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
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SHE MAY NEED MORE THAN ARTIFICIAL TEARS TO DISRUPT INFLAMMATION IN DRY EYE DISEASE.1,2 Her eyes deserve a change. Choose twice-daily Xiidra for lasting relief that can start as early as 2 weeks.3*

*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.
She may need more than artificial tears to disrupt inflammation in dry eye disease. 

Her eyes deserve a change.

Choose twice-daily Xiidra for lasting relief that can start as early as 2 weeks. 

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 prunus 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.


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

8.2  **Lactation**

Risk Summary

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

8.4  **Pediatric Use**

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

8.5  **Geriatric Use**

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

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A new clinical study from the DCR 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)
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 acquisition? 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 eyelid 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)
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:

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

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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 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 mimic.” 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 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.

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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!!”

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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<0.001) 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.


(Continued on p. 22)
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REVIEW OF OPHTHALMOLOGY

ROBERT M. KERSHNER, MD, MS,

REVIEW OF OPHTHALMOLOGY

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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) 0.36%
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
In acute postoperative inflammation and pain after cataract surgery, administer one drop of LOTEMAX® SM into the conjunctival sac of the affected eye three times daily beginning the day after surgery and continue 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 infections 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 untreated or uncontrolled 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 coincidently 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 frequent 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. Malformations were observed in rats at doses 1068 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 Studies. Embryofetal studies were conducted in pregnant rabbits administered loteprednol etabonate or 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 meningoceles) 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 (1006 times the RHOD). Embryofetal lethality (resorption) was observed at 100 mg/kg (2133 times the RHOD). The NOAEL for developmental toxicity in rats was 3 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 atresia, and delayed ossification (106 times the RHOD) produced maternal toxicity (reduced body weight gain, death), decreased number of live-born offspring, decreased birth weight, and delays in skeletal development. A NOAEL for maternal toxicity 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).

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Clinical significance of these preclinical data has not been established.

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 result in posterior subcapsular cataract formation.
- 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.


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**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.

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

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...
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 purportedly 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,5,6 when used by nonophthalmic staff in an emergency room,7 and when tested on Chinese and Australian individuals.8

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. 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.

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

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.

WARNINGS AND PRECAUTIONS
Alpha-adrenergic agonists may impact blood pressure. UPNEEQ should be used with caution in patients with severe or unstable cardiovascular disease, orthostatic hypotension, and/or 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.

POTENTIATION OF VASCULAR INSUFFICIENCY
UPNEEQ should be used with caution in patients with cerebral or coronary insufficiency, or 50-year-old’s syndrome. Advise patients to seek immediate medical care if signs and symptoms of potentiation of vascular insufficiency develop.

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.

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.

ADVERSE REACTIONS
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.

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.

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

USE IN SPECIFIC POPULATIONS
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).

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.

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

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.

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

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

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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 sequelae 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.
IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

• EYLEA is contraindicated in patients with ocular or periorcular 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.

EYLEA is a registered trademark of Regeneron Pharmaceuticals, Inc.
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\(^5\, 6\, 11\, 12\, 13\, 14, 15\, 16\)

<table>
<thead>
<tr>
<th>Initial Gains (Month 5)</th>
<th>Primary Endpoint (Year 1)</th>
<th>Prespecified Exploratory Endpoint (Year 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VISTA</strong></td>
<td><strong>VIVID</strong></td>
<td><strong>VISTA</strong></td>
</tr>
<tr>
<td>EYLEA Q4</td>
<td>+10.3 (n=154)</td>
<td>+12.5 (n=154)</td>
</tr>
<tr>
<td></td>
<td>+9.3 (n=136)</td>
<td>+10.5 (n=136)</td>
</tr>
<tr>
<td></td>
<td>+10.4 (n=154)</td>
<td>+10.3 (n=136)</td>
</tr>
<tr>
<td>EYLEA Q8(^1)</td>
<td>+9.9 (n=151)</td>
<td>+10.7 (n=151)</td>
</tr>
<tr>
<td></td>
<td>+9.3 (n=135)</td>
<td>+10.7 (n=135)</td>
</tr>
<tr>
<td></td>
<td>+10.5 (n=151)</td>
<td>+11.7 (n=135)</td>
</tr>
<tr>
<td>Control</td>
<td>+1.8 (n=154)</td>
<td>+0.2 (n=154)</td>
</tr>
<tr>
<td></td>
<td>+1.8 (n=132)</td>
<td>+1.2 (n=132)</td>
</tr>
<tr>
<td></td>
<td>+1.4 (n=154)</td>
<td>+1.6 (n=132)</td>
</tr>
</tbody>
</table>

\(P<0.01\) 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\(^5\, 6\).

**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.\(^1\)

\(^1\)Last observation carried forward; full analysis set.

\(^2\)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\(^3\) (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).


Please see Brief Summary of Prescribing Information on the following page.
**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 the clinical trials of a drug.

**6.2 Immunogenicity**

As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity consistent with those seen in the phase 3 VIVID and VISTA trials (see Table 3 above).

**6.3 Maternal and Lactation Nursing**

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. 6.4 Pediatric Use 6.5 Pregnancy

The pregnancy category of EYLEA is C. In animal reproduction studies, aflibercept did not produce any evidence of harm to the fetus. 6.6 Lactation

Adverse drug reactions reported in >1% of the patients treated with EYLEA were hyperglycemia, hypotension, and conjunctival hemorrhage.

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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>EYLEA (N=142)</th>
<th>Control (N=91)</th>
<th>Baseline to Week 12</th>
<th>Baseline to Week 52</th>
<th>Baseline to Week 66</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular hyperemia</td>
<td>3%</td>
<td>0%</td>
<td>3%</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Conjunctival edema</td>
<td>2%</td>
<td>0%</td>
<td>2%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>2%</td>
<td>0%</td>
<td>2%</td>
<td>3%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Less common adverse reactions reported in >1% of the patients treated with EYLEA were hypertension, conjunctival hemorrhage, and vitreous hemorrhage.

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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Baseline to Week 52 (N=578)</th>
<th>Baseline to Week 100 (N=578)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular hyperemia</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Conjunctival edema</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Less common adverse reactions reported in >1% of the patients treated with EYLEA were hypertension, conjunctival hemorrhage, and vitreous hemorrhage.

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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Baseline to Week 52 (N=1824)</th>
<th>Baseline to Week 100 (N=1824)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctival edema</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Ocular hyperemia</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Vitreous hemorrhage</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Less common adverse reactions reported in >1% of the patients treated with EYLEA were hyperglycemia, hypertension, and conjunctival hemorrhage.

**Table 4: Most Common Adverse Reactions (≥2%) in Wet AMD Studies**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Baseline to Week 52 (N=1223)</th>
<th>Baseline to Week 100 (N=1223)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular hyperemia</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Conjunctival edema</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Ocular hypertension</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Less common adverse reactions reported in >1% of the patients treated with EYLEA were hyperglycemia, hypertension, and conjunctival hemorrhage.

**Table 5: Most Common Adverse Reactions (≥1%) in DME Studies**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Baseline to Week 52 (N=578)</th>
<th>Baseline to Week 100 (N=578)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular hyperemia</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Conjunctival edema</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Ocular hypertension</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Less common adverse reactions reported in >1% of the patients treated with EYLEA were hyperglycemia, hypertension, and conjunctival hemorrhage.
Screening Refractive Surgery Patients

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

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 online at simplypsychology.org/eysenck-inventory.pdf, can be directly administered online at ilugu.ru/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.
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**: 54.11 (ranging from 53.66 to 54.70);
- **Sanguine**: 52.60 (ranging from 51.5 to 53.60);
- **Melancholic**: 44.57 (ranging from 43.89 to 46.44); and
- **Choleric**: 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 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 predominately 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 unstable/neurotic.

### Ocular Symptoms & Mood Disorder-Related Issues

<table>
<thead>
<tr>
<th>Patient type</th>
<th>Ocular symptoms linked to pathology</th>
<th>Ocular complaints absent pathology</th>
<th>Mood disorder-related complaints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phlegmatic (n=12)</td>
<td>50%</td>
<td>42%</td>
<td>8%</td>
</tr>
<tr>
<td>Sanguine (n=3)</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Melancholic (n=23)</td>
<td>22%</td>
<td>48%</td>
<td>30%</td>
</tr>
<tr>
<td>Choleric (n=8)</td>
<td>13%</td>
<td>38%</td>
<td>50%</td>
</tr>
</tbody>
</table>
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*)

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

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.

Formulated with HYDRELLA™ for comfort.

Visit MyZERVIATE.com for more information.

Available by prescription only

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ZERVIATE™ (cetirizine ophthalmic solution) 0.24%

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.

DOSEAGE 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/m² 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 Cmax = 311 ng/mL) that were 100 times higher than the observed human exposure (Mean Cmax = 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/m² 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/m² 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/m² 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/m² 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

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introduced 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.4,5

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.


ABOUT THE AUTHORS

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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-
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.”

Treat ing 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 Trienese 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 herpetic 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.”

“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 Trience.”

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\(^*\)
  [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\(^*\)

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**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. J7314. For more information, visit YUTIQ.com
YUTIQ™ (fluocinolone acetonide intravitreal implant) 0.18 mg, for intravitreal injection
Initial U.S. Approval: 1983

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.

2. 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 when 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, sham injection-controlled, 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.

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

<table>
<thead>
<tr>
<th>ADVERSE REACTIONS</th>
<th>YUTIQ (N=226 Eyes) n (%)</th>
<th>Sham Injection (N=94 Eyes) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataract1</td>
<td>63/113 (56%)</td>
<td>13/56 (23%)</td>
</tr>
<tr>
<td>Visual Acuity Reduced</td>
<td>33 (15%)</td>
<td>11 (12%)</td>
</tr>
<tr>
<td>Macular Edema</td>
<td>25 (11%)</td>
<td>33 (35%)</td>
</tr>
<tr>
<td>Uveitis</td>
<td>22 (10%)</td>
<td>33 (35%)</td>
</tr>
<tr>
<td>Conjunctival Hemorrhage</td>
<td>17 (8%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Eye Pain</td>
<td>17 (8%)</td>
<td>12 (13%)</td>
</tr>
<tr>
<td>Hypotony Of Eye</td>
<td>16 (7%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Anterior Chamber Inflammation</td>
<td>12 (5%)</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>Dry Eye</td>
<td>10 (4%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Vitreous Opacities</td>
<td>9 (4%)</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>9 (4%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Posterior Capsule Opacification</td>
<td>8 (4%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Ocular Hyperemia</td>
<td>8 (4%)</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>Vitreous Haze</td>
<td>7 (3%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Foreign Body Sensation In Eyes</td>
<td>7 (3%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Vitritis</td>
<td>6 (3%)</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>Vitreous Floaters</td>
<td>6 (3%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Eye Pruritus</td>
<td>6 (3%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Conjunctival Hyperemia</td>
<td>5 (2%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Ocular Discomfort</td>
<td>5 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Macular Fibrosis</td>
<td>5 (2%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>4 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Photopsia</td>
<td>4 (2%)</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>

(continued)

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. Systemic 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

Cover Story

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

(Triesence), and an intravitreal dexa-methasone 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
Cover Story  UVEITIS

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 antimitabolite 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 periocular 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 antimitabolite, 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 antimitabolite 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 pericellular 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.

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

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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.

Richard J. Mackool, MD

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**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.

**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.

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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 (Orenica). 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—is 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.”
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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

A dult-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. “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
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-
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, rounded 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. Han. “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
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Clinical Trials Experience—Because clinical trials are conducted under conditions of the eye, corticosteroids may mask infection or enhance existing infection. 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 mate to a 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 based on body surface area, assuming 100% absorption). Spina bifida (including meningocoele) 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. The 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 or in vivo in the Ames test, the mouse lymphoma thymidine kinase (tk) assay, or in a chromosome aberration test in human lymphocytes, or in vivo in the single dose mouse micronucleus assay. 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).

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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 hyperreflective 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 hyperreflective space, don’t assume it’s subretinal fluid,” he points out. “When we see hyperreflective 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 hyperreflective 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 hypoaufotfluorescence. 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
“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 electro-oculogram. “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.”

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**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 hyper-reflective 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.
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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.

Dr. 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 aberrometry 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...
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 preoperative 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.”

**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 preoperative symptoms not related to the 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...”
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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 thinking 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
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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, 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, 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.”

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. “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
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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, 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. 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.”

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. 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-
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 combo. 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

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**MEDICATIONS TO TREAT OCULAR ALLERGY**

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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.”

“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.”

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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.”

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 the 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.4


— Robert Latkany, MD

Take a comprehensive approach and attack the source of the problem rather than the symptom.

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NEVER any Cryopreservants, Antibiotics, Cross Linkers or Ethanol
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, but the term conjunctivochalasis was coined in 1942 by Wendell Holmes, MD. 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) 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.

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. 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, the condition’s link to pterygia is thought to be related to dry eye and a shared association with inflammatory cytokines.

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

Also like pterygia, the conjunctivochalasis tissue itself has been shown to have increased levels of matrix metalloproteinases, which are enzymes that degrade matrix proteins. The tissue has also been shown to have increased reactive oxygen species that lead to oxidative stress. Why these
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; 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
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. 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 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, 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 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. 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. 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 cauternization and amniotic membrane used to reinforce Tenon’s capsule. 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
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fail, surgical options include shrinkage of redundant tissue, removal of redundant tissue and increased adhesion between conjunctiva and sclera.

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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.

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.

Tenwek Mission Hospital campus, located in southwest Kenya, serves as a referral hospital for the region.
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
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
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 unparalled, 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 (far right) and his family (from left), Jenny, his wife; Luke, Isaac and Nate, split their time between Kenya and Birmingham, Alabama.

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

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...
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, WIS.

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.

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-
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. 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 -1 dB 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. 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
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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 electoretinogram 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
I didn’t realize STARS were little dots that twinkled

—Misty L, RPE65 gene therapy recipient

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GLAUCOMA MANAGEMENT | Glaucoma in the Presence of Retinal Disease

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.


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.
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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 retinopathy, 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.

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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.

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.
**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.

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**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).

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. The condition was first described in 1969. 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. Previously reported ocular adnexal sites of EH include the eyelid, intracanal and extracanal soft tissue, lacrimal gland and conjunctiva. The patients with ocular adnexal EH most commonly present with symptoms that include swelling, proptosis, diplopia, ptosis, vision loss, pruritis, epiphora and/or pulsation. 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-
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ondary to an arteriovenous shunt.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 (Kaposi sarcoma and angiosarcoma). Absence of significant nuclear atypia, cellularity and/or mitotic activity favors EH over more aggressive tumors. Absence of significant nuclear atypia, cellularity and/or mitotic activity favors EH over more aggressive tumors. EH lacks CAMTA1 and TFE3 gene rearrangements (Kaposi sarcoma and angiosarcoma). 15 Presence of reassuring features like FOSB gene rearrangement may support the diagnosis of EH.\textsuperscript{3}

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.\textsuperscript{3,13} Well-circumscribed lesions, such as that in our patient, tend to have low recurrence rates.\textsuperscript{1,4} 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.\textsuperscript{3,11,12,14,18} In less-severe cases, observation for spontaneous regression following incisional biopsy and tissue diagnosis may be appropriate.\textsuperscript{2}

More recently, systemic propranolol has been proposed as a treatment for EH, based upon its efficacy in regression of pediatric capillary hemangiomas.\textsuperscript{17} Proposed mechanisms of action include vasocostriction, inhibition of angiogenesis and induction of apoptosis.\textsuperscript{10} One case of an epithelioid hemangioma with rapid progression, despite two subtotal excisions, steroids and chemotherapy agents, completely resolved with systemic propranolol.\textsuperscript{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.\textsuperscript{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.\textsuperscript{1,14} 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.\textsuperscript{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.

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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].

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.

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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.

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