1 job board

Leverage our skilled recruiters

Build your brand with recruitment marketing

The largest eyecare partner network

We're pleased to partner with Jobson Optical Group to extend the reach of your job listings. Jobs are automatically shared across 12+ eyecare and hiring websites.

Find your next hire at eyesoneyecare.com/hire-now

Going the Distance for Underserved Patients

The rewards—and challenges—of bringing vitreoretinal care to Kenya.

BENJAMIN ROBERTS, MD
BOMET, KENYA

Art imitates life, but sometimes work imitates life, too. This thought occurred to me as I jogged along a rural road in Bomet, Kenya, where I'd moved in 2006 to set up a new, improved vitreoretinal clinic for a local populace who had gone without for a woefully long time. I'd always start one of these runs with the intention to be by myself, with only my thoughts and endorphins to keep me company. This never lasted. Soon, I'd have a crowd of kids following me, calling out, "Mzungu!" (an affectionate term for someone with fair skin) "How are you?"

It was on these runs, surrounded by the folks I was there to help, that I realized that my ambitious goal of establishing a vitreoretinal center, with all of its challenges and unforeseen problems, was going to be a lot more like a marathon than a sprint: You're not ready to run a marathon overnight, and the race isn't over until you've overcome weariness, pain and doubts of finishing. *Work had imitated life.*

Here's my account of bringing the dream of sustainable eye care to a corner of sub-Saharan Africa across the finish line.

An Eye-opening Trip

My interest in global medicine, specifically global ophthalmology, began long before I attended medical school.

I spent one summer in Jamaica after my sophomore year in college, working with a small team of ophthalmologists to provide eye care to communities on the north side of the island. The locals' access to medical care was limited, and I was humbled by the circumstances and difficult challenges that many of these patients faced. Then I saw the transformation these same patients underwent after having vision-restoring cataract surgery.

My eyes were opened.

I suddenly realized the impact that ophthalmologists could have not just in Jamaica, but worldwide, both in the delivery of eye care and the education of eye-care providers.

I returned to my life in the United States with renewed vigor, and in medical school I investigated which areas of the world had a combination of the greatest rates of blindness and the fewest ophthalmologists per capita. Sub-saharan Africa met both of these criteria. So, in 1998, as a senior medical student, I traveled to Bomet, Kenya's Tenwek mission hospital to gauge its ability to care for the blind. What I saw when I arrived was a small, 40-year-old hospital with an eye clinic that performed outreach into the community and focused mainly on helping patients in need of cataract surgery. At the time, manual small-incision cataract surgeries were being done by the occasional visiting ophthalmologist and an ophthalmic clinical officer (the Kenyan equivalent of an ophthalmology-oriented physician assistant). Patients with complex eye problems were often referred to Nairobi, Kenya's capital. This was an unreasonable request, however, since most patients could afford neither the cost of transportation nor the medical care in the capital city. They needed an option closer to home.

Tenwek Mission Hospital campus, located in southwest Kenya, serves as a referral hospital for the region.

It was decided, then: After my two-month medical-student experience, I departed Kenya with dreams of establishing affordable, comprehensive eye care for this community. Seven years later, after completing my ophthalmology residency and fellowship training in vitreoretinal surgery, I returned to Tenwek Hospital to get to work.

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.

The new Tenwek Eye Clinic is equipped for comprehensive eye care.

Getting Up to Speed

We faced many challenges trying to set up a clinic in rural Africa that would be capable of delivering specialized eye care. I spent much of my two-year retina fellowship just preparing for the move to Kenya. For instance, during that time, I intentionally saved all the disposables after each surgical case; with help, I cleaned, repackaged and sterilized them to be used again. I also worked with industry to secure donations of equipment—specifically a vitrectomy machine. I met with private donors to help fund the purchase of other equipment, like a microscope suitable for retina surgery, a variety of surgical instruments, a slit lamp and a laser that could be shared between the clinic and the operating room.

Once I got back to Tenwek Hospital, I spent several weeks learning how the clinic functioned and slowly began to introduce novel ideas, and offer surgeries that hadn't been done there before. Though I was highly motivated, the first few retina surgeries we attempted were quite grueling—I realized that I should have paid more attention to the excellent scrub nurses I had during my fellowship training. After (re)learning how to maneuver through the menu screens and choose the right settings for the vitrectomy machine, I had taught the scrub techs the same. Though the technicians were accomplished in assisting with MSIC surgery, they had no experience with the computerized machines used in eye surgeries like vitrectomy and phaco. So, personnel training became a necessity if we were to continue using all of this technology. Thankfully, in a short time, these same staff became very proficient with the equipment and are now vital assets to every surgery.

Another hurdle was the potential

TENWEK HOSPITAL: THE RESIDENT EXPERIENCE

SAMIR PATEL, MD

As a resident, my short-term global ophthalmology experience in rural Africa provided a limited, but important, perspective on the unique considerations surrounding international ophthalmology. Having arrived in the second half of my third year of residency, and having already matched into a vitreoretinal fellowship, I was particularly excited to spend two weeks with Dr. Roberts and the entire ophthalmology team at Tenwek Mission Hospital in Bomet, Kenya. Dr. Roberts is fellowship-trained as a vitreoretinal surgeon, and Tenwek Hospital is one of only a handful of referral centers in Eastern Africa that have the resources to treat retinal pathology. As an aspiring retina specialist, I was eager to learn about the practice patterns of a vitreoretinal surgeon in this environment.

Opened in 2018, the Tenwek Eye and Dental Center houses the clinic and operating rooms, and the physical environment is almost identical to what you'd expect in the United States. By design, Dr. Roberts has labored under the conviction that every patient—whether in rural Kenya or back on his furloughs in Alabama—deserves the same excellent, compassionate care.

Since his arrival in 2006, Dr. Roberts has expanded Tenwek's ophthalmology department into a tertiary eye referral center that's able to manage nearly any ocular pathology. On the edge of the Rift Valley, the clinic is filled with the latest gadgets, including optical coherence tomography, fluorescein angiography, B-scan ultrasonography, digital fundus photography, laser indirect ophthalmoscopy and pattern-scanning lasers. My clinic days were charged with the feelings of a final exam: Some of the most obscure diagnoses you'd expect to see only on a standardized test were daily walk-ins at the Tenwek Eye Clinic. Furthermore, I was most surprised by the degree of complexity of common pathologies. For example, the vast majority of patients with retinal detachments in Eastern Africa will never have access to a retina specialist, so they'll go untreated. The patients who do present to the clinic almost always have chronic detachments with extensive proliferative vitreoretinopathy and a prognosis so poor that they require combined treatment modalities, such as combined pars plana vitrectomy, scleral buckling and silicone oil.

Just like the clinic, the operating rooms are equipped with the latest technologies, including Alcon Constellation vitrectomy machines using 23-, 25-, and 27-ga. systems and Zeiss microscopes. All surgeries are performed using the Resight noncontact viewing system, and there's access to endolaser, perfluorocarbons, SF6, C3F8 and silicone oil. In addition to retina surgeries, the operating rooms are equipped for corneal cases, including corneal transplants and cross-linking; cataract surgery using phacoemulsification or MSICS; and glaucoma surgeries, including glaucoma drainage implant devices and cyclophotocoagulation.

I found that the clinic and operating rooms face unique challenges because of working in an environment where nothing is thrown away or wasted. It was humbling to discover that a significant proportion of my perceived surgical skill was directly attributable to the state-of-the-art equipment and supplies we had available in the Wills Eye Hospital OR. In this rural environment, there's no option to buy another device when the first one breaks, or to bring in on-site technical support. You're as much a surgeon as you are a technician who can take apart and repair complex machines.

One of the long-term goals of the hospital is to help local ophthalmologists take the reins of their community's health care. The hospital serves as an educational site for trainees of all levels, including medical students, interns, residents, consultants and regional ophthalmologists who hope to specialize in retina care. Dr. Roberts and the entire ophthalmology department have created a unique niche within the global ophthalmology field, and I look forward to witnessing the continued expansion of its ophthalmic community.

Catherine Kareko, vitreoretinal surgeon, recently joined Tenwek's staff, and is one of the few fellowship retina-trained ophthalmologists in the country.

for poor patient follow-up—once you do a procedure on someone in East Africa, you might never see that patient again. This mandated making clinical/surgical decisions as if this were going to be our last interaction with the person. For instance, a patient presenting with high-risk proliferative diabetic retinopathy may receive full PRP laser treatment in one session as well as a bevacizumab injection—all at the first visit. With time, however, patients have begun keeping more of their follow-up visits, which has improved our ability to care for their diseases.

The other major challenge is as old as cataract surgery itself: Technology is great until it stops working. The eye staff and myself were excited about the addition of a new array of diagnostic and surgical equipment at the clinic and surgery suite since it improved the care of our patients—until we had our first malfunction. We soon discovered that there was no trained technician in the entire country capable of repairing the devices used in ophthalmology. In response, we had to learn how to solve problems and communicate with technicians in the United States or Europe in order to diagnose and repair the problems.

These experiences emphasized the importance of one of the lessons frequently touted by U.S. Navy SEALs: "Keep it simple." This rule goes double when dealing with technology in the developing world—keeping diagnostic and treatment paradigms simple helps eye care be more affordable and sustainable.

Retinal Disease in East Africa

The prevalence of diabetes is rapidly increasing in Africa; the current estimated prevalence in Kenya is more than 4 percent. This translates to significant diabetic eye disease presenting in our clinics. And, of those patients presenting with diabetic retinopathy, most have moderate to severe disease. Fortunately, in our armamentarium we have lasers, intravitreal medications and vitrectomy surgery to treat these diabetic patients. Several of the anti-VEGF agents are now available in Kenya and, as expected, bevacizumab is the most affordable. We're working closely with the diabetic medical clinic at Tenwek Hospital to ensure that all diabetic patients receive an annual dilated eye exam and have optimal control of their disease.

As expected in this African population, there's not much macular degeneration. Those patients who do have this disease usually have a variant like polypoidal choroidal vasculopathy. These are typically treated with anti-VEGF injections.

There are also many patients who present with uveitis involving the posterior segment. The burning question is always whether the etiology is infectious or not. Our laboratory diagnostic abilities are limited, but they do allow us to check for HIV, TB and syphilis. At present we don't have PCR capabilities to look for toxoplasmosis or viral etiologies of uveitis/retinitis, so we have to rely upon our clinical acumen. There's definitely a higher incidence of TB in the population, leading us to treat empirically for presumed ocular TB in some cases.

The problems related to vitreous and vitreoretinal interface (vitreomacular traction, macular hole, retinal detachment) are similar in incidence to what's found in the United States. The only difference is the time to presentation after these problems first occur. It's not uncommon to have a patient present with a large chronic macular hole in one eye and a smaller, recently occurring macular hole in the fellow eye. Similarly, patients with retinal detachments usually don't present in a timely manner. Over the past 15 years, I've treated hundreds of patients with detachments, but fewer than 10 were truly macula-sparing. As quality, affordable eye-care centers evolve in sub-Saharan Africa, I can only believe that patients will present sooner when their vision deteriorates.

Strategies for Care

As alluded to above, there are many challenges in bringing quality vitreoretinal care to the rural, low-resource settings of sub-Saharan Africa. Sustainable technology, reliable supply chains and affordability are all barriers that need to be addressed.

In our effort to provide improved care for our patients at Tenwek, the greatest strategy involves better education and training. There are some talented, very skilled ophthalmologists delivering excellent eye care across the continent, but very few are trained vitreoretinal specialists. Most countries don't even have retina training programs, requiring interested African ophthalmologists to leave their country—and often the continent—to receive fellowship training. Depending on the program, the quality of that training varies widely.

At Tenwek, we're doing our best to contribute to the training of young ophthalmologists, enabling them to grow in experience and confidence as they join the battle against blindness. While we don't have an independent ophthalmology residency, we do work closely with the only recognized residency program in the country, located in Nairobi. Many of their residents do rotations with us to gain both clinical and surgical experience.

As far as vitreoretinal training goes, we're working with the few other retina specialists in the country to establish at least one, and hopefully several, retina fellowships, to increase

the number of qualified vitreoretinal specialists in Kenya and East Africa. This will no doubt help meet the growing demand for VR surgeons. Two years ago, a young Kenyan ophthalmologist, Catherine Kareko, who had completed a one-year retina fellowship outside of the African continent joined our team. She was looking for a place equipped to provide retina care where she could be mentored and gain experience. Over the past two years, she has flourished and is now one of the growing leaders in this subspecialty in Kenya.

Dr. Roberts (far right) and his family (from left), Jenny, his wife; Luke, Isaac and Nate, split their time between Kenya and Birmingham, Alabama.

The Right Reasons

I've been working in Kenya for 15 years now, in rotations consisting of four years in Africa followed by one year back in the States, and will be returning to Africa this August. As you've read, it's been immensely rewarding.

After reading this account, then—or maybe hearing about other physicians' experiences—you may be thinking of getting involved in global eye care yourself. After all, you've likely got the skills to dramatically change a person's life: Offering vision to patients, especially to those who are truly blind, is a gift like no other. Indeed, there's been a significant increase in interest and involvement in providing eye care to underserved areas over the past decade on the part of U.S.-trained ophthalmologists. But before diving head first into a global ophthalmology adventure, even if you've already had some international experience, make sure you're doing it for the right reasons.

The main thing is to understand your motives for going. There are some good—even great—reasons for participating in global eye care, but there are some undesirable—and possibly destructive—reasons for participating in global ophthalmology, as well. For example, if your underlying motivation for involvement in an eye mission is to have an adventure and see "exotic" parts of the world, then you've merely become a medical tourist; this can be detrimental to the patients and communities you intend to serve. If you think your western training is unparalleled, and your goal is teaching the locals "your way" of doing things, then you may be teaching skills and techniques that are inappropriate and unsustainable for that culture.

On the other hand, if you want to donate your time and resources to providing eye care for a local community that otherwise wouldn't receive it, that's a very good thing. But I challenge you to consider an even better purpose. Go beyond just providing care and take the opportunity to train local eye-care providers, empowering them to care for their own people. All the while, do it with humility and a willingness to become a student of their culture. This is the type of purpose that can have an incredible impact on both the individuals and the communities you serve.

Be sure to keep these goals in mind as you run toward the finish line in the long, sometimes arduous, trek to providing medical care to those most in need of it. ◀

ABOUT THE AUTHORS

Dr. Roberts is ophthalmologist-in-chief at Tenwek Mission Hospital in Bomet. He's also a clinical assistant professor of ophthalmology at the University of Alabama in Birmingham.

Dr. Patel is a pursuing a Fellowship in retina at Wills Eye Hospital in Philadelphia.

ADVERTISER INDEX

This advertiser index is published as a convenience and not as part of the advertising contract. Every care will be taken to index correctly. No allowance will be made for errors due to spelling, incorrect page number, or failure to insert.

Evaluating Glaucoma With Retinal Disease

Determining the condition of the eye and the cause of any changes can be challenging in this situation. Here's help.

YAO LIU, MD, MS
MADISON, WISC.

Diagnosing and monitoring glaucoma isn't always straightforward, and that's especially true when retinal pathology is present. When glaucoma and retinal disease coexist, it can be difficult to determine whether glaucoma has progressed—or even if the patient actually *has* glaucoma. Similarly, a change in retinal status can alter test results, leading us to believe a glaucoma patient's disease may have worsened when the change is actually due to a retinal condition.

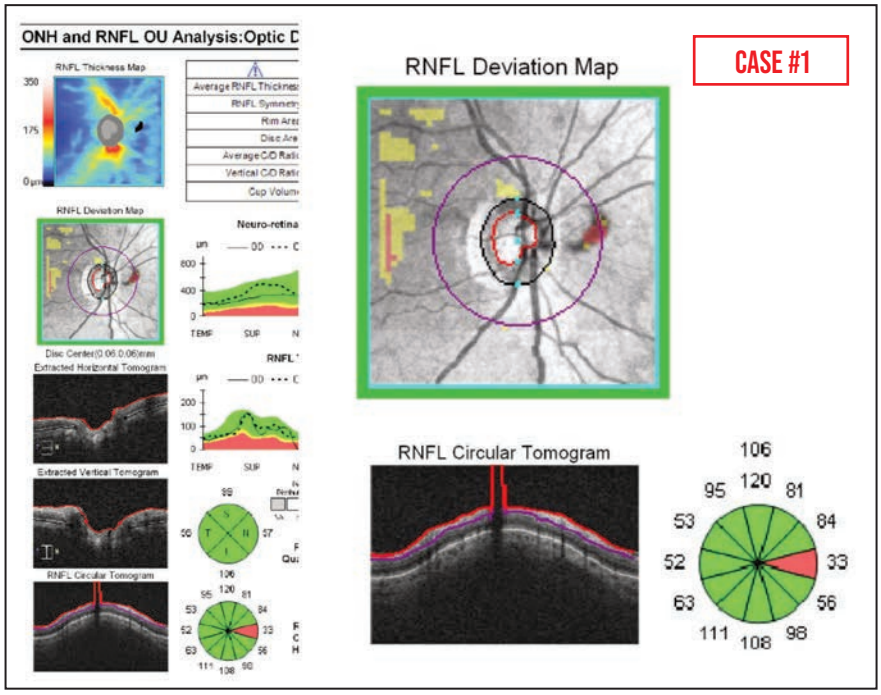
In this article I'll focus on how retinal issues can affect visual fields and optical coherence tomography data when evaluating glaucoma. Many retinal conditions can affect the results of these tests, including abnormalities of the vitreoretinal interface such as posterior vitreous detachment and epiretinal membranes; vascular abnormalities; macular diseases such as age-related macular degeneration; retinal detachments; and other conditions such as retinal dystrophies, chorioretinitis, sickle-cell retinopathy and retinopathy of prematurity. Furthermore, treatments used to address retinal disease such as panretinal photocoagulation, pars plana vitrectomy, membrane peeling and the use of silicone oil or hydroxychloroquine, can have iatrogenic effects on the results of the tests we use to evaluate glaucoma progression.

Here, I'll provide an overview of how retinal conditions can impact a glaucoma clinical evaluation; then I'll review several case examples of situations in which common (and less-common) retinal conditions affected test results with significant implications for clinical decision-making and management. Finally, I'll share strategies for distinguishing between real glaucoma progression and issues related to retinal disease.

Don't Assume It's Glaucoma

The first and most important strategy when managing a patient who has (or may have) glaucoma is: Don't assume a change in test results means that the patient's glaucoma has progressed.

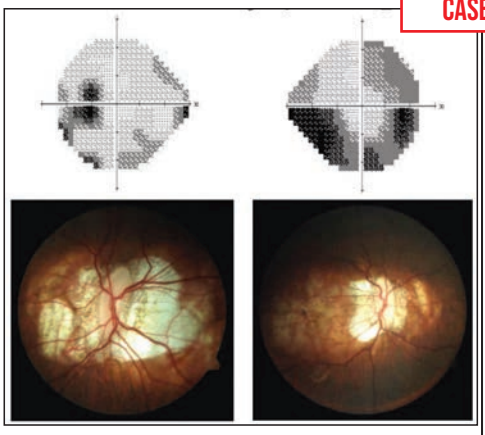
Sometimes, for example, you may find that there's been a major change in one or more tests since the patient's previous visit. If there's a sudden change in the test results, it's important to assess the validity of the test and look for possible retinal artifacts. After checking on the test's reliability, I look through the patient's history and perform a detailed dilated eye exam. Did the patient develop a new medical or retinal condition, or undergo a surgery or laser procedure in the intervening period? That might explain the sud-

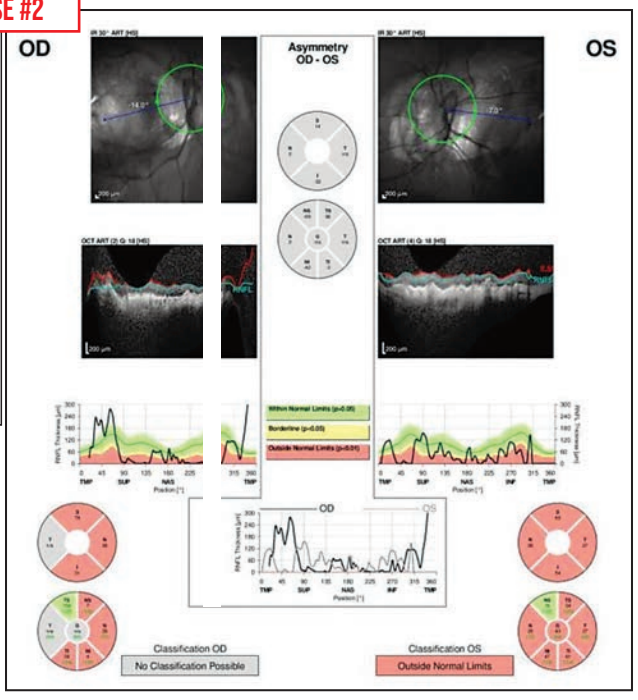


This article has no commercial sponsorship.

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.

CASE #2





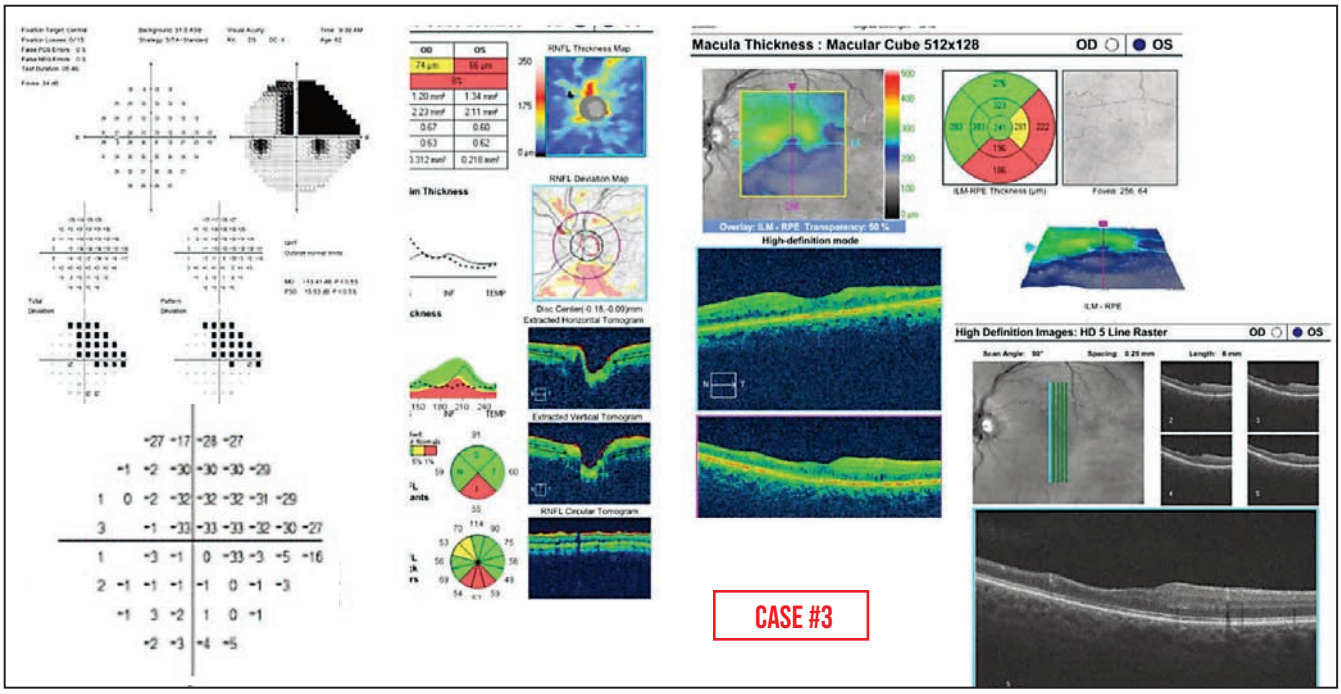
den change.

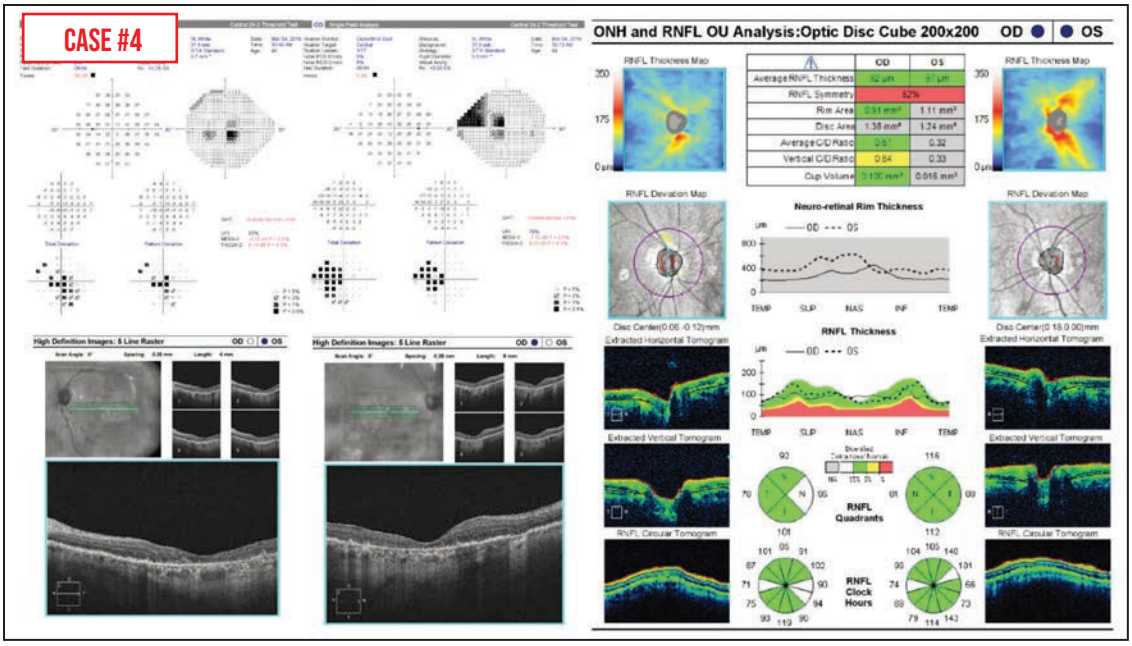
For example, I've seen patients who had a dense arcuate defect when the visual field was previously normal. A clinician could certainly interpret that to mean that the patient has worsening glaucoma. However, a macular OCT may show that the defect can be explained by profound ischemic thinning of the retinal nerve fiber layer and other inner retinal layers—changes that happened as a consequence of a branch retinal artery occlusion that occurred during the intervening time period.

Retinal surgery can also lead to artifacts by altering the thickness of the RNFL. We know that a pars plana vitrectomy with membrane peel can release traction on the retina, causing a decline in RNFL thickness. Using silicone oil can also potentially have toxic effects on the RNFL. Finally, patients who have proliferative diabetic retinopathy can develop glaucoma, and it can be hard to monitor these patients because they can develop visual field defects and OCT abnormalities related either to the diabetic retinopathy itself or to treatments such as PRP.

PRP can be related to a number of testing artifacts. First, laser destruction of retinal tissue can cause visual field defects. Second, regressed neovascularization can appear as fibrous tissue on the optic nerve; this can create artifacts on an OCT scan by affecting RNFL thickness measurements.

Interestingly, reports on PRP's impact on RNFL thickness have been inconsistent; some studies have found that the laser treatment increases RNFL thickness, while others have found that it decreases the thickness. Either way, it's important to be aware that OCT measure-





ment of the RNFL in a patient with diabetic retinopathy may be altered by the disease and its treatment. This contributes to the difficulty of looking for signs of glaucoma and/or glaucomatous progression in patients with a history of proliferative diabetic retinopathy.

The bottom line is that retinal problems can create significant changes in glaucoma test results, making it harder to determine the status of an individual's glaucoma.

Real-world Case Histories

Here are some examples of patients in whom retinal changes affected the test results on which we'd normally base our glaucoma evaluation.

Case #1 *(p. 76)*: This elderly patient with ocular hypertension appeared to have a new area of nasal RNFL thinning on OCT. However, this was an artifact caused by a PVD blocking the scan circle. (Partial PVDs can also lead to falsely thin RNFL measurements, due to erroneous segmentation.)

It's worth noting that partial PVDs are common—they're visible in up to 40 percent of peripapillary RNFL OCT scans—and traction caused by epiretinal membranes can also increase OCT RNFL thickness measurements over time.[1,2] This can lead to the appearance of focal RNFL thinning, due to the release of the attachment to the posterior hyaloid face following vitrectomy with membrane peel.

Case #2 *(p. 77)*: This patient had myopic degeneration and large areas of peripapillary atrophy. Traditional testing for glaucoma in a high myope (-6 D or greater) tends to produce abnormal results; the visual field, optic nerve and OCT scans may all look abnormal. That can make it quite difficult to determine whether the abnormalities are the result of high myopia or glaucoma.

The best way to proceed in this situation is to perform all of the usual baseline glaucoma tests and then look for change over time, when possible, as you follow the patient. If you find progressive change, glaucoma rather than myopia is likely to be the cause of some of those abnormalities.

It's worth noting that in this situation, visual field testing may be more useful than OCT scans. The RNFL in these patients is often anomalous and already too thin to follow for changes. But if the visual field is deteriorating over time, that suggests that glaucoma is present and worsening.

Case #3 *(p. 77)*: Retinal diseases typically cause dense defects on visual field testing. Here we see an abrupt transition between -33 and -1dB on the OCT pattern deviation plot, corresponding to a region of marked inner retinal atrophy that was caused in this case by a branch retinal artery occlusion.

Case #4 *(above)*: Macular degeneration is another condition that can make it difficult to tell how much of a patient's vision change was caused by glaucoma progression, in part because advanced age-related macular degeneration can cause central visual field defects.[3] In this situation, peripapillary RNFL OCT—rather than either macular OCT or visual field testing—may be more helpful for assessing glaucoma progression. That was the case for this patient, who had geographic atrophy and abnormal visual field tests but healthy optic nerves. In addition, I'll often check the macular OCTs of patients with a history of macular degeneration to look for any subretinal fluid or other problem that might be treatable.

If an older patient has both macular degeneration and glaucoma, it can be really challenging to parse out exactly how much vision loss is being caused by the progression of either condition. Sometimes, in cases where it's not possible to distinguish the two, we lower the intraocular pressure in the hope of preventing further vision loss, in case it's being caused by glaucoma.

Case #5 *(p. 80)*: This patient had a

ENGAGING NEW LOOK, SAME TRUSTED CONTENT

REVIEW® of OPHTHALMOLOGY

Clinical advice you can trust

After 20 years, it's time for a new look!

Since its launch in 1994, you've welcomed *Review* into your practice, and relied on its timely, clinically-relevant information to get the best results for your patients. Today, that valuable content is still here, but in a fresh new design that showcases it better than ever.

LAYOUTS PUT CONTENT FRONT AND CENTER

Feature THE COVID CHRONICLES

THE COVID CHRONICLES: PAST, PRESENT & FUTURE

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

BY CHRISTOPHER KENT
SENIOR EDITOR

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

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

In the Eye of the Storm

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

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

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

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

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

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

"Here at New York Eye and Ear we have busy walk-in eye clinics," he says. "We wanted to be visible. If the hospital and department leaders are doing Zoom calls from home, that doesn't engender a lot of confidence. So we managed the hospital and clinics by walking around and being available. We made sure the residents, fellows, attending physicians, nurses and staff knew they were not alone on the front lines."

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

Reinventing the Status Quo

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

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

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

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

REFRACTIVE/CATARACT RUNDOWN

Phaco Update: Getting The Right Setting

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

BY LORI MCKINNEY
SENIOR EDITOR

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

Beyond Routine: Uncertainty

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

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

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

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

Continuous, Pulse and Burst

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

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

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

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

Managing the Pulse Rate

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

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

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

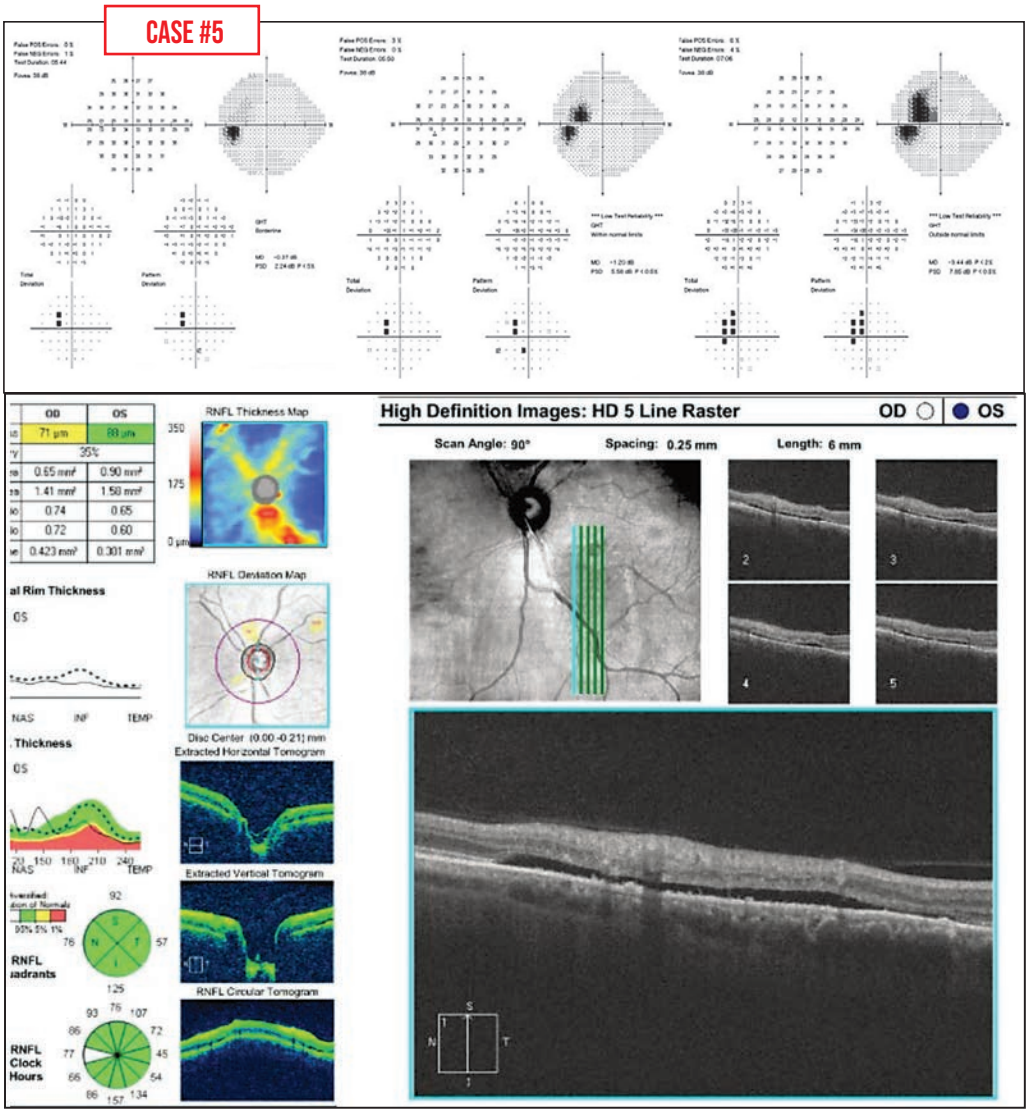
"Our ability to program timing and duration in combination with the directional modes, such as transverse and torsional phaco, can result in highly sculpture-control and precise ultrasound power delivery," says Dr. Park.

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

Remember Your Parameters

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

Dr. Auran points out that, according to *in vitro* data, increasing the IOP to as high as 110 mmHg in the Alcon Centurion system can make the machine more efficient.' Another study found that, in the Whitestar Signature Pro system (Johnson & Johnson Vision), increasing bottle height to 130 cm increases efficiency in the pentolithic continuous mode.' However, another study involving



healthy optic nerve, but an enlarging field defect was noted. The problem was central serous retinopathy. A subsequent field showed a decrease in the size of the defect over time, which corresponded to a reduction in subretinal fluid.

Case #6 *(p. 82)*: This teenager with an inferior arcuate defect was referred for possible glaucoma. However, subretinal fluid was noted on the peripapillary RNFL OCT. This revealed a previously undiscovered, low-lying retinal detachment.

One other situation is worth mentioning. Sometimes a patient will have both advanced glaucoma and retinal dystrophy, making it very difficult to determine which disease is causing vision deterioration. In this situation, optimizing IOP control, consultation with an experienced retina specialist, and possible serial electroretinogram testing could be helpful for determining the relative contributions of these two entities to any progressive vision loss.

Strategies for Success

Here are a few strategies that can help you distinguish glaucoma progression from retinal disease:

• ***Obtain baseline testing data.*** Change over time may be key to determining whether glaucoma is present and whether there's any glaucoma progression. Performing a variety of tests at baseline allows for comparisons to be made over time, which can be helpful for distinguishing between real glaucoma progression and retinal disease.

• ***Don't rely on a single type of test for following glaucoma patients.*** Some test modalities are better suited for following glaucoma progression in certain patients. OCT can be very useful for assessing progression in glaucoma patients who have yet to develop glaucomatous visual field defects, but for high myopes, visual field testing can provide more useful information than OCT. If macular pathology is present, peripapillary RNFL OCT scans may be more helpful. Baseline testing can help you determine which tools may be most useful for monitoring a particular patient.

• ***Check for structure-function correlation between the optic nerve examination, visual field and OCT.*** Agreement or disagreement can assist in resolving ambiguities, since there should be correspondence between the location of structural thinning on the optic nerve and functional visual field defects.

• ***Closely inspect peripapillary RNFL OCT B-scans and macular OCT scans.*** We sometimes focus primarily on the quantitative values seen on scans, but examination of the actual peripapillary RNFL and macular OCT scans themselves can help identify possible artifacts and retinal pathology.

• ***Remember that visual field defects associated with retinal disease tend to be deep, and often don't respect the horizontal midline.*** Some artifacts may resemble typical glaucomatous damage, but atypical visual field defects provide a strong

WE'RE SEEING AMAZING RESULTS. AND SO ARE THEY.

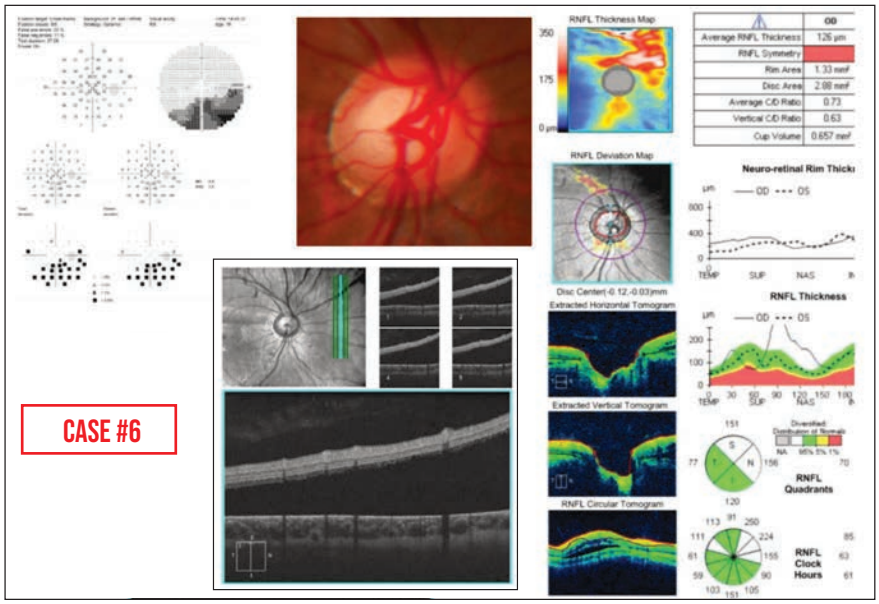
At the Foundation Fighting Blindness our mission is everybody's vision. Our work shines a light on the darkness of inherited retinal diseases (IRDs).

We're the world's leading organization searching for treatments and cures. We need your help to fuel the discovery of innovations that will illuminate the future for so many. We have robust disease information, a national network of local chapters and support groups, local educational events, and our My Retina Tracker® Registry to help keep your patients connected with clinical and research advancements.

Help accelerate our mission by donating at ECPs4Cures.org.

FOUNDATION FIGHTING BLINDNESS

FightingBlindness.org



clue that something other than glaucoma may be responsible. Retinal abnormalities tend to cause very deep defects with sharp borders that often don't respect the horizontal midline on visual field testing.

• ***If change isn't occurring over time, glaucoma progression probably isn't the cause of the abnormal test data.*** As a general rule, even if baseline test results are markedly abnormal, if the results don't change over time and the patient reports stable visual function, the glaucoma probably isn't worsening.

• ***Your tech may catch something you overlooked.*** Sometimes a retinal detachment is hard to see when it's low-lying, as in Case #6 above. In this case, several eye-care providers had seen the patient and not noticed a retinal detachment. In our clinic, we ordered a peripapillary RNFL OCT prior to performing our dilated eye exam, as we usually do for glaucoma evaluation. The technician said, "This doesn't look right to me. There's fluid under the retina that shouldn't be there." So she did some additional scans and found the retinal detachment. She was the one who actually picked it up.

• ***If you can't determine whether the patient has glaucoma, consider treating for it.*** In some cases, you're not certain the patient actually has glaucoma. This can be particularly challenging if you know the patient already has another vision-threatening condition such as proliferative diabetic retinopathy. Maybe their eye pressure isn't very high, but their nerves look a little suspicious. I'll often discuss with the patient whether they'd like to be treated, just in case they do have glaucoma, because they're already at such high risk of vision loss.

Of course, glaucoma treatment can be a long-term burden with a major impact on quality of life, so it's important to discuss options with each patient and tailor management to the patient's preferences. I might say, "We're not sure whether or not you have glaucoma. But given that you already have a condition that's putting you at risk of severe vision loss, would you like to be proactive and be treated for possible glaucoma?" Many times, patients will say yes. At the same time, many patients will say they don't want to be treated for something we're not sure they have. So you have to assess the patient's priorities and what level of risk they're comfortable with.

• ***When in doubt, consult with glaucoma and retina colleagues.*** They can be very helpful when assessing the relative contributions of glaucoma and retinal disease in patients with progressive vision loss caused by these coexisting ocular conditions.

Making the Best of It

Differentiating glaucoma and retinal conditions can be challenging. Sometimes, even with all the tests and all of the experience you've accumulated, you still may not be sure if the glaucoma is getting worse or vision loss is occurring because of retinal disease. Discuss the case with your glaucoma and retina colleagues and then make the best decision you can. The reality is, it's not always possible to differentiate these conditions with 100-percent certainty.

Nevertheless, many patients are referred because the doctor has concluded that the patient's glaucoma must be getting worse: "Just look at these terrible test results!" However, a detailed history and examination may uncover an alternate cause. So it's important to take into consideration that retinal diseases and procedures can affect test results used in glaucoma evaluation.

Whenever you see a major change in the test data, or a glaucoma patient comes in with a new visual complaint, be aware that a retinal problem could very well be the cause—and do your best to navigate the wisest path forward. ◀

1. Liu Y, Baniasadi N, Ratanawongphaibul K, Chen TC. Effect of partial posterior vitreous detachment on spectral-domain optical coherence tomography retinal nerve fibre layer thickness measurements. Br J Ophthalmol 2020;104:11:1524-1527.
2. Asrani S, Essaid L, Alder BD, et al. Artifacts in spectral-domain optical coherence tomography measurements in glaucoma. JAMA Ophthalmol 2014;132:4:396-402.
3. Garas A, Papp A, Holló G. Influence of age-related macular degeneration on macular thickness measurement made with fourier-domain optical coherence tomography. J Glaucoma 2013;22:3:195-200.

ABOUT THE AUTHOR

Dr. Liu is an assistant professor in the Department of Ophthalmology and Visual Sciences at the School of Medicine and Public Health, at the University of Wisconsin-Madison. She reports no financial ties relevant to this article.

A PUBLICATION BY REVIEW of OPHTHALMOLOGY

RETINA SPECIALIST

Retina Specialist focuses on the latest advances in the diagnosis, medical management and surgical treatment of diseases of the retina, along with practical, real-world advice from leading clinicians and other experts on managing the successful retina practice.

KEEP UP WITH CUTTING-EDGE SCIENCE IN RETINA.

Watch for issues in:

- JANUARY/FEBRUARY
- MARCH/APRIL
- MAY/JUNE
- JULY/AUGUST
- SEPTEMBER/OCTOBER
- NOVEMBER/DECEMBER

FOR INQUIRIES CONTACT

RETINASPECIALIST@JOBSON.COM

ADVERTISING OPPORTUNITIES

MICHAEL HOSTER • PUBLISHER • 610-492-1028 • MHOSTER@JOBSON.COM
JIM HENNE • 610-492-1017 • JHENNE@JOBSON.COM
MICHELE BARRETT • 215-519-1414 • MBARRETT@JOBSON.COM
JONATHAN DARDINE • 610-492-1030 • JDARDINE@JOBSON.COM

www.retina-specialist.com

@RetSpecMag RetinaSpecialistMag

PRODUCT NEWS

New items on the market to improve clinical care and strengthen your practice.

IMAGING & DIAGNOSTICS

A Fully Automated Fundus Camera

US Ophthalmic's new non-mydriatic, 100-degree field of view, 12-megapixel digital fundus camera, the EFC-2600, and its EZER operating system, is fully automatic and will make early detection and diagnosis of vision-threatening eye conditions quick, efficient and affordable for all patients, according to the company.

The EFC-2600 has 10 fixation targets and an automatic mosaic modality function that combines several image fields into a wider field of view of the retina. The company says this feature will aid in rapid diagnosis of diabetic retinopany, glaucoma and other pathology. The camera can also image the anterior segment.

For information, visit usophthalmic.com or call +1-888-881-1122.

AS-OCT Upgrade from Oculus

Oculus' Pentacam AXL Wave is the newest addition to the company's Pentacam line and supplements its anterior segment tomography and optical biometry with retroillumination and total-eye wavefront and object refraction with the addition of a Hartmann-Shack sensor.

The AXL Wave analyzes optical performance of the total cornea, total eye and crystalline lens or IOL. Oculus also notes that the AXL Wave has a new examination routine that guides users through the patient-friendly imaging process; clinicians will be able image both eyes in under five minutes. All parameters for corneal screening, IOL power selection and calculation, ICL selection and calculation, and pupil diameter under dimmed and dark conditions appear on the overview display, and the software package includes an IOL calculator and the company's built-in IOL database.

For information, visit pentacam.com/axl-wave.

CATARACT SURGERY

New Phacoemulsification System from J&J

The Veritas Vision System is a next-generation phacoemulsification system that features improved fluidics and ergonomics. Johnson & Johnson says Veritas offers optimal safety, efficiency and user experience. New technology allows surgeons to guide through any lens density with less surge and more stability, says the company.

The Johnson & Johnson Vision Veritas phaco system, which will be commercially available later in 2021, helps control surge and promote stability, the company says.

Veritas was FDA 510(k)-approved and received the CE mark in April, with a full global commercial launch planned for later this year according to the company.

For information visit jjvision.com.

REFRACTION

A Vectorial Approach to Refraction

Essilor says the Vision-R 700 is a refraction system that features a precisely-controlled optical module with variable focus and digital infinite refraction technology. Vision-R 700 includes simultaneous and continuous variations of sphere power, cylinder axis and cylinder power for a new cylinder-search method based on a vectorial approach to refraction, Essilor says.

Automated smart programs in the Vision-R 700 guide the practitioner for optimal efficiency, Essilor says. The company believes its digital infinite refraction technology will provide the basis for refraction-method advances, such as remote refraction and telemedicine.

For information or an appointment for a demonstration, visit essilorinstrumentsusa.com.

A Compact Refraction System for Any User

The Visionix Eye Refract system from Luneau Technology USA received its next-generation upgrade earlier this year.

Luneau says the second-generation Eye Refract occupies 8 square feet of space and features an automated, binocular, dynamic digital phoropter with wavefront-based auto-refractometry and keratometry, a digital acuity short chart and integrated lens analyzer.

For information, visit luneautechusa.com. ◀

Mysterious swelling around the eye brings a young woman to Wills Eye.

BONNIE SKLAR, MD, MARY STEFANYSZYN, MD,
RALPH C. EAGLE JR., MD, AND TATYANA MILMAN, MD
PHILADELPHIA

Presentation

A 29-year-old Middle-Eastern female was referred to Wills Eye Hospital for evaluation of swelling of the left medial canthal region that had gradually enlarged over the course of a year. The patient denied having pain, discomfort, blurry vision, diplopia, pain with eye movements, erythema, epiphora, drainage, pulsatility, skin lesions, fevers, chills, malaise or fatigue. There was no history of trauma.

Medical History

Past medical history was notable only for hypothyroidism controlled with levothyroxine 75 mcg daily. Her surgical history included a cosmetic rhinoplasty several years prior to presentation. Family history was negative for chronic conditions. She denied alcohol, tobacco and illicit drug use.

Exam

The patient's vital signs were stable and within normal limits. Visual acuity was 20/20 in both eyes. She had no relative afferent pupillary defect. Confrontational visual fields and extraocular movements were full bilaterally. She was orthophoric in primary gaze. Intraocular pressure was within normal limits bilaterally. External examination showed a palpable, mobile, subcutaneous mass of the left medial canthus (*Figure 1, right*). No proptosis was noted. Anterior slit lamp examination was unremarkable. She did not have palpable lymphadenopathy.

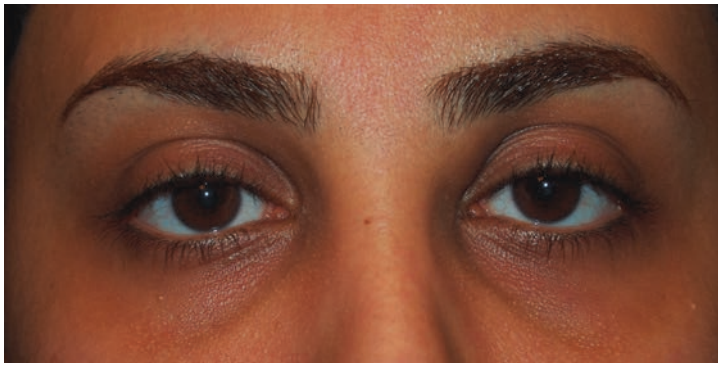


Figure 1. External photograph depicting swelling of the left medial canthal region that gradually enlarged over one year.

What is your diagnosis? What further workup would you pursue? The diagnosis appears on p.86.

Work-up, Diagnosis, and Treatment

CT scan revealed a well-circumscribed, soft tissue mass in the left medial canthal region. There was no evidence of destruction or remodeling of the adjacent bone. The paranasal sinuses were clear (*Figure 2, right*). Based on clinical and radiographic features, the differential diagnosis for an indolent, painless, circumscribed, extraconal orbital mass in a young patient was broad. Entities considered included congenital lesions (dermoid cyst), fibrocystic lesions (solitary fibrous tumor), peripheral nerve sheath lesions (schwannoma, neurofibroma), vascular lesions (cavernous-venous malformation, arteriovenous malformation, lymphatic-venous malformation), secondary orbital lesions (mucocele), inflammatory lesions (IgG4-related sclerosing disease, sarcoidosis) and, less likely, foreign body due to remote trauma, infectious etiologies (orbital abscess, dacryocystitis), and malignant tumors (soft tissue tumors, lymphoma, metastasis).

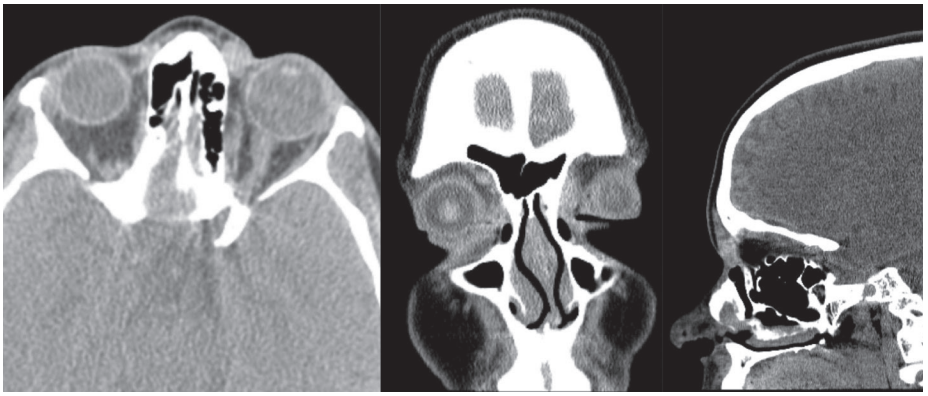


Figure 2. CT scan demonstrating well-circumscribed, soft tissue mass in the left medial canthal region.

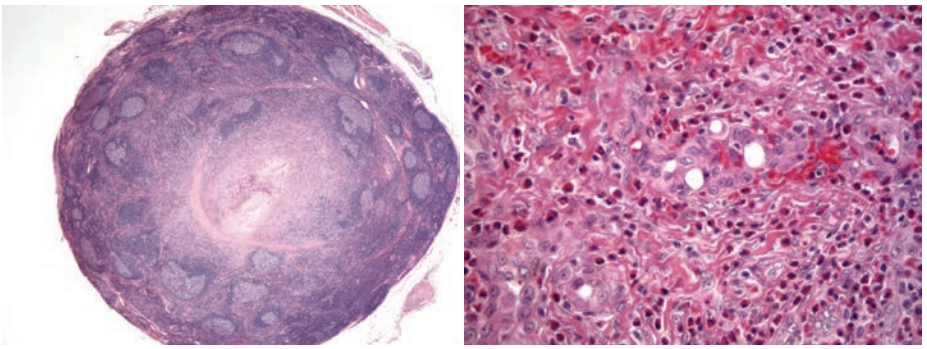


Figure 3. Well-circumscribed neoplasm composed of central vascular proliferation, surrounded by reactive lymphoid follicles (left). Higher-magnification photomicrograph demonstrates characteristic plump vascular endothelium with clear intracytoplasmic vacuoles and the surrounding inflammatory infiltrate, rich in eosinophils (right) (H&E stain).

The patient underwent left orbitotomy with excision of the mass. The lesion was well-circumscribed, tan and red in color, rubbery, and measured 16 x 9 x 8 mm. Histopathology showed a circumscribed proliferation of mostly small-caliber vascular channels associated with a larger vessel. The vascular channels were variably cellular and lined by epithelioid endothelium with focal tombstone configuration and occasional intracytoplasmic vacuoles. A prominent inflammatory response, rich in eosinophils, was associated with the vascular proliferation. The periphery of the lesion was rimmed by reactive follicles (*Figure 3, above*). No lymph node tissue was identified. There was no evidence of significant nuclear atypia, cellular sheeting, necrosis or mitotic activity. Immunohistochemical stains for CD31 and ERG highlighted the vascular endothelial proliferation, tombstoning and intracytoplasmic vacuoles. The histopathologic findings were compatible with epithelioid hemangioma. The postoperative period was uneventful, and no additional treatment was required. No recurrence of the lesion was noted at two-year follow-up.

Discussion

Epithelioid hemangioma (EH), also known as angiolymphoid hyperplasia with eosinophilia (ALHE) is an uncommon, benign vascular proliferative disorder.[1,2] The condition was first described in 1969.[1] EH most frequently occurs in the subcutaneous tissue or dermis of the head and neck region and can rarely affect the orbit and ocular adnexa.[2,3] Previously reported ocular adnexal sites of EH include the eyelid, intraconal and extraconal soft tissue, lacrimal gland and conjunctiva.[3-11] The patients with ocular adnexal EH most commonly present with symptoms that include swelling, proptosis, diplopia, ptosis, vision loss, pruritis, epiphora and/or pulsation.[2-16] The pathogenesis of EH remains unclear at this time; proposed etiologies include neoplasm of endothelial cell origin, reactivity secondary to vascular injury, or a process sec-

"I was only seeing light flashes early on, but light FLASHES when you've not seen anything for so many years—it was wonderful"

—Keith H, retinal prosthesis recipient

WE'RE SEEING AMAZING RESULTS. AND SO ARE THEY.

At the Foundation Fighting Blindness our mission is everybody's vision. Our work shines a light on the darkness of inherited retinal diseases (IRDs).

We're the world's leading organization searching for treatments and cures. We need your help to fuel the discovery of innovations that will illuminate the future for so many. We have robust disease information, a national network of local chapters and support groups, local educational events, and our My Retina Tracker® Registry to help keep your patients connected with clinical and research advancements.

FOUNDATION FIGHTING BLINDNESS

FightingBlindness.org

Help accelerate our mission by donating at ECPs4Cures.org.

ondary to an arteriovenous shunt.[4,15] Malignant transformation has not been reported.

Histopathologic studies are essential for accurate diagnosis of EH, as the presenting clinical and radiologic signs are often nonspecific.[3] The classic histopathological finding in EH is proliferation of "plump," vacuolated, epithelioid-appearing endothelial cells that line vascular channels. Vascular proliferation of capillaries, arterioles and venules is accompanied by chronic inflammatory infiltrate, which may include lymphocytes, plasma cells, numerous eosinophils and lymphoid follicles.[3,4,15] Immunohistochemically, vascular endothelial cells are typically positive for markers CD34, CD31, Factor VIII and ERG and may co-express lymphatic endothelial marker D2-40.[15]

EH must be distinguished from Kimura's disease, which can closely resemble EH histopathologically, and in the past was regarded as an entity on a spectrum with EH.[1,3] Kimura's disease has a predilection toward young Asian males and is characterized by prominent lymphadenopathy, peripheral blood eosinophilia, elevated serum IgE and possible associated nephrotic syndrome. In the ocular adnexa, Kimura's disease classically affects the lacrimal gland and lacks the characteristic vascular proliferation of EH.[3,4,13] By contrast, EH tends to occur more frequently in females in their third or fourth decade of life, and is not associated with systemic manifestations like Kimura's disease.[2,4]

EH also must be distinguished histopathologically from other vascular neoplasms of borderline malignancy (epithelioid hemangioendothelioma) and malignant vascular neoplasms (Kaposi sarcoma and angiosarcoma). Absence of significant nuclear atypia, cellularity and/or mitotic activity favors EH over more aggressive tumors. Additionally, EH lacks CAMTA1 and TFE3 gene rearrangements that may be observed in epithelioid hemangioendothelioma.[15] Presence of reassuring features like FOSB gene rearrangement may support the diagnosis of EH.[15]

The traditional treatment of choice for EH is complete surgical excision. The recurrence rate may be as high as 33 percent, which is most likely attributable to lesions with poorly demarcated margins.[4,13] Well-circumscribed lesions, such as that in our patient, tend to have low recurrence rates.[14] In cases with extensive involvement, traditional treatment methods including systemic steroids, intralesional steroids, cryotherapy, radiotherapy, cyclophosphamide and subcutaneous methotrexate have been tried with limited success.[4,12,14,18] In less-severe cases, observation for spontaneous regression following incisional biopsy and tissue diagnosis may be appropriate.[2]

More recently, systemic propranolol has been proposed as a treatment for EH, based upon its efficacy in regression of pediatric capillary hemangiomas.[17] Proposed mechanisms of action include vasoconstriction, inhibition of angiogenesis and induction of apoptosis.[16] One case of an epithelioid hemangioma with rapid progression, despite two subtotal excisions, steroids and chemotherapy agents, completely resolved with systemic propranolol.[12] A second case of EH that couldn't be fully excised due to adherence to surrounding tissues was also treated successfully with oral propranolol.[16] Several case reports have described EH in which angiography identified high-level arterial flow, with subsequent embolization of vessels to decrease blood flow prior to surgical removal of the lesion.[14,15] Finally, it's been proposed that IL-5 inhibitors (e.g., mepolizumab) may be a promising treatment for EH, as seen in one patient with a refractory lesion and elevated IL-5 who experienced symptomatic relief with cytokine inhibition.[18]

In summary, we describe a patient with characteristic clinical, radiographic and histopathologic findings of EH and summarize the recent molecular genetics and management modalities for this unusual lesion. EH needs to be considered in the differential diagnosis of a circumscribed soft tissue vascular mass in a female patient. Complete excision is curative. Although this tumor can recur following incomplete excision, there have been no reports of malignant behavior. ◀

1. Wells GC, Whimster IW. Subcutaneous angiolymphoid hyperplasia with eosinophilia. Br J Dermatol 1969;81:1:1-15.

2. Cunniffe G, Alonso T, Dinarès C, et al. Angiolymphoid hyperplasia with eosinophilia of the eyelid and orbit: The Western cousin of Kimura's disease? Int Ophthalmol 2014;34:1:107.

3. Azari AA, Kanavi MR, Lucarelli M, et al. Angiolymphoid hyperplasia with eosinophilia of the orbit and ocular adnexa: Report of 5 cases. JAMA Ophthalmol 2014;132:5:633-636.

4. Mukherjee B, Kadaskar J, Priyadarshini O, et al. Angiolymphoid hyperplasia with eosinophilia of the orbit and adnexa. Ocul Oncol Pathol 2016;2:1:40-47.

5. Shields CL, Shields JA, Glass RM. Bilateral orbital involvement with angiolymphoid hyperplasia with eosinophilia (Kimura's disease). Orbit 1990;9:2:89-95.

6. Hidayaat AA, Cameron JD, et al. Angiolymphoid hyperplasia with eosinophilia (Kimura's disease) of the orbit and ocular adnexa. Am J Ophthalmol 1983;96:2:176-89

7. Sánchez-Acosta A, Moreno-Arredondo D, Rubio-Solornio RI, et al. Angiolymphoid hyperplasia with eosinophilia of the lacrimal gland: A case report. Orbit 2008;27:3:195-198.

8. Cook HT, Stafford ND. Angiolymphoid hyperplasia with eosinophilia involving the lacrimal gland: Case report. Br J Ophthalmol 1988;72:9:710-712.

9. Bostad L, Petterson W. Angiolymphoid hyperplasia with eosinophilia involving the orbita: A case report. Acta Ophthalmologica 1982;60:3:419-426.

10. Eisenberg E, Lowlicht R. Angiolymphoid hyperplasia with eosinophils: A clinical-pathological conference. J Oral Maxillofac Pathol 1985;14:3:216-223.

11. Kennedy SM, Pitts JF, Lee WR, et al. Bilateral Kimura's disease of the eyelids. Br J Ophthalmol 1992;76:12:755-757.

12. Moss HB, Sines DT, Blatt J, et al. Epithelioid hemangioma responsive to oral propranolol. Ophthalmic Plast Reconstr Surg 2012;28:4:e88-e90.

13. McEachren TM, Brownstein S, Jordan DR, et al. Epithelioid hemangioma of the orbit. Ophthalmology 2000;107:4:806-810.

14. Sedran L, Bonaso M, Mettus A, et al. Epithelioid hemangioma of the face. J Craniofac Surg 2018;29:8:e736-e739.

15. Stiefel HC, Ng JD, Wilson DJ, et al. Orbital cellular epithelioid hemangioma. Ocul Oncol Pathol 2019;5:6:424-431.

16. Lee SM, Khwarg SI, Ahn JH. Epithelioid hemangioma of the orbit treated with oral propranolol in adults. Can J Ophthalmol 2018;53:6:e244-e246.

17. Léauté-Labrèze C, Hoeger P, Mazereeuw-Hautier J, et al. A randomized, controlled trial of oral propranolol in infantile hemangioma. N Engl J Med 2015;372:735-746.

18. Braun-Falco M, Fischer S, Plötz SG, et al. Angiolymphoid hyperplasia with eosinophilia treated with anti-interleukin-5 antibody (mepolizumab). Br J Dermatol 2004;151:5:1103-

Career Opportunities

OPHTHALMOLOGIST
Danbury, CT

Ophthalmologist to share office with long standing Ophthalmologist in Danbury, CT. High quality equipment. $1850 per month or adjoining office without equipment- $1500 per month.

203-545-3539 or 203-748-2020
email mehrimd@aol.com

REVIEW of Ophthalmology

Do you have Products and Services for sale?

CONTACT US TODAY
FOR CLASSIFIED ADVERTISING
Toll free: **888-498-1460**
E-mail: **sales@kerhgroup.com**

REVIEW of Ophthalmology

Targeting Ophthalmologists?

CLASSIFIED ADVERTISING WORKS

Contact us today
for classified advertising:
Toll free: **888-498-1460**
E-mail: **sales@kerhgroup.com**

KERHGROUP

REVIEW of Ophthalmology

Targeting Ophthalmologists?

CLASSIFIED ADVERTISING WORKS

• JOB OPENINGS • CME PROGRAMS
• PRODUCTS & SERVICES • AND MORE...

Contact us today for classified advertising:
Toll free: **888-498-1460**
E-mail: **sales@kerhgroup.com**

KERHGROUP

Managing Recurrent Wet AMD after Treat & Extend

Investigators assessed the recurrence rate of active macular neovascularization in patients with neovascular age-related macular degeneration previously followed in a treat-and-extend regimen in which treatment had been stopped due to disease stability, as part of a prospective cohort study.

A total of 105 nAMD patients previously followed in a treat-and-extend regimen with aflibercept injections were included. All patients with a dry macula on three consecutive visits 12 weeks apart were eligible to participate. Patients were examined at baseline, and then monitored for disease recurrence four, six, eight, 10 and 12 months after the last injection.

Main outcome measures included the proportion of patients with recurrent disease within 12 months after the last injection, and BCVA change at the time of recurrence and after resumed therapy.

Here are some of the findings:

• Evidence of recurrent nAMD was seen in 54/102 patients (52.9 percent) after 12 months of follow-up.

• The mean time to recurrence after the last injection was 6.7 ±2.2 months. The best-corrected visual acuity decreased from 71.7 ±10 ETDRS letters at baseline to 68.1 ±11.1 letters at the recurrence (p=0.12).

• After treatment was resumed, BCVA increased to 71.4 ±10 letters (p=NS compared to baseline).

• Patients with a pigment epithelial detachment at baseline had a 74 percent (14/19) recurrence rate compared to 48 percent (40/83) in subjects without a PED (p<0.05).

• Only 22/54 (40.7 percent) of the patients with recurrent disease had symptoms of visual loss or metamorphopsia.

Investigators reported that recurrent nAMD was common in previously stable patients when anti-VEGF injections were suspended. They wrote that it was difficult to predict which patients would have a recurrence, as most didn't have symptoms in the early stages of reactivation. Investigators stressed the importance of long-term follow-up and noted that early detection of recurrent disease can improve the chances of maintained visual function.

Ophthalmol Retina 2021; Mar 25 [Epub ahead of print].
Aslanis S, Amrén U, Lindberg C, et al.

OCTA Artifacts in Glaucoma

Researchers determined the prevalence of different artifacts on optical coherence tomography angiography images of healthy and glaucomatous eyes, and evaluated the characteristics associated with the increased likelihood of obtaining poor quality images.

A total of 649 eyes of 368 healthy individuals, glaucoma suspects and glaucoma patients were included.

Angiovue high-density and non-HD optic nerve head and macula OCTA images of participants were evaluated by four expert reviewers for the presence of different artifacts, including: eye movement; defocus; shadow; decentration; segmentation error; blink; and Z offset in the superficial vascular layer. Each OCTA scan was designated as good or poor quality based on the presence of artifacts. Researchers evaluated the association of demographic and ocular characteristics with the likelihood of obtaining poor-quality OCTA images, using a generalized linear mixed model.

Main outcome measures included the prevalence of OCTA artifacts and factors associated with increased likelihood of capturing poor-quality OCTA images.

A total of 5,263 OCTA images were evaluated. Here are some of the findings:

• Overall, 33.9 percent of the OCTA images had poor quality.

• The majority of images with acceptable quality scores (QS ≥4) had no artifacts (76.6 percent).

• Other images had one (13.6 percent), or two or more artifacts (9.8 percent).

• Older age (p<0.001), male gender (p=0.045), worse visual field mean deviation (p<0.001), absence of eye tracking (p<0.001) and macular scan area (p<0.001) were associated with a higher likelihood of obtaining poor-quality images.

• In images with acceptable quality scores, commercially available quality measures, including quality scores and signal strength index, had area under the ROC curves of 0.65 and 0.70, respectively, detecting good-quality images.

Researchers advise that clinicians should conduct a systematic scan review to ensure appropriate interpretation of OCTA images. The investigators add that OCTA images should be reacquired whenever an apparent and correctable artifact is present on the captured image. ◀

Ophthalmol 2021; April 2 [Epub ahead of print].
Kamalipour A, Moghimi S, Hou H, et al.

TearCare® System

Open your eyes to TearCare®

Universal. Precise. Consistent.

Portable smart system.

LEARN MORE

TearCare.com

The TearCare® system is indicated for the application of localized heat when the current medical community recommends the application of warm compress to the eyelids. Such applications would include Meibomian Gland Dysfunction (MGD), Dry Eye, or Blepharitis. TearCare® may not be right for everyone. Please see Instructions for Use or visit TearCare.com for Contraindications, Warnings, Precautions and Adverse Events.

iLink™
CROSS-LINKING PROCEDURE

Using Photrexa® Viscous (riboflavin 5′-phosphate in 20% dextran ophthalmic solution), Photrexa® (riboflavin 5′-phosphate ophthalmic solution), and the KXL® system, the iLink™ corneal cross-linking procedure from Glaukos is the only FDA-approved therapeutic treatment for patients with progressive keratoconus and corneal ectasia following refractive surgery.*[1]

GET THERE IN TIME

iLink™ is the only FDA-approved cross-linking procedure that slows or halts progressive keratoconus to help you preserve vision.

Now from GLAUKOS
LEARN MORE AT **GLAUKOS.COM**

INDICATIONS

Photrexa® Viscous (riboflavin 5′-phosphate in 20% dextran ophthalmic solution) and Photrexa® (riboflavin 5′-phosphate ophthalmic solution) are indicated for use with the KXL System in corneal collagen cross-linking for the treatment of progressive keratoconus and corneal ectasia following refractive surgery. Corneal collagen cross-linking should not be performed on pregnant women.

IMPORTANT SAFETY INFORMATION

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

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

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

You are encouraged to report all side effects to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

*Photrexa® Viscous and Photrexa® are manufactured for Avedro. The KXL System is manufactured by Avedro. Avedro is a wholly owned subsidiary of Glaukos Corporation.

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

MA-01953A

GLAUKOS®