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REVIEW® of Ophthalmology

November 2015

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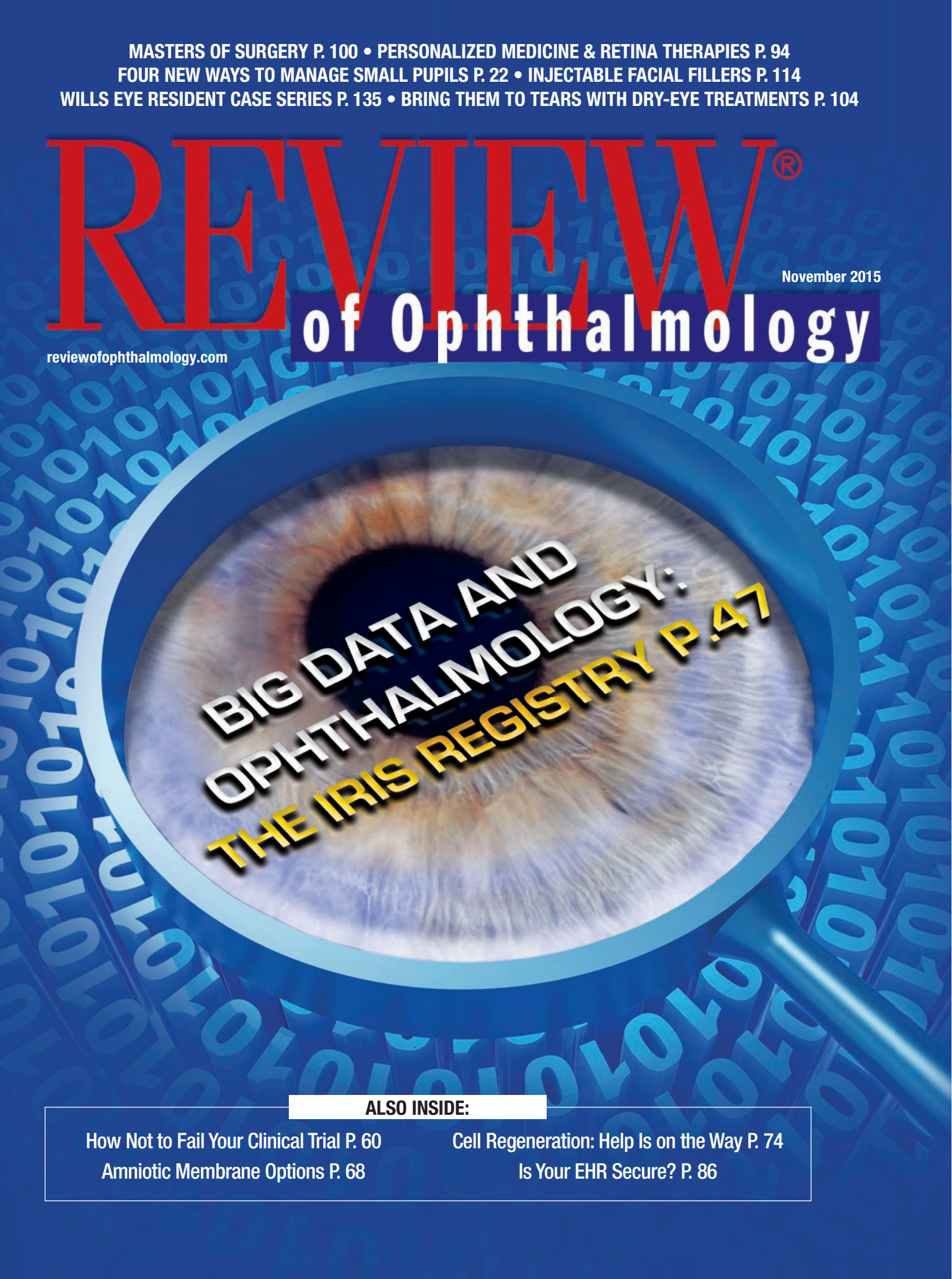

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REVIEW NEWS
Volume XXII • No. 11 • November 2015

Penn Study Stops Vision Loss in Late-Stage Canine X-linked RP

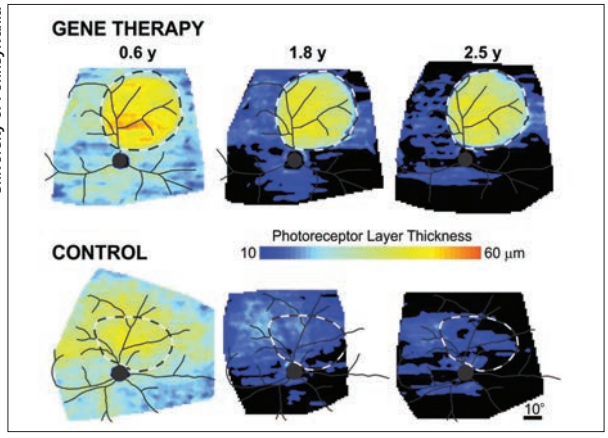
Three years ago, a team from the University of Pennsylvania announced that they had cured X-linked retinitis pigmentosa, a blinding retinal disease, in dogs. Now they've shown that they can cure the canine disease over the long term, even when the treatment is given after half or more of the affected photoreceptor cells have been destroyed.

Because the disease affects humans in almost the same fashion as it does dogs, the results suggest that this treatment could be effective and lasting in humans and could set the stage for safety studies that precede a human clinical trial.

"The 2012 study showed that gene therapy was effective if used as a preventive treatment or if you intervene right after the onset of cell death," said William A. Beltran, DVM, PhD, co-lead author and associate professor of ophthalmology at Penn's School of Veterinary Medicine. "That was obviously very encouraging. But now we've gone further, showing that the treatment is long-lasting and effective even when started at mid- and late-stage disease."

"This happens to be a very severe disease with very early onset in the first two decades of life in humans," said Artur V. Cideciyan, PhD, co-lead author and research professor of ophthalmology in the Scheie Eye Institute at Penn's Perelman School of Medicine. "Because the progression of disease in dogs matches up with the progression in humans, this gives us a lot of confidence about translating these results to eventually treat humans."

The work involved a close collaboration between Drs. Beltran and Cideciyan as well as Samuel G. Jacobson, professor of ophthalmology at Scheie, and Gustavo D. Aguirre, VMD, PhD, the paper's senior author and professor of medical genetics and ophthalmology at Penn Vet. The Penn researchers have also long partnered with University of Florida scientists led by William Hauswirth, PhD, the Rybaczki-Bullard Professor of Ophthalmology in the College of Medicine. Their work appears in *Proceedings of the National Academy of Sciences*.



University of Pennsylvania

Using gene therapy to augment normal levels of the RPGR gene resulted in long-term rescue of photoreceptors within the retinal region of gene therapy injection, but not within the control injection. The rescue lasted at least 2.5 years when the disease was treated in its later stages.

X-linked retinitis pigmentosa, or XLRP, arises primarily from mutations in the RPGR gene, leading to progressive vision loss starting at a young age. Because it is an X chromosome-linked recessive disease, it overwhelmingly affects boys and men. It is one of the most common forms of inherited retinal disease.

Though rigorously studied, little is understood about the function of RPGR. It is believed to play a role in the function of the connecting cilium, a structure that is present in both rod and cone cells, the photoreceptor cells involved in dim-light and bright-light vision, respectively.

In XLRP, these photoreceptor cells progressively degenerate and die. To counter this effect, the Penn group's earlier gene therapy work used a viral vector to deliver a normal copy of RPGR specifically to rods and cones using a subretinal injection.

In the new publication, the team reports that the therapy, which occurred when dogs were 5 weeks old, successfully stopped photoreceptor cell loss and maintained vision in dogs for more than three years of study.

This study also went further, using the same viral vector and same approach, except this time beginning the gene therapy intervention at two later time points: At 12 weeks of age, which the researchers term "mid-stage disease," when approximately 40 percent of the eye's photoreceptor cells have

already died, or at 26 weeks of age, "late-stage disease," when about 50 to 60 percent of the rods and cones were lost.

The team had concerns about treating at these later stages, both that the retina might not properly reattach following the therapeutic subretinal injection and that there could be toxicity from the viral vector due to the greater extent of photoreceptor cell degeneration. They saw no indications of either being a problem in their follow-up.

"We have spent a lot of time working to make sure the therapeutic gene is tightly regulated in terms of when and where it is expressed," said Dr. Aguirre. "And, thankfully, we have seen that this therapy appears to be well-tolerated in the retina."

Instead, what they saw, using non-invasive tests used in human medicine, including electroretinography and optical coherence tomography imaging, was a remarkable and lasting halt in the degeneration of photoreceptor cells in the treated region of the retina. Dogs treated at these later stages of disease even had some of the structural abnormalities in the rods and cones reversed. And these findings translated to improved performance on visual behavior tests, a Y maze that tested whether the dogs could detect a dim light and an obstacle course that assessed their visual navigational skills. The dogs' performances endured for at least two and a half years after treatment, the latest time point examined, in the late-stage group.

"What the dog studies show, especially those that are treated at a later stage, is that you can treat a relatively small region—20 percent or less of the retinal surface, where you already had 50 percent of photoreceptor cells that died before treatment—and still see not only an electrophysiological improvement and rescue but an actual rescue of visual behavior," Beltran said.

(continued on page 8)

Ophthalmic Product Development Insights

George Ousler, Lisa Smith and Matthew Chapin • Ora Inc., Andover, Mass.

It's the Thought that Counts

In prior columns, we have discussed novel therapeutics, identification of unmet needs, partnering and funding, and other topics related to product development. We have explored various ways in which entrepreneurs have partnered products for development, and have discussed a consistent message of "beginning with the end in mind." Many times investment in a new venture starts with a specific technology. Other times the physician-entrepreneur may only have a concept to address a need that has yet to be reduced to practice or aligned with any one specific technology. If integrated with appropriate support and a funding source, this can be a very focused manner of product development, in that the need can be defined and the target product profile outlined, so that the best approach can be followed. In this installment, we will discuss how the identification of a clinical need by an entrepreneur led to partnering on the early concept and execution on development of this novel product. This may potentially assist clinicians, as well as researchers in designing optimized clinical trials.

The Clinical Need

Dry-eye disease is enigmatic, both from the perspective of its pathophysiology and from that of its treatment. It is loosely defined as a dysfunction of the tear film, yet this dysfunction can be the end result of numerous causes: insufficient aqueous tear production following autoimmune damage to the lacrimal and accessory glands; meibomian gland dysfunction causing accelerated evaporation of aqueous tears due to lack of the protective lipid layer; or mucin changes brought on by age, endocrine dysfunction or inflammatory processes. The profound effect of environmental and behavioral circumstances that lead to a constantly variable presentation of signs and symptoms contributes further complexity. The final piece that stumps researchers and clinicians is the seeming disassociation of signs and symptoms: Some patients have terrible discomfort without much signs of damage; others have blatant keratitis—yet without a complaint. The logical outcome of this plurality is that pathology-based subgroups of dry eye exist, and a further tailoring of treatments specifically focused on a pathological subgroup should greatly improve our treatment of this disease.

All these complexities have contributed to the well-known difficulty of establishing efficacy of dry-eye treatments. The success of Restasis (cyclosporine emulsion 0.05%), with close to $1 billion sales worldwide, is testament to the marketability and unmet need that draw startups and venture capital to the world of dry eye. Yet even the Restasis label targets a subgroup of patients for whom the drug may "increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca." This subgroup-specific labeling highlights the need for selecting the proper treatment that is most appropriate for the patient. Consequently, researchers have to be able to design proper studies to select the right subgroup for evaluating novel therapies.

None of the various tools available to diagnose dry eye provides the whole picture. Some of the most commonly used are the Schirmer's test, which measures aqueous tear production; tear-film breakup time, which determines how quickly the tear film evaporates; and fluorescein or lissamine green staining, which visualize the endgame of epithelial damage. Symptoms of the disorder are variable, but quantitative assessments typically employ questionnaires such as the Ocular Surface Disease Index (OSDI) or other symptomatology scales.

Many drugs for dry eye are indeed progressing to Phase III trials and beyond. If and when these come to fruition, the result will be a polypharmacy of treatment choices. It will be up to physicians to decide which treatment best suits their patients. Potential approvals will allow for additional anti-inflammatory agents such as lifitegrast (Shire); mucogenics (e.g., MIM-D3: Mimetogen) that target evaporative dry eye; multifunctional approaches such as anti-oxidant/anti-inflammatory (SKQ1: Mitotech); improved barrier-function molecules, such as modified hyaluronic acid to increase mucoadhesion, optimize wetting, prolong protection and stabilize tears, as well as combating inflammation and providing a bandage effect to promote healing. It is even more likely that patients will receive multiple therapies that target various aspects of their disease. While refined clinical assessment will help define patients, there is a need for additional diagnostics to complement the clinical assessment.

The Approach

TeaRx, is a biomarker panel originally conceived by an entrepreneurial researcher, Eran Eilat. Dr. Eliat recognized that dry eye is a multifactorial disease that has been difficult to study and whose proper subgroups are difficult to define. His concept was to create a diagnostic that would address these issues, and that would be useful to clinicians, pharmaceutical companies developing new products and researchers conducting clinical research. He approached a life sciences investment group in Israel, BioLight, with his idea to look at dry eye through a different lens (or rather multiple lenses), creating an objective, multi-parameter kit for a multifactorial disease. BioLight is focused on investing in various unique ophthalmology products. Without being tied to any specific test method, they embarked on the journey together, creating DiagnosTear. BioLight is implementing a unique business model that combines novel ophthalmic technologies to narrow in on ophthalmic conditions from various angles, affording a synergy in economies of scale and knowledge that is in line with the entrepreneur's vision. They first identified the key elements of dry eye and of the tear film, and potential markers that can be measured. They identified key constituents in the tear film (e.g., lysozyme, lactoferrin, proteins and others) that have been well-researched and connected to dry eye of various forms, and can potentially highlight important indicators of the health of the tear film and ocular surface. They developed technology for easy, rapid test strips that semi-quantitatively measure the levels of the four different markers in one test strip.

Says Suzana Nahum Zilberberg, BioLight CEO: "The clinical need for a better protocol of treatment for dry-eye patients is clear and growing. The multi-parameter approach that was presented by Dr. Eilat was clearly in line with our approach of targeting ophthalmic needs from multiple angles, which made us invest in the concept in a very early stage. In a relatively short timeframe we have developed a pool of biomarkers related to dry-eye patient populations that have the potential to provide solutions not only for better diagnostics but also for a better treatment."

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200 subjects has been completed in the United States implementing the DiagnosTear panel in suspected dry-eye and normal subjects. Widely used tests for dry eye (Schirmer's, TFBUT), as well as staining of corneal and conjunctival epithelial cell damage and patient questionnaires, were compared with the TeaRx diagnostic parameters. There were positive statistical correlations between these widely used benchmark tests and the TeaRx diagnostic parameters tests. The positive correlations identified between certain TeaRx diagnostic parameters and subjective testing standards that are widely used today indicate a unique ability for improving the dry-eye syndrome diagnosis by objective quantification of measures over subjective evaluation. This is a major advancement in the proper diagnosis of dry eye and has potential to provide physicians with an efficient approach to selecting treatments for individual patients. These results led to a further study and advancement of the regulatory program of TeaRx towards commercial development.

The goals and vision for this particular diagnostic are to have TeaRx generate three revenue streams, leveraging the unmet need in the field:

- as a leading point-of-care solution that will assist ophthalmologists to better diagnose and treat dry-eye patients;
- as a companion diagnostic product to assist in introducing personalized treatment to the market (by better defining endpoints for clinical development, increasing efficacy by targeting the specific responder sub-population, supporting the reimbursement process and providing a cost-effective solution); and
- a valuable research and clinical trials tool.

This model also highlights that diagnostics can generate revenue not only by being sold to clinicians, but by following a path of licensing for incorporation into pharmaceutical trials.

In early development of diagnostics for dry eye, other tests have become available; however, these all measure a single marker. The advantage of the TeaRx system is that different measured parameters could enable identifying specific dry-eye subgroups characterized in aqueous tear deficiency such as inflammation, evaporative dry eye and others. In-office data from this panel of compounds informs the physician on how to treat the patient, the ultimate goal of any diagnostic.

The recognition that we need to understand and categorize our patients to the upcoming drugs has opened the market for precise diagnostics. Opportunities have arisen for pharma, physicians and entrepreneurs to bring their ideas forward. The bundling of various parameters that together define the diagnosis of dry eye, as performed by DiagnosTear, is an elegant example of an unmet need leading to translational science, and evolving into a marketable idea.

Mr. Chapin is senior vice president of the Corporate Development Group, Mr. Ousler is vice president of Dry Eye, and Ms. Smith is a senior medical writer at Ora Inc. Ora provides a comprehensive range of product development, clinical-regulatory and product consulting for developers, investors and buyers; clinical trial services and regulatory submissions; and asset and business partnering support in ophthalmology. We welcome comments or questions related to this or other development topics. Please send correspondence to mchapin@oraclinical.com.

(continued from page 5)

"Based on my experience developing gene therapies in animal models for many other inherited retinal diseases," said the University of Florida's Dr. Hauswirth, "I believe this report describes perhaps the strongest case yet for eventual successful therapy in humans for XLRP."

As in their earlier work, the researchers showed that the function of both rods and cones was rescued and that these photoreceptor cells were properly connected to the neurons that transmit visual signals to the brain.

"Because this is a photoreceptor disease that affects both rods and cones, or night- and day-vision cells, to show that both were rescued was very wonderful to see," Dr. Cideciyan said.

"I worry a lot about my patients who have lost photoreceptor cells and possibly have abnormal connectivity and structure in their retina, whether gene therapy would still work for them at later stages of disease," Dr. Jacobson said. "What we showed here is that the therapy resulted in downstream neurons that were robust and connected, which is exceptionally important for eventual human treatment."

The group is also studying the other genetic "partners" that function along with RPGR in the connecting cilium to see if there could be additional targets for therapy.

Study Supports Home Monitoring To Detect CNV

Use of a qualification test within a retinal practice appeared to be effective in predicting which patients with intermediate age-related macular degeneration would be good candidates to initiate use of a home monitoring device for progression to more severe AMD, according to a study published online by *JAMA Ophthalmology*.

Choroidal neovascularization from AMD left untreated or unmanaged after substantial vision loss has occurred remains a leading cause of irreversible blindness in people age 50 years or older throughout much of the world. In the United States, approximately 8 million people have intermediate AMD or monocular advanced AMD, of whom 1.3 million people will develop advanced AMD during the ensuing five years. Patients with intermediate AMD using a home monitoring device (includes looking at a computer screen and using a mouse) have less loss of visual acuity, on average, at detection of choroidal neovascularization than do individuals using standard care monitoring techniques (such as viewing a grid on a piece of paper). Patients must establish a baseline set of responses during a limited series of initial home testing to monitor AMD progression using this device. There is little known about the proportion of patients with high-risk non-neovascular AMD who

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REVIEW News

may be able to incorporate the device successfully into their home monitoring regimen, according to background information in the article.

The developers of the home device designed an in-office qualification test to identify individuals most likely to be able to use the device successfully. Neil M. Bressler, MD, of the Johns Hopkins University School of Medicine, Baltimore, and editor of *JAMA Ophthalmology*, and colleagues studied 131 participants within a university-based retina practice with intermediate AMD in at least one eye who completed an in-clinic qualification test for the home monitoring device. The qualification test protocol included a short explanation by the study coordinator, explanatory tutorial administered through the device, a trial or practice test administered through the device (an opportunity to mark areas of artificial distortion), an opportunity for the participant to ask questions and the actual qualification test.

A total of 129 participants had reliable qualification test results; 91 participants (70 percent) who completed this test attained a score that suggested they would be able to successfully use the home device. Among the 91 participants who could initiate home testing, 83 did so, including 80 participants (88 percent) who established a baseline value that could be used as a reference for future monitoring. Younger participants were more likely to qualify for home testing. Visual acuity at study enrollment did not appear to be associated with successful qualification.

"These data support the likelihood that a larger percentage of individuals at high risk of progressing to CNV from AMD who successfully complete a qualification test to use this home monitoring device will be able to establish a baseline value for subsequent monitoring at home. These individuals can continue to increase their chance of detecting neovascular AMD between scheduled office visits while the lesion is relatively small and associated with visual acuity that is relatively good," the authors write.

Sealing Protein May Key Dry-Eye Breakthrough

Recent research by Keck Medicine of the University of Southern California scientists, published in *PLOS ONE*, suggests a new approach to treating dry eye. Using an experimental mouse model, the researchers demonstrated for the first time that the natural tear protein clusterin seals the ocular surface barrier, while also protecting against further damage.

Findings show that clusterin blocks uptake of fluorescein dye, a clinical test used to diagnose dry eye, according to senior and corresponding author Shinwu Jeong, PhD, assistant professor of research ophthalmology in the Institute for Genetic Medicine at the Keck School of Medicine of USC. "It is well known that clusterin protects cells and proteins," he said. "A problem in dry eye appears to be that natural clusterin is depleted. We predicted that adding it back would be beneficial, however the novel mechanism of sealing was unexpected."

The researchers studied the ocular surface barrier rather than upstream effects of tear production, tear chemistry and inflammation that contribute to dry-eye conditions. "We are the first to report functions for this protein in dry eye and shed some light on its potential use for ophthalmology treatments," said Aditi Bauskar, a PhD, lead author on the paper. "Our pre-clinical results are very promising and make a strong case to use clusterin as a biological drug to prevent or treat not only dry eye, but also other corneal disorders involving damage to the ocular surface barrier." REVIEW

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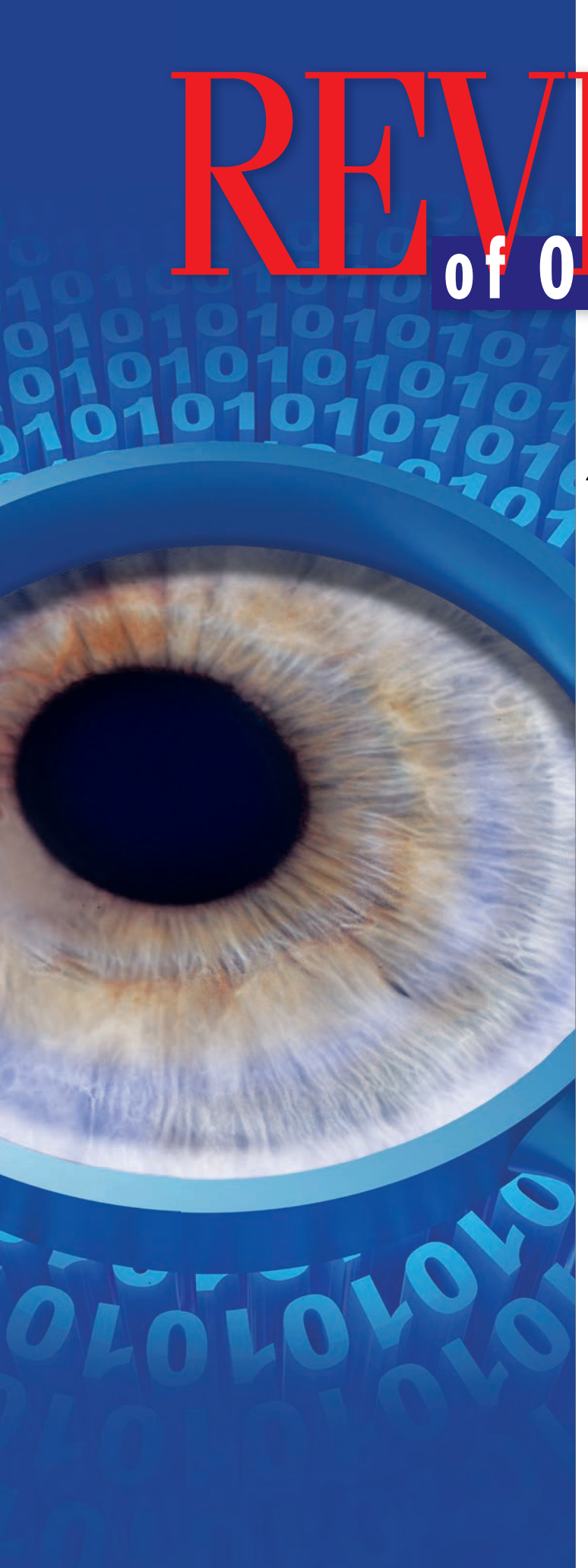

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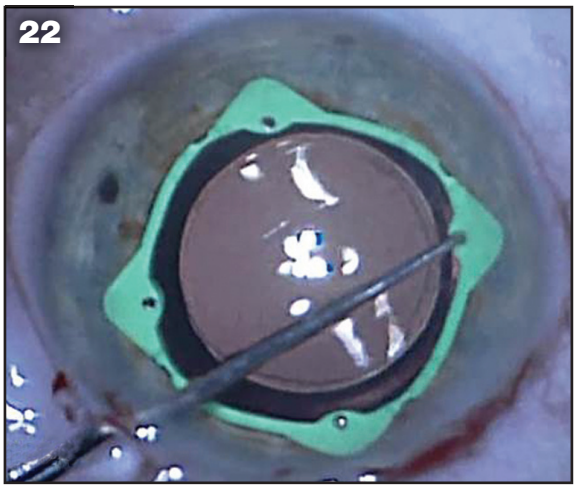

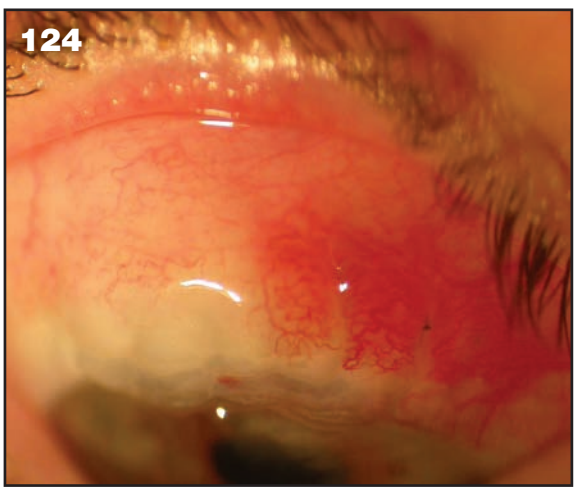

The Quintessential

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BACITRACIN OPHTHALMIC OINTMENT USP

Proven therapeutic utility in blepharitis, conjunctivitis, and other superficial ocular infections

- **Profound bactericidal effect against gram-positive pathogens**[1]
- **Excellent, continued resistance profile**—maintains susceptibility,[2,3] even against methicillin-resistant *Staphylococcus aureus*[4]
- Ointment provides **long-lasting ocular surface contact time** and **greater bioavailability**[5]
- **Anti-infective efficacy** in a lubricating base[6]
- **Unsurpassed safety profile**—low incidence of adverse events[6]
- **Convenient dosing**—1 to 3 times daily[6]
- **Tier 1 pharmacy benefit status**—on most insurance plans[7]

Bacitracin Ophthalmic Ointment is indicated for the treatment of superficial ocular infections involving the conjunctiva and/or cornea caused by Bacitracin susceptible organisms.

Important Safety Information

The low incidence of allergenicity exhibited by Bacitracin means that adverse events are practically non-existent. If such reactions do occur, therapy should be discontinued.

Bacitracin Ophthalmic Ointment should not be used in deep-seated ocular infections or in those that are likely to become systemic.

This product should not be used in patients with a history of hypersensitivity to Bacitracin.

www.perrigobacitracin.com

Please see adjacent page for full prescribing information.

References: 1. Kempe CH. The use of antibacterial agents: summary of round table discussion. *Pediatrics*. 1955;15(2):221-230. **2.** Kowalski RP. Is antibiotic resistance a problem in the treatment of ophthalmic infections? *Expert Rev Ophthalmol*. 2013;8(2):119-126. **3.** Recchia FM, Busbee BG, Pearlman RB, Carvalho-Recchia CA, Ho AC. Changing trends in the microbiologic aspects of postcataract endophthalmitis. *Arch Ophthalmol*. 2005;123(3):341-346. **4.** Freidlin J, Acharya N, Lietman TM, Cevallos V, Whitcher JP, Margolis TP. Spectrum of eye disease caused by methicillin-resistant *Staphylococcus aureus*. *Am J Ophthalmol*. 2007;144(2):313-315. **5.** Hecht G. Ophthalmic preparations. In: Gennaro AR, ed. *Remington: the Science and Practice of Pharmacy*. 20th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2000. **6.** Bacitracin Ophthalmic Ointment [package insert]. Minneapolis, MN: Perrigo Company; August 2013. **7.** Data on file. Perrigo Company.

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Bacitracin Ophthalmic Ointment USP

STERILE **Rx Only**

DESCRIPTION: Each gram of ointment contains 500 units of Bacitracin in a low melting special base containing White Petrolatum and Mineral Oil.

CLINICAL PHARMACOLOGY: The antibiotic, Bacitracin, exerts a profound action against many gram-positive pathogens, including the common Streptococci and Staphylococci. It is also destructive for certain gram- negative organisms. It is ineffective against fungi.

INDICATIONS AND USAGE: For the treatment of superficial ocular infections involving the conjunctiva and/or cornea caused by Bacitracin susceptible organisms.

CONTRAINDICATIONS: This product should not be used in patients with a history of hypersensitivity to Bacitracin.

PRECAUTIONS: Bacitracin ophthalmic ointment should not be used in deep-seated ocular infections or in those that are likely to become systemic. The prolonged use of antibiotic containing preparations may result in overgrowth of nonsusceptible organisms particularly fungi. If new infections develop during treatment appropriate antibiotic or chemotherapy should be instituted.

ADVERSE REACTIONS: Bacitracin has such a low incidence of allergenicity that for all practical purposes side reactions are practically non-existent. However, if such reaction should occur, therapy should be discontinued.

To report SUSPECTED ADVERSE REACTIONS, contact Perrigo at 1-866-634-9120 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DOSAGE AND ADMINISTRATION: The ointment should be applied directly into the conjunctival sac 1 to 3 times daily. In blepharitis all scales and crusts should be carefully removed and the ointment then spread uniformly over the lid margins. Patients should be instructed to take appropriate measures to avoid gross contamination of the ointment when applying the ointment directly to the infected eye.

HOW SUPPLIED:

NDC 0574-**4022**-13 3 - 1 g sterile tamper evident tubes with ophthalmic tip.

NDC 0574-**4022**-35 3.5 g (1/8 oz.) sterile tamper evident tubes with ophthalmic tip.

Store at 20°-25°C (68°-77°F)
[see USP Controlled Room Temperature].

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Four New Ways to Manage Small Pupils

New pupil-expansion devices and an irrigation solution additive promise to make some tough cases easier.

Christopher Kent, Senior Editor

One of the challenges faced by ophthalmologists performing surgery is working in eyes with small pupils. For example, a small pupil makes virtually every step of a cataract procedure more problematic. It limits the size of the capsulorhexis, makes nuclear disassembly more difficult, increases the risk of iris injury and reduces visualization, both during cortex removal and intraocular lens implantation.

Not surprisingly, over the years surgeons have developed numerous techniques and devices that help to offset the problems created by a small pupil—usually by temporarily enlarging it. Recently, several new ways to manage small pupils during surgery have become available. Here, surgeons familiar with their use discuss the advantages of each option.

The Malyugin Ring 2.0

MicroSurgical Technologies (Redmond, Wash.) will be releasing Malyugin Ring 2.0—a new version of the popular Malyugin Ring—in early 2016. Like the existing version, the new model will be available in two sizes, 6.25 and 7 mm, and will be placed inside the eye through the main surgical incision with no need for extra paracenteses. Both the original and new rings, which resemble a square with a loop at each corner, provide eight points of iris fixation, making the pupil very close to round when the device is in place. *(See images, top of p. 25.)* Each ring comes with a disposable injector, and a manipulator specifically designed for the device is available. The new ring is softer and more elastic than the previous model and comes with a redesigned inserter that can easily fit through a 2-mm clear corneal incision. (The earlier version required a larger incision.)

The designer of the rings, Boris Malyugin, MD, a professor of ophthalmology in the department of cataract and implant surgery at the S. Fyodorov Eye Microsurgery Complex in Moscow, notes that a trend toward the use of smaller incisions has recently been evident in cataract surgery. "The existing version of the Malyugin Ring easily goes through an incision that's 2.2 mm or bigger," he notes. "But today, cataract surgery can be done through 1.8- to 2-mm incisions, so the device had to be redesigned to stay in line with the most up-to-date cataract technology.

"The other reason for the redesign is the slow-but-steady worldwide adoption of femtosecond laser cataract surgery," he continues. "In this type of surgery the Malyugin Ring can address the problem of inadequate pupil size. A small pupil can make it impossible to fragment the lens and create an anterior capsulorhexis, as well as triggering miosis if laser spots are fired too close to the pupil margin. When using the ring in this circumstance, a smaller opening for insertion is better and safer for the eye because the incision will have less chance to leak during the docking of the laser."

Robert H. Osher, MD, a professor in the Department of Ophthalmology at the University of Cincinnati College of Medicine, and Medical Director Emeritus at the Cincinnati Eye Institute in Ohio, was the first surgeon to use the new Malyugin Ring 2.0, in December 2014; to date, he's used about 50 of the new rings. "The original injector had a large finger that required a pretty good vertical excursion," he notes. "Many surgeons had

ADD SIMBRINZA® Suspension to a PGA for Even Lower IOP[1]*

INDICATIONS AND USAGE

SIMBRINZA® (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2% is a fixed combination indicated in the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

Dosage and Administration

The recommended dose is one drop of SIMBRINZA® Suspension in the affected eye(s) three times daily. Shake well before use. SIMBRINZA® Suspension may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

IMPORTANT SAFETY INFORMATION

Contraindications

SIMBRINZA® Suspension is contraindicated in patients who are hypersensitive to any component of this product and neonates and infants under the age of 2 years.

Warnings and Precautions

Sulfonamide Hypersensitivity Reactions—Brinzolamide is a sulfonamide, and although administered topically, is absorbed systemically. Sulfonamide attributable adverse reactions may occur. Fatalities have occurred due to severe reactions to sulfonamides. Sensitization may recur when a sulfonamide is readministered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation.

Corneal Endothelium—There is an increased potential for developing corneal edema in patients with low endothelial cell counts.

Severe Hepatic or Renal Impairment (CrCl <30 mL/min)—SIMBRINZA® Suspension has not been specifically studied in these patients and is not recommended.

Contact Lens Wear—The preservative in SIMBRINZA® Suspension, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of SIMBRINZA® Suspension but may be reinserted 15 minutes after instillation.

Severe Cardiovascular Disease—Brimonidine tartrate, a component of SIMBRINZA® Suspension, had a less than 5% mean decrease in blood pressure 2 hours after dosing in clinical studies; caution should be exercised in treating patients with severe cardiovascular disease.

Adverse Reactions

SIMBRINZA® Suspension

In two clinical trials of 3 months' duration with SIMBRINZA® Suspension, the most frequent reactions associated with its use occurring in approximately 3-5% of patients in descending order of incidence included: blurred vision, eye irritation, dysgeusia (bad taste), dry mouth, and eye allergy. Adverse reaction rates with SIMBRINZA® Suspension were comparable to those of the individual components. Treatment discontinuation, mainly due to adverse reactions, was reported in 11% of SIMBRINZA® Suspension patients.

Prescribe SIMBRINZA® Suspension as adjunctive therapy to a PGA for appropriate patients

SIMBRINZA® Suspension should be taken at least five (5) minutes apart from other topical ophthalmic drugs

Learn more at myalcon.com/simbrinza

For additional information about SIMBRINZA® Suspension, please see Brief Summary of full Prescribing Information on adjacent page.

Reference: 1. Data on file, 2014.

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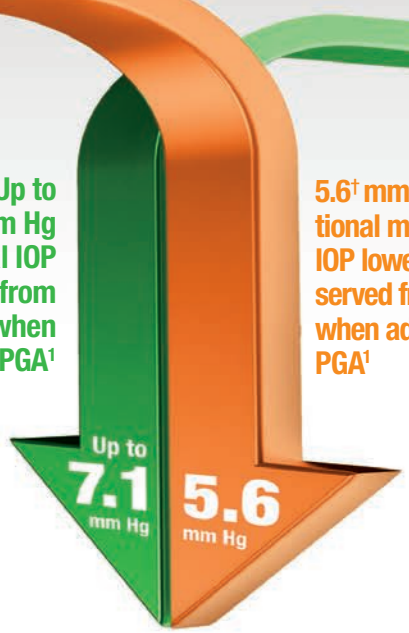
Up to 7.1 mm Hg additional IOP reduction from baseline when added to a PGA[1]

5.6† mm Hg additional mean diurnal IOP lowering observed from baseline when added to a PGA[1]



		IOP Time Points (mm Hg)[1‡]			
Treatment Arm		8 AM	10 AM	3 PM	5 PM
PGA + SIMBRINZA® Suspension (N=83)	Baseline§	24.5	22.9	21.7	21.6
	Week 6	19.4	15.8	17.2	15.6
PGA + Vehicle (N=92)	Baseline§	24.3	22.6	21.3	21.2
	Week 6	21.5	20.3	20.0	20.1

‡Least squares means at each Week 6 time point. Treatment differences (mm Hg) and *P*-values at Week 6 time points between treatment groups were: -2.14, *P*=0.0002; -4.56, *P*<0.0001; -2.84, *P*<0.0001; -4.42, *P*<0.0001.
§Baseline (PGA Monotherapy).

		Mean Diurnal IOP (mm Hg)[1‖]
Treatment Arm		
PGA + SIMBRINZA® Suspension (N=83)	Baseline¶	22.7
	Week 6	17.1
PGA + Vehicle (N=92)	Baseline¶	22.4
	Week 6	20.5

‖Treatment difference (mm Hg) and *P*-value at Week 6 was -3.4, *P*<0.0001.
¶Baseline (PGA Monotherapy).

Study Design: A prospective, randomized, multicenter, double-blind, parallel-group study of 189 patients with open-angle glaucoma and/or ocular hypertension receiving treatment with a PGA. PGA treatment consisted of either travoprost, latanoprost, or bimatoprost. Patients in the study were randomized to adjunctive treatment with SIMBRINZA® Suspension (N=88) or vehicle (N=94). The primary efficacy endpoint was mean diurnal IOP (IOP averaged over all daily time points) at Week 6 between treatment groups. Key secondary endpoints included IOP at Week 6 for each daily time point (8 AM, 10 AM, 3 PM, and 5 PM) and mean diurnal IOP change from baseline to Week 6 between treatment groups.[1]

*PGA study-group treatment consisted of either travoprost, latanoprost, or bimatoprost.
†Treatment difference (mm Hg) and *P*-value at Week 6 was -3.7, *P*<0.0001.

SIMBRINZA®
(brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

SIMBRINZA® (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2% is a fixed combination of a carbonic anhydrase inhibitor and an alpha 2 adrenergic receptor agonist indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

DOSAGE AND ADMINISTRATION

The recommended dose is one drop of SIMBRINZA® Suspension in the affected eye(s) three times daily. Shake well before use. SIMBRINZA® Suspension may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

DOSAGE FORMS AND STRENGTHS

Suspension containing 10 mg/mL brinzolamide and 2 mg/mL brimonidine tartrate.

CONTRAINDICATIONS

Hypersensitivity - SIMBRINZA® Suspension is contraindicated in patients who are hypersensitive to any component of this product.

Neonates and Infants (under the age of 2 years) - SIMBRINZA® Suspension is contraindicated in neonates and infants (under the age of 2 years*) see Use in Specific Populations*

WARNINGS AND PRECAUTIONS

Sulfonamide Hypersensitivity Reactions - SIMBRINZA® Suspension contains brinzolamide, a sulfonamide, and although administered topically is absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulfonamides may occur with topical administration of SIMBRINZA® Suspension. Fatalities have occurred due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Sensitization may recur when a sulfonamide is re-administered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation *[see Patient Counseling Information]*

Corneal Endothelium - Carbonic anhydrase activity has been observed in both the cytoplasm and around the plasma membranes of the corneal endothelium. There is an increased potential for developing corneal edema in patients with low endothelial cell counts. Caution should be used when prescribing SIMBRINZA® Suspension to this group of patients.

Severe Renal Impairment - SIMBRINZA® Suspension has not been specifically studied in patients with severe renal impairment (CrCl < 30 mL/min). Since brinzolamide and its metabolite are excreted predominantly by the kidney, SIMBRINZA® Suspension is not recommended in such patients.

Acute Angle-Closure Glaucoma - The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. SIMBRINZA® Suspension has not been studied in patients with acute angle-closure glaucoma.

Contact Lens Wear - The preservative in SIMBRINZA® Suspension, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of SIMBRINZA® Suspension but may be reinserted 15 minutes after instillation *[see Patient Counseling Information]*.

Severe Cardiovascular Disease - Brimonidine tartrate, a component of SIMBRINZA® Suspension, has a less than 5% mean decrease in blood pressure 2 hours after dosing in clinical studies; caution should be exercised in treating patients with severe cardiovascular disease.

Severe Hepatic Impairment - Because brimonidine tartrate, a component of SIMBRINZA® Suspension, has not been studied in patients with hepatic impairment, caution should be exercised in such patients.

Potentiation of Vascular Insufficiency - Brimonidine tartrate, a component of SIMBRINZA® Suspension, may potentiate syndromes associated with vascular insufficiency. SIMBRINZA® Suspension should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans.

Contamination of Topical Ophthalmic Products After Use - There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers have been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface *[see Patient Counseling Information]*.

ADVERSE REACTIONS

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

SIMBRINZA® Suspension - In two clinical trials of 3 months duration 435 patients were treated with SIMBRINZA® Suspension, and 915 were treated with the two individual components. The most frequently reported adverse reactions in patients treated with SIMBRINZA® Suspension occurring in approximately 3 to 5% of patients in descending order of incidence were blurred vision, eye irritation, dysgeusia (bad taste), dry mouth, and eye allergy. Rates of adverse reactions reported with the individual components were comparable. Treatment discontinuation, mainly due to adverse reactions, was reported in 11% of SIMBRINZA® Suspension patients.

Other adverse reactions that have been reported with the individual components during clinical trials are listed below.

Brinzolamide 1% - In clinical studies of brinzolamide ophthalmic suspension 1%, the most frequently reported adverse reactions reported in 5 to 10% of patients were blurred vision and bitter, sour or unusual taste. Adverse reactions occurring in 1 to 5% of patients were blepharitis, dermatitis, dry eye, foreign body sensation, headache, hyperemia, ocular discharge, ocular discomfort, ocular keratitis, ocular pain, ocular pruritus and rhinitis.

The following adverse reactions were reported at an incidence below 1%: allergic reactions, alopecia, chest pain, conjunctivitis, diarrhea, diplopia, dizziness, dry mouth, dyspnea, dyspepsia, eye fatigue, hypertonia, keratoconjunctivitis, keratopathy, kidney pain, lid margin crusting or sticky sensation, nausea, pharyngitis, tearing and urticaria.

Brimonidine Tartrate 0.2% - In clinical studies of brimonidine tartrate 0.2%, adverse reactions occurring in approximately 10 to 30% of the subjects, in descending order of incidence, included oral dryness, ocular hyperemia, burning and stinging, headache, blurring, foreign body sensation, fatigue/drowsiness, conjunctival follicles, ocular allergic reactions, and ocular pruritus.

Reactions occurring in approximately 3 to 9% of the subjects, in descending order included corneal staining/erosion, photophobia, eyelid erythema, ocular ache/pain, ocular dryness, tearing, upper respiratory symptoms, eyelid edema, conjunctival edema, dizziness, blepharitis, ocular irritation, gastrointestinal symptoms, asthenia, conjunctival blanching, abnormal vision and muscular pain.

The following adverse reactions were reported in less than 3% of the patients: lid crusting, conjunctival hemorrhage, abnormal taste, insomnia, conjunctival discharge, depression, hypertension, anxiety, palpitations/arrhythmias, nasal dryness and syncope.

Postmarketing Experience - The following reactions have been identified during postmarketing use of brimonidine tartrate ophthalmic solutions in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to brimonidine tartrate ophthalmic solutions, or a combination of these factors, include: bradycardia, hypersensitivity, iritis, keratoconjunctivitis sicca, miosis, nausea, skin reactions (including erythema, eyelid pruritus, rash, and vasodilation), and tachycardia.

Apnea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in infants receiving brimonidine tartrate ophthalmic solutions *[see Contraindications]*.

DRUG INTERACTIONS

Oral Carbonic Anhydrase Inhibitors - There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and brinzolamide ophthalmic suspension 1%, a component of SIMBRINZA® Suspension. The concomitant administration of SIMBRINZA® Suspension and oral carbonic anhydrase inhibitors is not recommended.

High-Dose Salicylate Therapy - Carbonic anhydrase inhibitors may produce acid-base and electrolyte alterations. These alterations were not reported in the clinical trials with brinzolamide ophthalmic suspension 1%. However, in patients treated with oral carbonic anhydrase inhibitors, rare instances of acid-base alterations have occurred with high-dose salicylate therapy. Therefore, the potential for such drug interactions should be considered in patients receiving SIMBRINZA® Suspension.

CNS Depressants - Although specific drug interaction studies have not been conducted with SIMBRINZA® Suspension, the possibility of an additive or potentiating effect with CNS depressants (alcohol, opiates, barbiturates, sedatives, or anesthetics) should be considered.

Antihypertensives/Cardiac Glycosides - Because brimonidine tartrate, a component of SIMBRINZA® Suspension, may reduce blood pressure, caution in using drugs such as antihypertensives and/or cardiac glycosides with SIMBRINZA® Suspension is advised.

Tricyclic Antidepressants - Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with SIMBRINZA® Suspension in humans can lead to resulting interference with the IOP lowering effect. Caution is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

Monoamine Oxidase Inhibitors - Monoamine oxidase (MAO) inhibitors may theoretically interfere with the metabolism of brimonidine tartrate and potentially result in an increased systemic side-effect such as hypotension. Caution is advised in patients taking MAO inhibitors which can affect the metabolism and uptake of circulating amines.

USE IN SPECIFIC POPULATIONS

Pregnancy - *Pregnancy Category C:* Developmental toxicity studies with brinzolamide in rabbits at oral doses of 1, 3, and 6 mg/kg/day (20, 60, and 120 times the recommended human ophthalmic dose) produced maternal toxicity at 6 mg/kg/day and a significant increase in the number of fetal variations, such as accessory skull bones, which was only slightly higher than the historic value at 1 and 6 mg/kg. In rats, statistically decreased body weights of fetuses from dams receiving oral doses of 18 mg/kg/day (180 times the recommended human ophthalmic dose) during gestation were proportional to the reduced maternal weight gain, with no statistically significant effects on organ or tissue development. Increases in unossified sternebrae, reduced ossification of the skull, and unossified hyoid that occurred at 6 and 18 mg/kg were not statistically significant. No treatment-related malformations were seen. Following oral administration of ^{14}C-brinzolamide to pregnant rats, radioactivity was found to cross the placenta and was present in the fetal tissues and blood.

Developmental toxicity studies performed in rats with oral doses of 0.66 mg brimonidine base/kg revealed no evidence of harm to the fetus. Dosing at this level resulted in a plasma drug concentration approximately 100 times higher than that seen in humans at the recommended human ophthalmic dose. In animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent.

There are no adequate and well-controlled studies in pregnant women. SIMBRINZA® Suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers - In a study of brinzolamide in lactating rats, decreases in body weight gain in offspring at an oral dose of 15 mg/kg/day (150 times the recommended human ophthalmic dose) were observed during lactation. No other effects were observed. However, following oral administration of ^{14}C-brinzolamide to lactating rats, radioactivity was found in milk at concentrations below those in the blood and plasma. In animal studies, brimonidine was excreted in breast milk.

It is not known whether brinzolamide and brimonidine tartrate are excreted in human milk following topical ocular administration. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from SIMBRINZA® (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2%, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use - The individual component, brinzolamide, has been studied in pediatric glaucoma patients 4 weeks to 5 years of age. The individual component, brimonidine tartrate, has been studied in pediatric patients 2 to 7 years old. Somnolence (50-83%) and decreased alertness was seen in patients 2 to 6 years old. SIMBRINZA® Suspension is contraindicated in children under the age of 2 years *[see Contraindications]*.

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

OVERDOSAGE

Although no human data are available, electrolyte imbalance, development of an acidotic state, and possible nervous system effects may occur following an oral overdose of brinzolamide. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored.

Very limited information exists on accidental ingestion of brimonidine in adults; the only adverse event reported to date has been hypotension. Symptoms of brimonidine overdose have been reported in neonates, infants, and children receiving brimonidine as part of medical treatment of congenital glaucoma or by accidental oral ingestion. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

PATIENT COUNSELING INFORMATION

Sulfonamide Reactions - Advise patients that if serious or unusual ocular or systemic reactions or signs of hypersensitivity occur, they should discontinue the use of the product and consult their physician.

Temporary Blurred Vision - Vision may be temporarily blurred following dosing with SIMBRINZA® Suspension. Care should be exercised in operating machinery or driving a motor vehicle.

Effect on Ability to Drive and Use Machinery - As with other drugs in this class, SIMBRINZA® Suspension may cause fatigue and/or drowsiness in some patients. Caution patients who engage in hazardous activities of the potential for a decrease in mental alertness.

Avoiding Contamination of the Product - Instruct patients that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions *[see Warnings and Precautions]*. Always replace the cap after using. If solution changes color or becomes cloudy, do not use. Do not use the product after the expiration date marked on the bottle.

Intercurrent Ocular Conditions - Advise patients that if they have ocular surgery or develop an intercurrent ocular condition (e.g., trauma or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container.

Concomitant Topical Ocular Therapy - If more than one topical ophthalmic drug is being used, the drugs should be administered at least five minutes apart.

Contact Lens Wear - The preservative in SIMBRINZA® Suspension, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of SIMBRINZA® Suspension, but may be reinserted 15 minutes after instillation.

U.S. Patent No:
6,316,441

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Fort Worth, Texas 76134 USA
1-800-757-9195
alcon.medinfo@alcon.com

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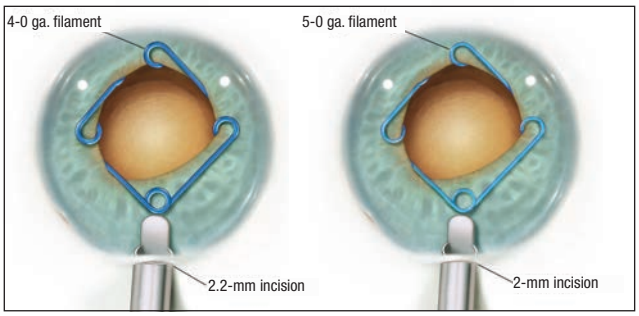
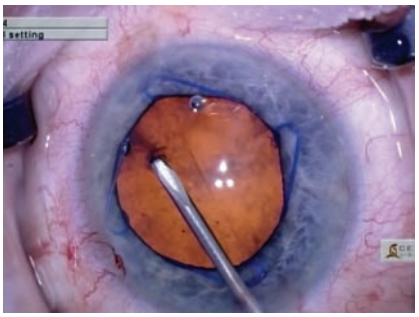




The new Malyugin Ring 2.0 is made of 5-0 prolene instead of 4-0, with a new injector that fits through a smaller incision. (See comparison, left.) Near right: the new ring in use.

difficulty with it. The new injector is dramatically different, with a tiny finger that's very easy to engage and disengage. The injector also was a tight fit in the incision, so the company has made the new version thinner; now, it's easy to get the injector through a 2-mm incision." (The new injector will now be included with all of the Malyugin rings.)

"The ring itself is no longer 4-0 prolene; it's 5-0, and the scrolls are larger," he continues. "It has greater flexibility. The existing manipulator, which I designed for the earlier generation Malyugin ring, works fine with the new ring. It's used with your left hand through the side port to help you position, engage and disengage the scrolls."

Dr. Osher says he uses Healon 5 to lift the iris away from the anterior capsule when inserting the ring. "I put some Healon 5 under the iris in the right, left and distal quadrants," he explains. "Then, through my second stab incision I place Healon 5 under the iris in the subincisional quadrant. The result is that the iris is lifted up on four little boluses of Healon 5. Next, I inject the ring, which is easy to do. The scrolls go into position beautifully. Then I disengage the proximal scroll, which is also easy to do with the new injector, and engage the border of the iris.

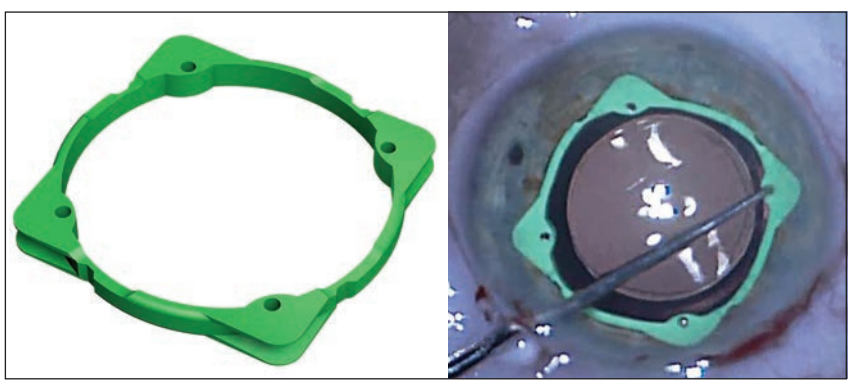
"Removing the ring is equally easy," he continues. "I always disengage the distal ring first and let it go into the angle. Then I free the right and left scrolls, and finally disengage the proximal ring. I move it as far toward the center of the pupil as I can. Putting a little Healon 5 around it freezes it in position so it's easy to put the injector in, capturing the proximal scroll. As I retract the little finger on the injector the ring folds into the injector housing. I use the second manipulator to depress the right and left scrolls onto the platform and they slide into the housing of the injector as well. The distal scroll follows, and I remove the device. It's easy, safe and simple. I'm certainly happy with it."

The Visitec I-Ring

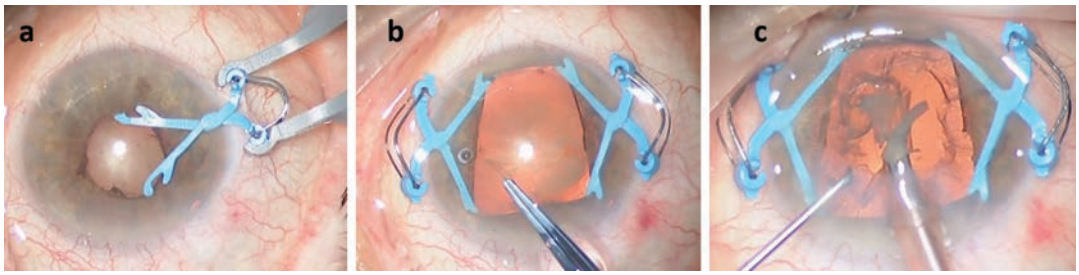
The Visitec I-Ring Pupil Expander is an atraumatic, single-use iris expander made of soft, resilient polyurethane. Unlike many approaches to iris expansion, the I-Ring engages the iris completely, expanding it evenly over 360 degrees, creating a uniform, circular opening 6.3 mm in diameter. (The circular shape can then help to guide the creation of a capsulorhexis.)

Although the space created by the ring is circular, the outside of the ring has four "corners" pointing away from the central opening, creating four pockets, or channels, that hold the iris in place. The channels are designed to never distort or pinch the iris, while providing vertical stability for the iris diaphragm and allowing the iris to engage and disengage easily. Each corner contains a positioning hole for a Sinskey hook, isolated from the channel in which the iris sits, to ensure that the Sinskey hook doesn't touch the iris during placement. The device's low profile is designed to facilitate the use of microsurgical instruments.

The I-Ring comes packaged in a "nest" with the inserter attached. When the surgeon is ready to use the ring, he retracts the slider on the inserter, causing the ring to fold as it's pulled into the inserter; the "nest" is then discarded. After injection of viscoelastic, the inserter is positioned inside the eye. Moving the slider forward slowly releases the ring above the iris, where it returns to its func-



The Visitec I-Ring Pupil Expander engages the iris 360°, creating a uniform circular opening that can be used as a guide during capsulorhexis creation.



The Assia Pupil Expander uses two spring-loaded devices inserted through 1.1-mm sideport incisions to widen the pupil. The devices can be placed assymetrically, if desired, to create a wider opening close to the surgical incision.

tional shape. Placement is accomplished using a Sinskey hook. Insertion, engagement and removal of the device can be done using one hand.

Kenneth R. Kenyon, MD, clinical professor at Tufts University School of Medicine, acts as consulting medical director for Beaver-Visitec International, manufacturer of the device. He was involved with the development of the I-Ring from its inception; since the product has been commercially available, he has used it in both routine small-pupil cataract procedures and more complex surgical scenarios. "I believe the I-Ring represents the next generation of pupil expansion devices," he says. "It incorporates advances in safety, reliability and consistency."

Dr. Kenyon says the I-Ring offers three major advantages. "First, the unique polyurethane material design reduces the risk of damage to the iris and other adjacent tissues," he says. "The material is remarkably gentle on the iris tissue, yet it's unique design firmly supports the entire pupillary margin. The resulting increase in stability and visibility improves the safety of small-pupil cataract surgery while also diminishing the risk of complications in more complex situations, such as IOL exchange and secondary implantation. The second advantage is that I-Ring insertion, engagement and removal are remarkably smooth and atraumatic to the iris, lens and cornea, and don't require any additional specialized instruments. This facilitates use of the I-Ring even with topical anesthesia. Finally, the intuitive design and handling of the ring and its inserter minimize the learning curve for surgeons and assistants."

Roberto Pineda II, MD, director of refractive surgery in the Cornea Service at Massachusetts Eye and Ear in Boston, was also involved in the early design of the I-Ring and has used the product in cataract surgery since its commercial availability in April 2015. "The I-Ring loads effortlessly," he agrees. "Unlike other pupil expansion rings, it provides three-dimensional stability to the iris. This is key to its ability to deal with cases of intraoperative floppy iris syndrome or trampolining of the iris. It's an incredibly valuable device for many of our cataract surgery patients."

You can watch online videos illustrating the use of the Visitec I-Ring at https://www.youtube.com/watch?t=191&v=zzfGIx9AJk0 or at http://www.beaver-visitec.com/products/i-ring-early-clinical-experience.cfm.

The Assia Pupil Expander

The Assia Pupil Expander (aka APX), from APX Ophthalmology in Haifa, Israel, achieves pupil expansion using two tiny spring-loaded devices that are inserted through 1.1-mm sideport incisions opposite each other. (The incisions are generally placed perpendicular to the main incision for the phaco instrument.) A specially designed forceps closes each device for insertion and removal. In the closed position, the curved tips are inserted through the pupil and behind the iris. The device is positioned by the surgeon as the forceps is gently released; when both devices have been inserted and positioned, they create a rectangular pupil opening about 6 x 6 mm. A hook near each tip prevents the shaft from sliding. No intraocular manipulation is required. If desired, the APX devices can be placed asymmetrically, rather than opposite each other, to create a trapezoidal-shaped opening. This allows the surgeon to create a wider opening closer to the surgical incision. *(See example, above.)* The company notes that the device can't fall into the vitreous cavity if the surgeon experiences a posterior capsule rupture, unlike rings placed completely inside the eye.

The APX device was designed by Ehud I. Assia, MD, professor of ophthalmology at the Sackler School of Medicine at Tel Aviv University in Israel, and medical director of the Ein Tal Eye Center. "Most current pupil dilators include either iris hooks or pupillary rings," he notes. "Hooks require four sideport incisions, and they're time-consuming. The shafts of the hooks outside the eye often extend beyond the surgical field, and occasionally the tips disengage from the pupillary margin and require repositioning during surgery. Rings that can be inserted through the existing surgical opening are quite effective, but they may require considerable intraocular manipulation during insertion and removal. Also, they occupy the entire pupillary margin, which means the surgical instruments must work over some part of the ring.

"I wanted to have a device that

An NSAID formulated to penetrate target ocular tissues

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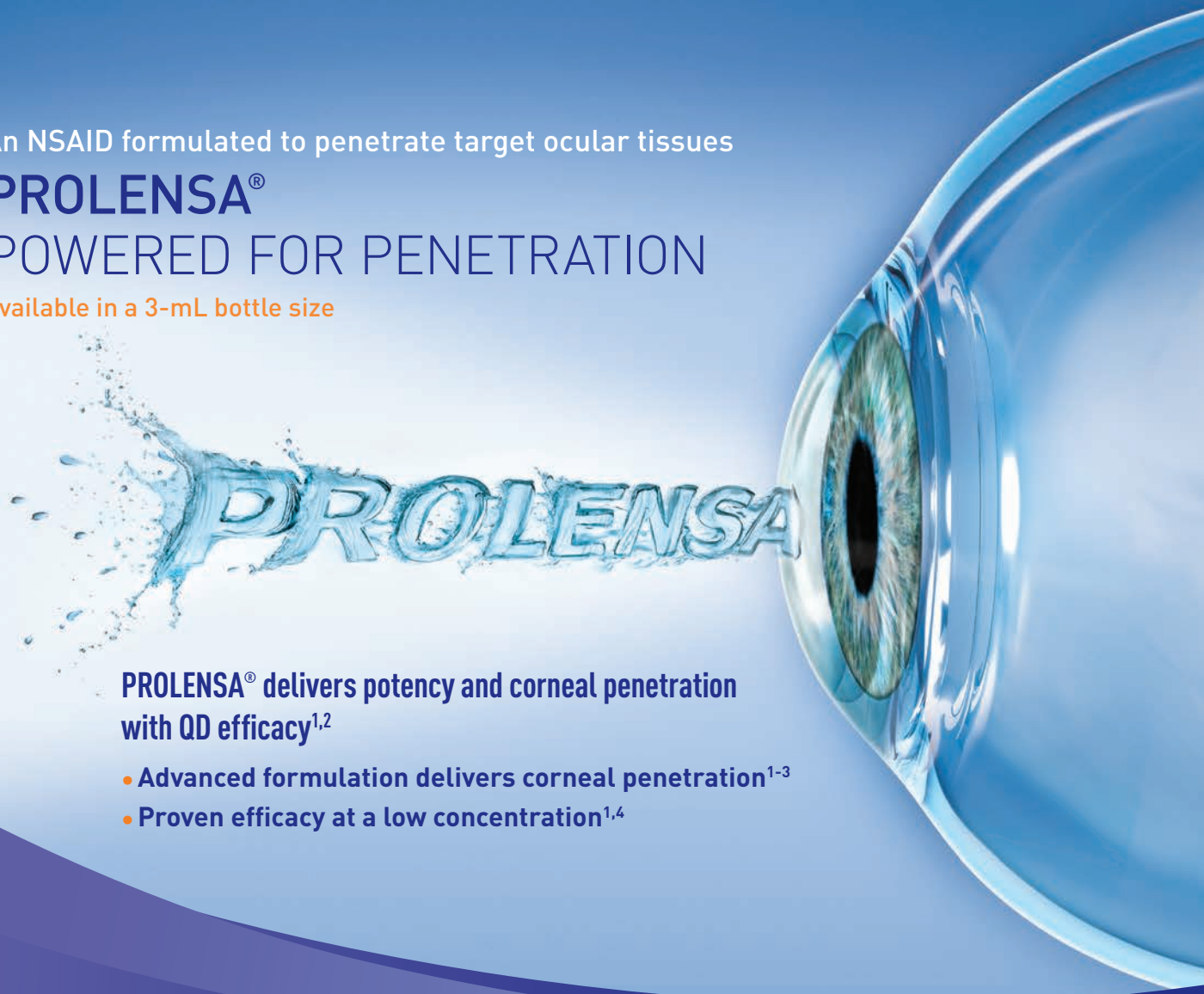

PROLENSA® delivers potency and corneal penetration with QD efficacy[1,2]

- **Advanced formulation delivers corneal penetration[1-3]**
- **Proven efficacy at a low concentration[1,4]**

INDICATIONS AND USAGE

PROLENSA® (bromfenac ophthalmic solution) 0.07% is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.

IMPORTANT SAFETY INFORMATION ABOUT PROLENSA®

Warnings and Precautions

- Sulfite allergic reactions
- Slow or delayed healing
- Potential for cross-sensitivity
- Increased bleeding of ocular tissues
- Corneal effects, including keratitis
- Contact lens wear

Adverse Reactions

The most commonly reported adverse reactions in 3%-8% of patients were anterior chamber inflammation, foreign body sensation, eye pain, photophobia, and blurred vision.

Please see brief summary of Prescribing Information on adjacent page.

References: 1. PROLENSA® Prescribing Information, April 2013. **2.** Data on file, Bausch & Lomb Incorporated. **3.** Baklayan GA, Patterson HM, Song CK, Gow JA, McNamara TR. 24-hour evaluation of the ocular distribution of 14C-labeled bromfenac following topical instillation into the eyes of New Zealand White rabbits. *J Ocul Pharmacol Ther*. 2008;24(4):392-398. **4.** BROMDAY® Prescribing Information, October 2012.

BAUSCH + LOMB

PROLENSA®
(bromfenac ophthalmic solution) 0.07%

Brief Summary

INDICATIONS AND USAGE

PROLENSA® (bromfenac ophthalmic solution) 0.07% is indicated for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.

DOSAGE AND ADMINISTRATION

Recommended Dosing

One drop of PROLENSA® ophthalmic solution should be applied to the affected eye once daily beginning 1 day prior to cataract surgery, continued on the day of surgery, and through the first 14 days of the postoperative period.

Use with Other Topical Ophthalmic Medications

PROLENSA ophthalmic solution may be administered in conjunction with other topical ophthalmic medications such as alpha-agonists, beta-blockers, carbonic anhydrase inhibitors, cycloplegics, and mydriatics. Drops should be administered at least 5 minutes apart.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Sulfite Allergic Reactions

Contains sodium sulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

Slow or Delayed Healing

All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including bromfenac, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Potential for Cross-Sensitivity

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including bromfenac. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

Increased Bleeding Time

With some NSAIDs, including bromfenac, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

It is recommended that PROLENSA® ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Keratitis and Corneal Reactions

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including bromfenac, and should be closely monitored for corneal health.

Post-marketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days post-surgery may increase patient risk for the occurrence and severity of corneal adverse events.

Contact Lens Wear

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

ADVERSE REACTIONS

Clinical Trial Experience

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

The most commonly reported adverse reactions following use of PROLENSA® ophthalmic solution following cataract surgery include: anterior chamber inflammation, foreign body sensation, eye pain, photophobia and vision blurred. These reactions were reported in 3 to 8% of patients.

USE IN SPECIFIC POPULATIONS

Pregnancy

Treatment of rats at oral doses up to 0.9 mg/kg/day (systemic exposure 90 times the systemic exposure predicted from the recommended human ophthalmic dose [RHOD] assuming the human systemic concentration is at the limit of quantification) and rabbits at oral doses up to 7.5 mg/kg/day (150 times the predicted human systemic exposure) produced no treatment-related malformations in reproduction studies. However, embryo-fetal lethality and maternal toxicity were produced in rats and rabbits at 0.9 mg/kg/day and 7.5 mg/kg/day, respectively. In rats, bromfenac treatment caused delayed parturition at 0.3 mg/kg/day (30 times the predicted human exposure), and caused dystocia, increased neonatal mortality and reduced postnatal growth at 0.9 mg/kg/day.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because of the known effects of prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), the use of PROLENSA® ophthalmic solution during late pregnancy should be avoided.

Nursing Mothers

Caution should be exercised when PROLENSA is administered to a nursing woman.

Pediatric Use

Safety and efficacy in pediatric patients below the age of 18 have not been established.

Geriatric Use

There is no evidence that the efficacy or safety profiles for PROLENSA differ in patients 70 years of age and older compared to younger adult patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (systemic exposure 30 times the systemic exposure predicted from the recommended human ophthalmic dose [RHOD] assuming the human systemic concentration is at the limit of quantification) and 5 mg/kg/day (340 times the predicted human systemic exposure), respectively, revealed no significant increases in tumor incidence.

Bromfenac did not show mutagenic potential in various mutagenicity studies, including the reverse mutation, chromosomal aberration, and micronucleus tests.

Bromfenac did not impair fertility when administered orally to male and female rats at doses up to 0.9 mg/kg/day and 0.3 mg/kg/day, respectively (systemic exposure 90 and 30 times the predicted human exposure, respectively).

PATIENT COUNSELING INFORMATION

Slowed or Delayed Healing

Advise patients of the possibility that slow or delayed healing may occur while using NSAIDs.

Sterility of Dropper Tip

Advise patients to replace bottle cap after using and to not touch dropper tip to any surface, as this may contaminate the contents. Advise patients that a single bottle of PROLENSA® ophthalmic solution, be used to treat only one eye.

Concomitant Use of Contact Lenses

Advise patients to remove contact lenses prior to instillation of PROLENSA. The preservative in PROLENSA, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of PROLENSA.

Concomitant Topical Ocular Therapy

If more than one topical ophthalmic medication is being used, the medicines should be administered at least 5 minutes apart.

Rx Only

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9317600
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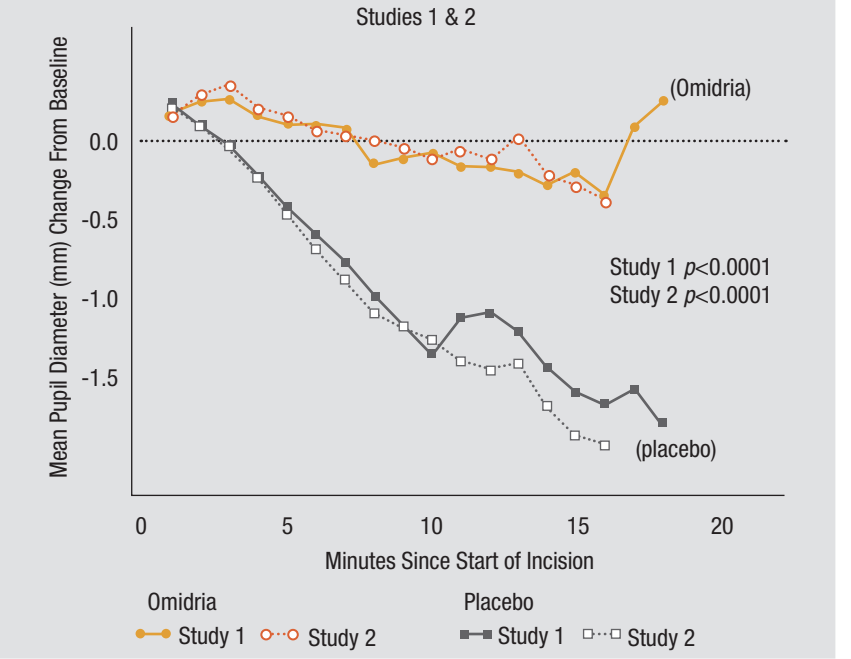
would be quick and easy to insert and remove, one that would provide adequate pupil dilation but would not interfere with surgery," he continues. "After trying various models and designs I concluded that a scissor-like configuration with blunt, rounded tips and an external spring would be the most efficient and practical. The first generation, the reusable metal APX-100, received an FDA 510K exemption in 2013. With feedback from surgeons we've now developed the second-generation APX-200, which is disposable. The complete product and package is expected to be ready for use in October 2015."

Dr. Assia says the APX-200 comes with two designated disposable forceps, allowing the nurse to load and lock the two devices while the surgeon prepares the sideport incisions, thus saving time. "Insertion and removal of the APX only takes a few seconds, and manipulations are entirely extraocular," he says. "The APX system can be used for superior, lateral or oblique surgical approaches, and it's been used during vitreoretinal surgery without interfering with the pars-plana vitrectomy instruments."

Alan Crandall, MD, clinical professor, senior vice chair of ophthalmology and visual sciences and director of glaucoma and cataract at the Moran Eye Center, University of Utah, says he has used the APX pupil expander in cases of intraoperative floppy iris syndrome, uveitis and—most importantly for him—pseudoexfoliation. "Leaving the sub-incisional area open is very helpful when I'm using the Ultra Chopper in very hard cataracts," he notes. "It also helps in eyes where I would like one side of the pupil to be slightly larger, as in cases of trauma, for example. I also like its broad iris touch that leaves no areas of depigmentation and no iris tears."

More information can be found at apx-ophthalmology.com, and a demonstration video can be viewed at https://www.youtube.com/watch?t=12&v=-BXeUfETiKQ.

Intraoperative Pupil Diameter (mm) Change from Baseline



Omidria is a combination of phenylephrine 1% and keterolac 3% that can be added to the irrigation solution during cataract surgery. It prevents intraoperative pupil constriction and reduces postoperative pain.

Omidria

In addition to mechanical devices, a new drug-based tool for managing small pupils during surgery also recently became available. In June 2014 the Food and Drug Administration approved Omeros Corp's Omidria, a combination of phenylephrine 1% (a pupil-dilating agent) and ketorolac 3% (a non-steroidal anti-inflammatory agent that reduces pain due to surgical trauma and inhibits surgically induced miosis). Omidria is added to the irrigation solution used during cataract surgery and intraocular lens replacement; it's designed to prevent intraoperative pupil constriction and reduce postoperative pain without requiring any change in the doctor's surgical routine. In a Phase II trial comparing Omidria to phenylephrine alone, 22 percent of subjects on phenylephrine had a pupil diameter smaller than 6 mm at some point during the surgery; only 6 percent of subjects receiving Omidria did (p=0.0221). (Other trials comparing Omidria to standard cataract surgery protocol found that Omidria also produced statistically significant and clinically meaningful reduction of postoperative pain.)

Dr. Osher, who published a paper on the pharmacology of Omidria coauthored by Ike Ahmed, MD,[1] says he's very impressed with it. "I use it on all of my Flomax patients," he notes. "I also use it on any pupil which I would say is intermediate size, around 4.5 to 5.5 mm. However, in my experience, Omidria does not add to the pupillary dilatation; it simply prevents the pupil from constricting—a very important function. In busy practices where they try to dilate the patient very quickly, it may add to the dilata-

tion. But in my practice, patients are in the preop area for a long time; they get lots of drops and gels and their pupils are maximally dilated. So, I find Omidria most beneficial when I'm working with a mid-sized pupil or a Flomax case, in concert with viscomydriasis using Healon 5.

"If the pupil is 4 mm or smaller, I prefer to use a Malyugin ring," he continues. "The ring takes care of widening the pupil. In theory, the ketorolac in Omidria might reduce the inflammation that one may see when manipulating the iris, but I think the Malyugin Ring is very gentle. In fact, my eyes look incredibly quiet when I use the Malyugin ring."

Richard L Lindstrom, MD, managing partner in Minnesota Eye Consultants and an attending surgeon at the Phillips Eye Institute and Minnesota Eye Laser and Surgery Center in Minneapolis, agrees that Omidria is designed to maintain dilation, not cause it. "Omidria is not labeled for 'creating' dilation of the pupil," he notes. "So, if a pupil is not large enough to safely remove a cataract, in the surgeon's opinion, pupil expanders are needed to create a larger pupil. If the pupil size at the beginning of the case seems adequate, Omidria will help maintain the pupillary dilation during surgery and reduce intraoperative miosis. It will also improve intraoperative and early postoperative patient comfort." (Dr. Lindstrom adds that he finds epi-lidocaine or epi-Shugarcaine injected into the anterior chamber at the beginning of surgery to be another useful adjunct.)

Small Pupil? No Problem.

"There have been a lot of small-pupil techniques over the years," notes Dr. Osher. "I've seen them all. They all have been very helpful, because regardless of what you do, when you enlarge the pupil, you make the surgery safer, easier and more enjoyable for the surgeon, and you get better patient outcomes. So it's worth spending the extra few moments it takes to manage the pupil." REVIEW

Dr. Pineda is a consultant for Beaver-Visitec International. Dr. Lindstrom is a consultant for Omeros. Dr. Osher is a consultant for MicroSurgical Technologies and Omeros but has no financial interest in any product discussed in the article.

1. Osher RH, Ahmed IK, Demopulos GA. OMS302 (phenylephrine and ketorolac injection) 1%/0.3% to maintain intraoperative pupil size and to prevent postoperative ocular pain in cataract surgery with intraocular lens replacement. Expert Review of Ophthalmology 2015:10;2;91-103.

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TheraTears® Dry Eye Therapy with Osmo-Correction™ corrects osmolarity imbalance to restore comfort with a unique hypotonic and electrolyte balanced formula that replicates healthy tears.

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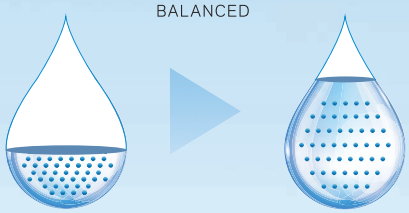

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RESTORE + CLEANSE + NOURISH

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Reference: 1. Research in dry eye report of the Research Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf.* Apr 2007; 5(2): 179-193.

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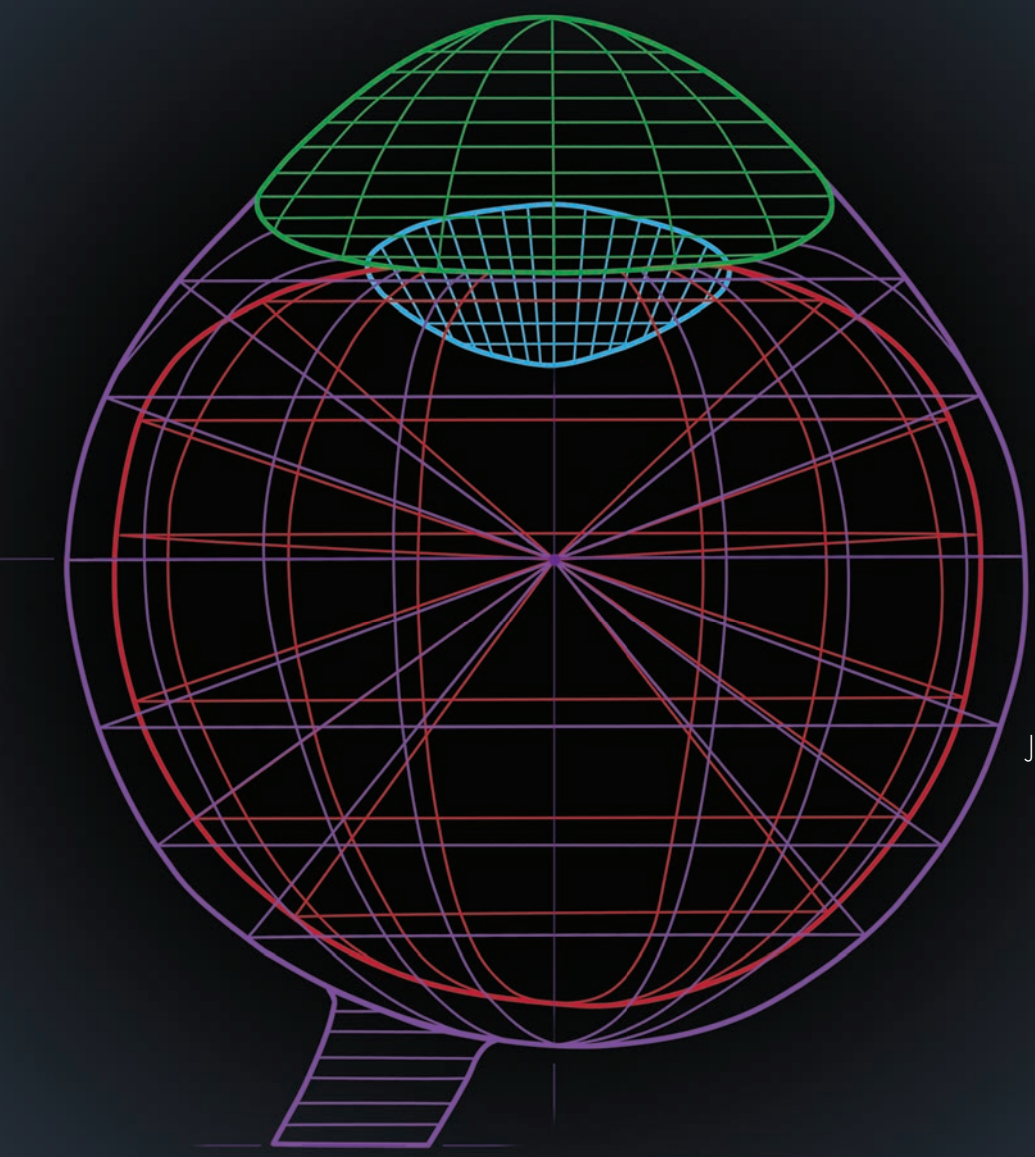

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REVIEW of Ophthalmology

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FACULTY

Robert N. Weinreb, MD: Dr. Weinreb is the chairman and distinguished professor of ophthalmology, Morris Gleich Chair, and the director of the Shiley Eye Institute at the University of California, San Diego. A graduate of Harvard Medical School, Dr. Weinreb has trained more than 140 post-doctoral fellows in glaucoma, many of whom hold distinguished academic and leadership positions throughout the world. In April 2015, his h-impact factor was 95.

James D. Brandt, MD: Dr. Brandt is professor and vice-chair of ophthalmology and vision science and director of the Glaucoma Service at the University of California, Davis. Dr. Brandt has served as the principal investigator of numerous clinical trials, including the Ocular Hypertension Treatment Study (OHTS). Dr. Brandt serves on the editorial boards of Ophthalmology and Journal of Glaucoma.

Nathan M. Radcliffe, MD: Dr. Radcliffe is the director, glaucoma service and clinical assistant professor, New York University Langone Ophthalmology Associates and a cataract and glaucoma surgeon at the New York Eye Surgery Center.

Felipe A. Medeiros, MD, PhD: Dr. Medeiros is Professor of Ophthalmology and the Ben and Wanda Hildyard Chair for Diseases of the Eye at the UCSD School of Medicine. He is also Medical Director of the Hamilton Glaucoma Center, University of California San Diego and Director of the Visual Performance Laboratory at the Shiley Eye Institute.

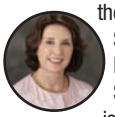
Jonathan S. Myers, MD: Dr. Myers is an associate attending surgeon on the glaucoma service of Wills Eye Hospital. He serves on the editorial boards of Glaucoma Today and the Journal of Clinical and Experimental Ophthalmology. Current research interests include perimetry and novel glaucoma surgeries.

Tony Realini, MD, MPH: Dr. Realini is an associate professor of ophthalmology at West Virginia University. Dr. Realini previously worked in the Department of Ophthalmology at the University of Arkansas for Medical Sciences. He has received numerous research grants, including two from the National Eye Institute, and has published widely in ophthalmic medical journals.

Ronald L. Gross, MD: Dr. Gross recently joined West Virginia University (WVU) as professor and chair of the Department of Ophthalmology and is the director of the WVU Eye Institute in Morgantown, West Virginia. He holds the Jane McDermott Shott Chair in Ophthalmology. He previously worked at the Cullen Eye Institute of Baylor College of Medicine in Houston, Texas, where he held the Clifton R. McMichael Chair and was a professor of ophthalmology.

Jeffrey M. Liebmann, MD: Dr. Liebmann is professor of ophthalmology at Columbia University Medical Center, New York, NY. Dr. Liebmann currently serves as president of the World Glaucoma Association, is past-president of the American Glaucoma Society, secretary-treasurer of the New York Glaucoma Society, and co-editor of Journal of Glaucoma and is a member of the board of governors of the World Glaucoma Association and boards of directors of The Glaucoma Foundation and the American Glaucoma Society Foundation.

Anne L. Coleman, MD, PhD: Dr. Coleman is a professor of epidemiology at UCLA's Jonathon and Karin Fielding School of Public Health and the David Geffen School of Medicine. She is also the Fran and Ray Stark Professor of Ophthalmology at the Stein Eye Institute. Dr. Coleman is the past chair of a 14-member panel of experts overseeing the National Eye Health Educational Program of the National Eye Institute, the prior Secretary of Quality of Care for the American Academy of Ophthalmology and the founding director of the AAO H. Dunbar Hoskins Center for Quality Care.



Murray Fingeret, OD: Dr. Fingeret, a graduate of the New England College of Optometry, completed a residency at the Joseph C. Wilson Health Center in Rochester, New York. Dr. Fingeret is chief of the Optometry Section, Brooklyn/St. Albans Campus, Department of Veterans Administration New York Harbor Health Care System. Dr. Fingeret is also a clinical professor at the State University of New York, College of Optometry.

John Flanagan, MCOptom, PhD: Dr. Flanagan is the dean and a professor at the School of Optometry and Vision Science Program, University of California, Berkeley. Until May 2014, he was professor at the School of Optometry and Vision Science, University of Waterloo and in the Department of Ophthalmology and Vision Sciences, University of Toronto. He was director of the glaucoma research unit, Toronto Western Research Institute and a senior scientist at the Toronto Western Hospital, University Health Network.

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Cover image: Gina Urwin, gina@urwinmed.com

The Role of CORNEAL HYSTERESIS

INTRODUCTION

Glaucoma is a complex, multifactorial disorder that affects the optic nerve and can lead to functional vision loss or blindness if not treated. Reduction of intraocular pressure remains the only established form of therapy to slow or halt the progression of glaucoma. The aggressiveness of therapy is often based on a global risk assessment. Risk factors for glaucoma are well established and include intraocular pressure, age, central corneal thickness, and ethnicity, among others. Corneal hysteresis—a measure of the viscoelastic biomechanical properties of the eye—is emerging as an additional important risk factor for glaucoma progression. Corneal hysteresis is easily measured in a noninvasive fashion in the office, and emerging data support its importance in the process of global risk assessment for glaucoma. In 2015, hysteresis was given a reimbursable CPT code.

Recently, a group of glaucoma specialists gathered in San Francisco to review and interpret the data supporting the role of corneal hysteresis in glaucoma risk assessment. This gathering was supported by Reichert—manufacturer of the Ocular Response Analyzer, the only device that measures corneal hysteresis.

This monograph is intended to share the key take-home messages derived from that meeting. These include a basic understanding of corneal hysteresis and its relationship to ocular biomechanics, familiarity with the data supporting the importance of hysteresis in glaucoma risk assessment, and guidance on incorporating hysteresis in the clinical management of glaucoma patients.

What is Corneal Hysteresis? Historical Perspectives of Central Corneal Thickness and Corneal Hysteresis as Risk Factors for Glaucoma

Robert N. Weinreb: Corneal hysteresis (CH) has been of great interest in glaucoma for more than ten years. There now are several hundred publications, many of which validate and support its use in glaucoma care. In clinical research studies, there is compelling evidence that CH is a powerful tool for predicting the development of glaucoma and its progression as well. Today's discussion discusses the use of CH in clinical glaucoma care.

Dr. Brandt: The emergence of CH as a risk factor for glaucoma is reminiscent of the path that central corneal thickness (CCT) followed in becoming a validated risk factor for glaucoma. The influence of CCT in IOP measurement had been recognized since the 1950s. Its widespread acceptance and use in risk modeling did not occur until the Ocular Hypertension Treatment Study (OHTS) provided strong evidence of its importance and practical guidance on how to incorporate it into the risk assessment process. Many of us were surprised that CCT was such a strong risk factor in OHTS, and it was helpful in establishing CCT's credibility that the European Glaucoma Prevention Study (EGPS) confirmed this finding.

Dr. Weinreb: We began to evaluate the role of CCT in glaucoma in the Diagnostic Innovations in Glaucoma Study (DIGS), which began in 1986. One early analysis from DIGS involved 98 patients with suspected preperimetric glaucoma—their optic nerves looked suspicious but their visual fields were full. After a follow-up period of about eight years, 60% had converted to glaucoma. But when the subjects were stratified into two groups based on thin or thick corneas, the rate of conversion to glaucoma was 46% in eyes with thin corneas compared to 11% in eyes with thicker corneas.[1]

Dr. Brandt: The question that arose then was this: is CCT truly a risk factor or is it merely a source of error in intraocular pressure (IOP) assessment? One possibility is that eyes with thin CCT have higher IOP than we measure using Goldmann tonometry, and that is why these eyes fare less well. An alternate possibility is that CCT is an indicator of more global ocular biomechanics. Several lines of research suggest that CCT is an important risk factor indepen-

dent of any effect on IOP measurement. In OHTS, CCT was an independent risk factor even in models that included IOP—in other words, CCT added information about risk that was not included in IOP.[2] Also in OHTS, correcting IOP on the basis of CCT using any of several formulas failed to fully explain the effect of IOP on risk.[3] In support of CCT as a biomarker for ocular biomechanics was a small, early study in which differential compliance of the lamina cribrosa was observed in eyes with thin vs. thick corneas.[4]

Dr. Radcliffe: CCT as a biomechanical indicator has limitations, and chief among them is that most models relating CCT and IOP assumed that the cornea is a purely elastic structure. In fact, the cornea is viscoelastic. To understand this difference, consider the shock absorbers in your car. On a bumpy road, they dampen the bumps and smooth out the ride. If you had only springs, which are elastic—and not shock absorbers, which are viscoelastic—you would feel every bump much more significantly. The shock absorbers dissipate energy. In terms of the eye, the cornea's response to deformation (for instance, applanation) is rate dependent: when moved rapidly like a car wheel hitting a bump, it dissipates some of the energy absorbed during the deformation. This differential tissue response to the load/unload of stress is called hysteresis, a term that was coined in the 19th century. CH is not a measure of the stiffness of the cornea, but rather a measure of how corneal tissue absorbs and dissipates energy during deformation and return. It can be considered a measure of tissue function rather than a geometrical attribute. There are correlates to CH in other bodily systems. The ascending aorta exhibits viscoelastic behavior with every heartbeat, expanding to accept blood from the heart and absorbing energy in the process, then rebounding and dissipating that energy as that blood flows more distally.

Dr. Brandt: Because both CCT and CH are biomechanical parameters of the cornea, they tend to be weakly correlated. Data suggest, however, that CH may be a better predictor of glaucoma than CCT. These data will be reviewed in the next section. So in summary, CH has followed a similar path as CCT in becoming recognized as a risk factor for glaucoma. CH may be more closely related to glaucoma risk than CCT. This likely relates to its functional nature (how the eye responds to dynamic changes in IOP compared to CCT's more structural nature (how thick it is).

››››› Corneal Hysteresis as an Indicator for Glaucoma Progression Risk

Dr. Radcliffe: It is useful to review the key studies supporting the clinical utility of CH as a risk factor for glaucoma and its progression.

Among the first studies to demonstrate this was a retrospective report of 230 glaucoma patients and suspects with the goal of identifying associations with progression.[5] The study utilized the OHTS criteria for the determination of both the presence of glaucoma and the progression of glaucoma. Among the associations for progression were patient age, lack of treatment, and CH. Of note, neither IOP nor CCT were found to be significant associations of progression. This study concluded that CH was the only ocular parameter associated with progression.

CH has also been associated with the risk of progression in normal-tension glaucoma (NTG). A retrospective study of 82 eyes being treated for NTG included an assessment of CH.[6] The average value of CH in the group was 10.1 mmHg. The study sample was then divided into two groups: those with CH higher than the mean and those with CH lower than the mean. The risk of progression of NTG was 67% in the 39 eyes with low CH, and only 35% in the 43 eyes with high CH. In a multivariate model of visual field progression, CH was highly predictive while CCT was not significantly predictive at all. This study demonstrated that CH can be utilized independently of IOP and CCT as a prognostic factor for glaucoma progression.

Asymmetry of primary open-angle glaucoma (POAG) may also be explained, at least in part, by CH. One hundred seventeen POAG patients with asymmetric glaucoma (with

asymmetry defined as an inter-eye difference in AGIS visual field score of >5 points) were observed in a prospective cross-over study to evaluate factors associated with asymmetry of glaucoma severity.[7] Among the potential factors evaluated were Goldmann IOP, CCT, the number of IOP-lowering medications used, and CH. Of these, only CH was significantly different between the fellow eyes, being lower in worse eyes (mean 8.2 versus 8.9 mmHg, p<0.001). This study demonstrated that CH offered the best discriminative power for discerning the worse eye in asymmetric POAG.

The rate of visual field progression may also be related to CH. A recent retrospective study of 152 glaucomatous eyes evaluated the correlation between CH and CCT and their relationship with the rate of visual field change over time.[8] This study found that rapidly progressing eyes had lower mean CCT and CH than stable or slowly progressing eyes, and that CH and CCT were modestly correlated (r=0.33). In a multivariate model of visual field progression, only age, peak IOP, and CH were predictive; CCT was not. This study demonstrates that glaucomatous eyes with low CH are at higher risk for progression and progress faster.

The Diagnostic Innovations in Glaucoma Study has been ongoing since the mid-1980s. Its goals are to develop better methods for detecting glaucoma progression, to characterize the rate of progression, and to identify risk factors for progression of glaucoma. Enrolled subjects were either healthy glaucoma suspects or established glaucoma patients. They underwent full eye examinations every six months. This database of patients provides a wealth of

Case 1. Progression Despite Low IOP

Dr. Radcliffe: One of my patients is a 54-year-old Hispanic lady with recently-diagnosed POAG. Her IOP on treatment is 10 mmHg. Her CCTs are in the 540s, her vertical cup-disc ratio is 0.8, and her optic nerves and visual fields are shown in the figure.

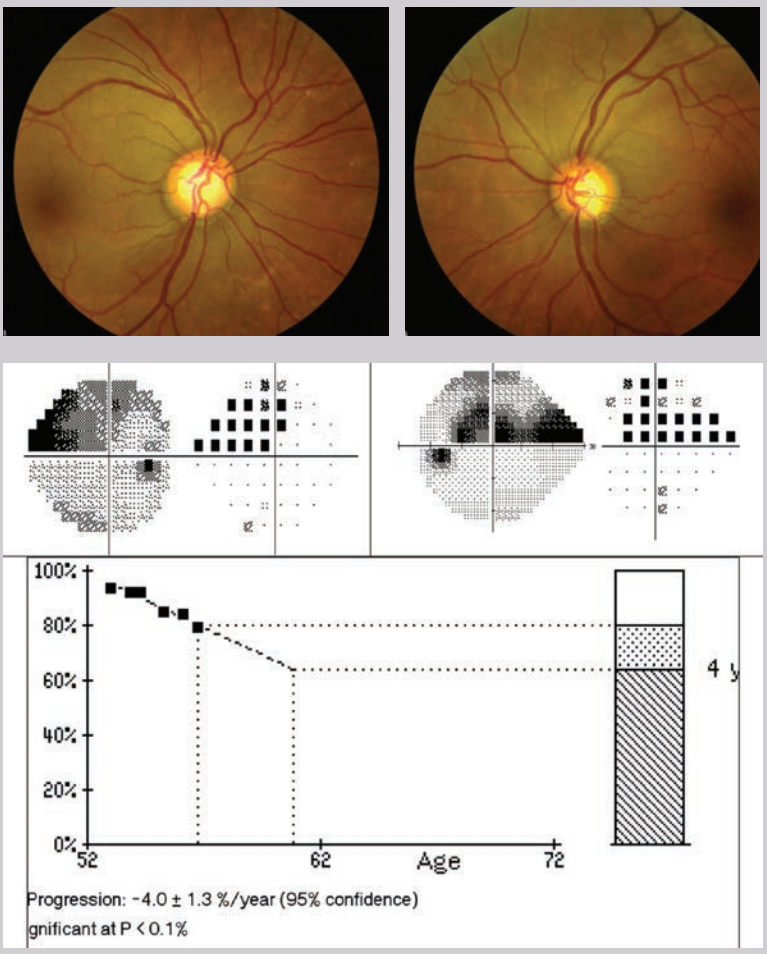


Figure. Optic nerve photographs (top) and visual fields (middle) from the patient described in Case 1. Visual field progression was noted over time (bottom).

Most of us would be satisfied that, with an IOP lowered to 10 mmHg, we have this patient's glaucoma adequately controlled. However, over the next several years, her visual field continues to progress despite maintaining an IOP in the 9-11 mmHg range. We measured her CH before we initiated treatment at the time of her diagnosis, and it was 6.1 mmHg. That's well below the normal range. That CH value indicates that she is at high risk for progression, and that is exactly what happened.

information about glaucoma, progression, and risk factors. A recent analysis of a subset of 68 glaucoma patients followed for four years revealed that Goldmann IOP was significantly influenced by CCT but not by CH, and that CH and CCT were modestly correlated (r=0.48).[9] In a multivariate model of glaucoma progression, CH was three times more strongly associated with the rate of progression than CCT. This study was among the first prospective studies to confirm the relationship between CH and the risk of glaucoma progression.

››› Is Corneal Hysteresis a Biomarker for Susceptibility to Glaucoma Damage?

Dr. Brandt: There are convincing data that CH is related to glaucoma risk and to progression risk. CH is lower in patients with glaucoma than in healthy subjects, and it is lower in glaucoma patients who progress than in glaucoma patients who remain stable. Is this association due solely to CH's effect on IOP measurement, or does CH also tell us something about the biomechanics of the eye? Can CH be a biomarker for optic nerve damage in glaucoma?

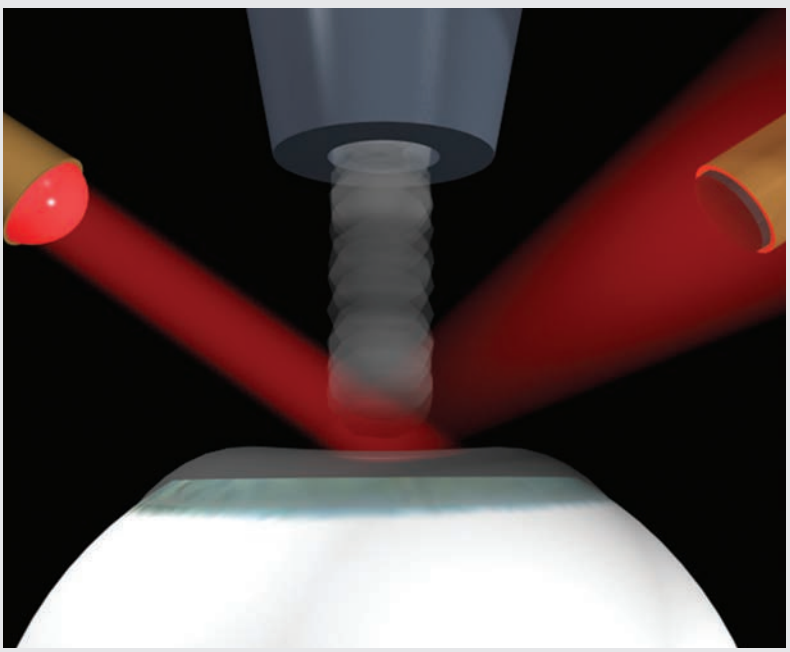
Dr. Radcliffe: There are some interesting studies that give in-

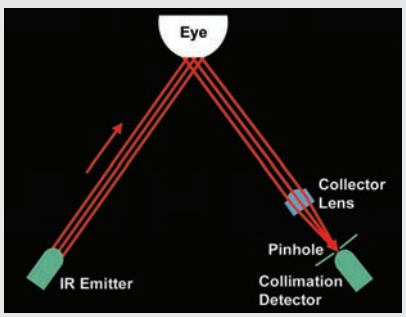
The Reichert Ocular Response Analyzer

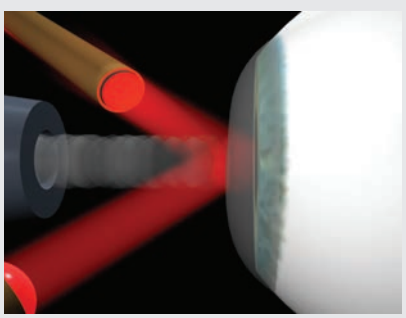
How It Works

Dr. Radcliffe: Corneal hysteresis is easily and noninvasively measured in the office. CH can only be measured using the Reichert Ocular Response Analyzer (ORA). This device functions very much like a noncontact tonometer. A metered puff of air is delivered to the cornea, flattening it into an applanation configuration, much like Goldmann tonometry (see figure). The air puff deforms the cornea past the applanation point, making it briefly concave. As the pressure of the air puff diminishes, the cornea returns to its normal configuration, passing through the applanation position a second time on its rebound. Interestingly, the pressure of the air puff at the point of the first and second applanations is different (being lower on rebound than it was upon initial applanation), as the cornea's viscoelastic nature dissipates some of the energy. The difference in IOP at each of these two applanation points is defined as the corneal hysteresis. If the cornea were perfectly elastic and did not dampen some of the energy, the two applanation points would occur at the same IOP level.

BELOW: Schematic diagrams of ORA measurement procedure.







Corneal Compensated IOP (IOPcc) Accuracy and Safety Advantages

Dr. Radcliffe: In addition to CH, the ORA provides two other parameters, both estimates of IOP. One is a Goldman equivalent IOP (IOPg), which is designed to match Goldmann values. The second is a cornea compensated IOP (IOPcc), which is an estimate of true IOP taking the biomechanics of the cornea into account.

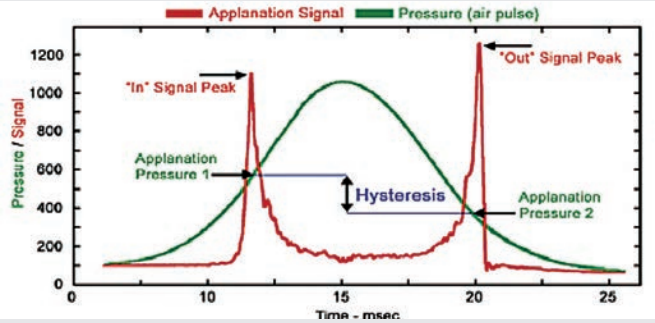
Dr. Medeiros: Goldmann tonometry remains the clinical standard for IOP measurement in most parts of the world. There are some limitations to Goldmann tonometry. Goldmann IOP is not objective—deciding when the mires are aligned is subjective. An objective tonometer that returns a value digitally without a subjective interpretation could make IOP measurement more objective. Likewise, a device that is fast and technician-friendly would be of value. If IOPg reasonably estimated Goldmann tonometry, the ORA could have value in clinical glaucoma management.

Dr. Radcliffe: There is definitely less random variability with IOP measured by the ORA compared to Goldmann tonometry. My experience has been that IOPg provides cleaner data than Goldmann IOP in mathematical models that incorporate IOP. Frankly, if I had an ORA in every one of my exam rooms, I would be comfortable using IOPg in place of Goldmann IOP in clinical practice.

Dr. Realini: The IOPcc measurement is interesting to me. Certainly the biomechanical properties of the cornea affect our IOP measurements regardless of the tonometer we use. None measures true intraocular pressure, and the difference between our measurement and true IOP is likely highly dependent upon corneal biomechanics. Before we had CH, we used CCT as a surrogate measure of corneal biomechanics. But CCT is not a measure of the functional biomechanical properties of the cornea—it is a structural measurement of corneal thickness. Not all thick corneas are stiff, and not all thin corneas are floppy. This is why I have never been a believer in the practice of correcting IOP based on CCT. They are—as Dr. Brandt pointed out—independent risk factors. Correcting Goldmann IOP based on CCT is akin to adding 5 mmHg to IOP for a positive family history—why would you combine two independent risk factors into one? However, CH is different from CCT in that in is a measure of the functional biomechanical structure of the cornea—it tells us how that individual cornea responds to being applanated. It makes far more sense to correct an IOP measurement based on CH than on CCT.

Dr. Fingeret: But the data also show that CH and IOP are independent risk factors, so doesn't the same logic apply? Wouldn't this approach also be combining two independent risk factors into one?

Dr. Realini: That's a valid point. Once we correct IOP based on CH, we have incorporated the component of CH's risk associated with IOP measurement error. Is there also a structural component to CH as a risk factor? Does it both affect our IOP measurement and tell us something about the susceptibility of the optic nerve head and lamina cribrosa to glaucoma damage? It would be interesting to know if CH remains significant in a model of glaucoma progression that includes IOPcc. This would tell us whether CH still brings relevant information to the table after a CH-based IOP correction.



Dr. Brandt: The IOPcc measurement may also be useful in eyes that have previously undergone refractive procedures. LASIK both flattens the cornea and dramatically changes its biomechanical properties. An IOP measurement that takes the altered biomechanics into consideration would be of value. In coming years more and more patients will have had corneal refractive procedures decades earlier and will forget to tell you or your technician about them.

Safety Advantages

Dr. Flanagan: The ability to obtain a Goldmann equivalent IOP using noncontact tonometry offers a variety of important safety issues. Obviously, the risk of corneal abrasion—although very small to begin with—is eliminated. Also, there is no need for anesthesia or fluorescein dye, so we also eliminate possible adverse reactions to these products as well. But perhaps the biggest advantage is the elimination of the risk of infection.

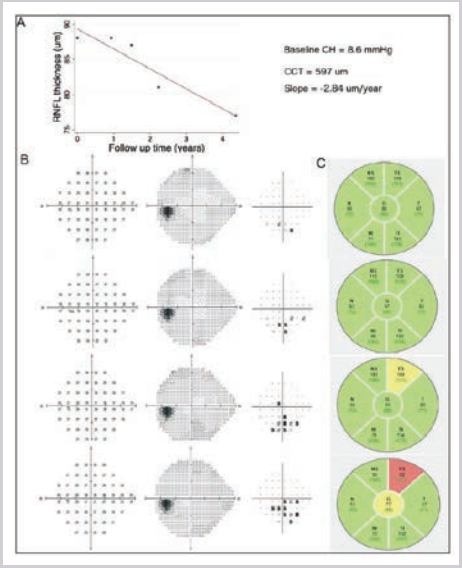
Dr. Coleman: There have been a number of significant outbreaks of epidemic keratoconjunctivitis in eye clinics. Among the methods by which microbes are transmitted from one patient to the next is the incomplete sterilization of the tonometer tip between patients. There are a variety of ways to clean the Goldmann tonometer tip. They can be soaked in bleach or alcohol for five to 20 minutes. Also, it requires that every room have multiple tips, which is costly. A more extreme approach is to sterilize them the same way we do our surgical instruments, but this can lead to cracking of the tip over time. These methods are most likely to be effective, but they come with inconveniences. There are more pragmatic approaches. They can be wiped off with an alcohol pad, or washed by hand with soap and water, or soaked in hydrogen peroxide, although the infection control experts are uncertain that these are adequate.

Dr. Liebmann: There are disposable Goldmann tonometer tips, but they cost approximately $1.25 apiece, which adds considerable expense to every eye examination.

Dr. Flanagan: In the United Kingdom, they have the added concern about prion-based diseases such as Creutzfeldt-Jakob disease. The use of reusable Goldmann tonometer tips ended in the UK more than 10 years ago—everything is now disposable.

Case 2: Progression with Thick Cornea

Dr. Medeiros: This patient from my practice also illustrates how CH might be useful in identifying the patients at risk for progression. This 70-year-old man with POAG has a CCT of nearly 600, which would suggest a relatively low risk of progression. Yet he is clearly progressing by both visual field and OCT criteria (figure). His CH, however, is 8.6, which is not as low as the CH in Dr. Radcliffe's patient, but is still moderately low. This is an eye in which CH revealed a propensity for progression that was in contrast to the CCT.



direct support for this idea. One demonstrated that CH was lower in glaucomatous eyes with acquired pits of the optic nerve than in glaucomatous eyes without such pits.[10] Interestingly, in this study the patients in both groups were matched for peak IOP, so it is less likely that acquired pits form as an IOP-dependent process. Perhaps CH is related to an IOP-independent mechanism of glaucomatous optic nerve damage.

Dr. Brandt: We conducted a study in which we measured axial length in glaucomatous eyes before and after trabeculectomy.[11] We also measured CCT and CH preoperatively. We found that CH was significantly associated with the shortening of axial length, while CCT was not. This study was confirmed by other investigators. These data suggest that the biomechanical responses of an eye to significant IOP reduction can be predicted in part by the CH measurement.

Dr. Radcliffe: There was also a study in which patients with and without glaucoma underwent optic nerve imaging before and after an induced IOP rise. In this study, the higher the CH, the more the lamina cribrosa was deformed backward in response to the pressure. In other words, eyes with higher CH were able to adapt to the IOP change and absorb it, while eyes with lower CH had less of a tissue adaptation to deal with the elevated IOP.

Dr. Brandt: Think of it as optic nerve head compliance. Eyes with higher CH were better able to buffer the IOP rise. As more indirect evidence of this, a study demonstrated that CH but not CCT was correlated with the structural parameters of glaucoma damage measured by confocal scanning laser ophthal-

Future Studies and Challenges

Dr. Fingeret: The data to date suggest that CH can play a role in glaucoma risk assessment. What additional studies would help us to fine tune our understanding of CH?

Dr. Myers: We should consider longitudinal studies. These will tell us several things. First, is CH stable over a patient's lifetime? We cannot answer this question with cross-sectional studies. Second, does CH change as glaucoma progresses? In other words, is low CH an indicator of progression risk or a consequence of it? And third, long-term studies will provide us with the data we need to better incorporate baseline CH values into a risk calculator for glaucoma progression.

Dr. Radcliffe: There are data that suggest CH changes in response to IOP reduction. Specifically, CH goes up as IOP is lowered. This may be a purely mechanical effect, as CH is known to be slightly correlated to IOP. But it may also be a sign that the low CH associated with glaucoma is recovering when glaucoma is treated. So it would be interesting to better characterize the effect of treatment on CH, and to see if the change in CH with treatment is predictive of progression vs. stability.

Dr. Gross: I would like to see a study of CH measured before and after trabeculectomy. Once there is an expansile reservoir incorporated into the eye—the bleb—I would expect the biomechanical compliance of the eye to increase. Also, I wonder if CH would help us to understand why some patients with very low postoperative IOP—say, 5 mmHg or less—develop hypotony maculopathy and others do not.

moscopy, with lower CH being associated with worse nerve damage.[12]

Dr. Realini: The question is: are these eyes progressing because they have low CH, or do they have low CH because they have glaucoma? Does glaucoma lead to a reduction in CH? In cross-sectional studies, this cannot be determined. A longitudinal study will be necessary to see if CH diminishes as patients progress from early glaucoma to moderate or advanced glaucoma.

Dr. Myers: This is an important point. In response to stress, bone creates more bone. In response to chronic hypertension, arteries produce more collagen and become stiffer and less compliant. Does a glaucomatous eye undergo connective tissue responses that would change its compliance and thus its hysteresis?

Dr. Realini: Either way, low CH is a sign of high risk for progression.

Billing for CH and Incorporating Into Clinical Practice

Dr. Radcliffe: The evidence supports a role for measuring CH in our patients with POAG. There is now a CPT code for the measurement and interpretation of CH. It is 92145. This is for one or both eyes. The frequency—once per year? once per lifetime?—has not been established, nor have the diagnostic codes that will support the test been established.

Dr. Gross: I suspect that even though Medicare has assigned the code and seems to be paying for it, that, like with many new codes, most private insurance providers will initially not pay for the service. But we need to bill for it anyway in order to demonstrate a volume of use that will play a role in making it payable eventually by private payers.

Dr. Brandt: As we move toward greater and greater office efficiency, we spend more time thinking about workflow. How can we best incorporate CH assessment into our clinical workflow? There are several issues. Who are the optimal patients for CH assessment—and who are not? How often does it need to be done? At what point in the workflow should it be done?

A new CPT code, 92145, has been published specifically for the Corneal Hysteresis measurement provided by the Reichert® Ocular Response Analyzer®. In the 2015 CPT handbook, a new, permanent, Category I CPT code, 92145 (Corneal hysteresis determination, by air impulse stimulation, unilateral or bilateral, with interpretation and report), replaces the prior temporary, Category III CPT code, 0181T. The new code took effect January 1, 2015.

According to "An Insider's View" published by the American Medical Association, this test achieved Category I status because the clinical utility has been established and usage has grown since 2007 when the Category III code was implemented. The code descriptor was changed slightly; it now describes a test performed on a single eye or both eyes (e.g., unilateral or bilateral).

"This change relieves a significant administrative burden for ophthalmologists and optometrists who perform corneal hysteresis and seek reimbursement for this diagnostic test. For most payers, including Medicare, Category III CPT codes are not covered while Category I codes are usually covered and reimbursed,"

—Kevin J. Corcoran, COE, CPC, CPMA, FNAO, president of Corcoran Consulting Group, during his presentation at the 2015 Hawaiian Eye meeting.

Dr. Myers: I think patient selection for measuring CH will be similar to that for CCT when it first emerged. We would want to know CH in patients who are glaucoma suspects to assess their risk of developing glaucoma. We would want it in treated patients who are progressing despite what appears to be adequate IOP control. We might want it in those odd patients who have markedly high IOP but no evidence of damage in order to better understand how the eye is tolerating the IOP.

Dr. Coleman: We should consider getting it in all of our established glaucoma patients if helps us decide which of them is at high risk for progression.

Dr. Brandt: I would add that patients who have undergone refractive surgery such as LASIK might be good candidates. The CH value may not be useful—it would be a measure of their altered cornea and not of their native eye. But the ORA IOP measurement (IOPcc) might be useful. We know that these

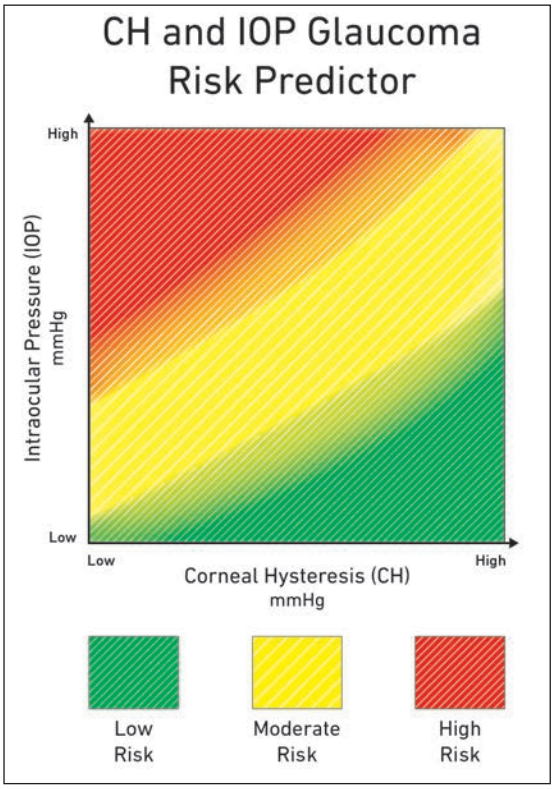
procedures alter the accuracy of Goldmann tonometry by altering corneal biomechanics in a way that the Goldmann tonometer cannot compensate for. IOPcc, may be a better measure of IOP than Goldmann IOP in these eyes.[13]

Dr. Radcliffe: Eyes with IOP over 30 mmHg may not be good candidates for CH measurement. In these eyes, the ORA will underestimate CH in order to avoid hitting the eye with an air puff strong enough to measure it accurately. This is not a significant limitation, however, because once the IOP is above 30, the need for IOP reduction is usually evident.

Dr. Realini: In those ocular hypertensives with high IOP and normal nerves, it might still be useful. If CH is underestimated in high-IOP eyes, an elevated CH in such an eye would be particularly compelling given that the true CH might be even higher.

Dr. Weinreb: In our 24-hour study, short-term variability of CH was not seen.[14] In studies by our group and others, CH does tend to diminish with age, by approximately 0.2 mmHg per decade.[15] But other studies suggest that CH may be a more dynamic measurement than CCT, especially when pathology is present.

Dr. Brandt: As for when to do it, I would ideally like to have it available when I see the patient. It should be available when I see the IOP, so I can use these two pieces of data together. It is not feasible to put an ORA into every exam room. One way to incorporate CH assessment into practice is to have a work-up area that all patients come through for their vision, pressures, and CH, then come to the exam room to be seen by the doctor.



Dr. Realini: That's a good point. Pachymeters are easily portable. But the ORA cannot come to the patient—the patient has to come to the ORA.

Dr. Brandt: Many of our devices are moving toward DICOM compatibility, so that they interface with our electronic health record. Therefore EHR software should have fields for corneal hysteresis. It is not clear yet whether EHR companies are incorporating this parameter.

Dr. Liebmann: One potential solution is to integrate this test in combination with our other standard glaucoma tests. Get CH after your visual fields, or after your OCT. Make it an automatic part of the process until you've gotten CH on all your patients.

Dr. Coleman: Once we have

Normal Values for CH

Dr. Radcliffe: In studies including healthy subjects from the United States, United Kingdom, South America, Europe and Asia, normal values for CH fall in the range of 10.1 to 10.9 mmHg.

Dr. Weinreb: We conducted a study several years ago in which 15 healthy subjects underwent 24-hour assessment of IOP, CCT and CH in our sleep laboratory at the Hamilton Glaucoma Center, University California San Diego. Both IOP and CCT demonstrated significant 24-hour variability, with highest values recorded during the nocturnal period. In contrast, CH was quite stable throughout the 24-hour period, with no significant variation at all.[14] Children tend to have high hysteresis (around 12 mmHg),[16,17] and our group and others have also demonstrated that CH does decrease slightly with age.[18,19] The significance of age-dependent decreases in CH is unknown.

Points of Consensus on Corneal Hysteresis

- CH is associated with the risk of glaucoma progression
- CH measurement would be valuable in assessing the risk of glaucoma suspects progressing to glaucoma, and in assessing the risk of progression of established glaucoma.
- At present, CH should be considered a semi-quantitative risk factor: low (CH <8 mmHg), medium (CH 8-12 mmHg) or high (CH >12 mmHg).
- Future research will enhance our understanding of how to best utilize CH in glaucoma risk assessment.

incorporated the testing process into our workflow, how do we incorporate the data into our patient management? What is the normal value for CH? What is the normal range? At what CH level should I consider my patient to be at increased risk of progression?

Dr. Radcliffe: The mean value in most normal populations is between 10 and 11 mmHg. The normal range is typically between 8 and 14 mmHg.

Dr. Brandt: I don't think we have adequate data yet to establish the risk of progression associated with specific values of CH. My approach will be to utilize the same approach I do with CCT. I think of the values as low, medium or high, and I think of the associated risk in the same way. A low CH with no other risk factors is no more compelling than a low CCT with no other risk factors. But in a patient you are already worried about—say, they have already gone blind in one eye or they have a strong family history of glaucoma blindness—in these patients, a low CH might be the straw that breaks the camel's back and prompts you to be more aggressive to prevent progression, while a normal or high CH might make you decide to maintain your current therapy and watch closely.

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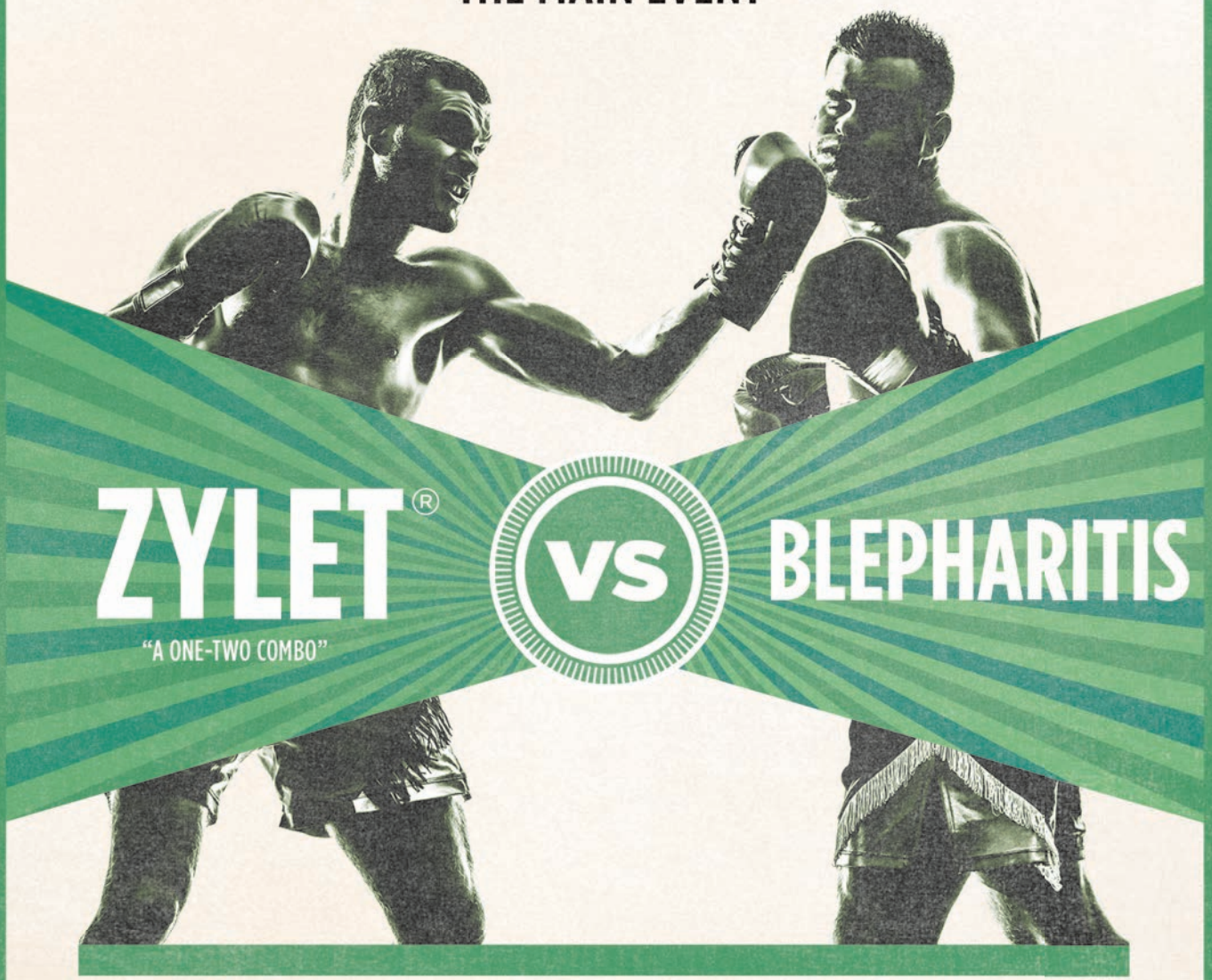
★ ★ ★ THE MAIN EVENT ★ ★ ★



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INDICATIONS AND USAGE

ZYLET® (loteprednol etabonate 0.5% and tobramycin 0.3% ophthalmic suspension) is a topical anti-infective and corticosteroid combination for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

Please see additional Indications and Usage information on adjacent page, including list of indicated organisms.

INDICATIONS AND USAGE (continued)

Ocular steroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, and where the inherent risk of steroid use in certain infective conjunctivitides is accepted to obtain a diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical, radiation or thermal burns, or penetration of foreign bodies.

The use of a combination drug with an anti-infective component is indicated where the risk of superficial ocular infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye.

The particular anti-infective drug in this product (tobramycin) is active against the following common bacterial eye pathogens: *Staphylococci*, including *S. aureus* and *S. epidermidis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains. *Streptococci*, including some of the Group A-beta-hemolytic species, some nonhemolytic species, and some *Streptococcus pneumoniae*, *Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis, Morganella morganii*, most *Proteus vulgaris* strains, *Haemophilus influenzae*, and *H. aegyptius, Moraxella lacunata, Acinetobacter calcoaceticus* and some *Neisseria* species.

IMPORTANT SAFETY INFORMATION

- ZYLET® is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.
- Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. If this product is used for 10 days or longer, intraocular pressure should be monitored.
- Use of corticosteroids may result in posterior subcapsular cataract formation.
- 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 a slit lamp biomicroscopy and, where appropriate, fluorescein staining.
- Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infections. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.
- Employment of corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and exacerbate the severity of many viral infections of the eye (including herpes simplex).
- Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use.
- Most common adverse reactions reported in patients were injection and superficial punctate keratitis, increased intraocular pressure, burning and stinging upon instillation.

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

With a one-two combo in the treatment of blepharitis and other steroid-responsive ocular conditions with the risk of bacterial infection, PRESCRIBE ZYLET® TODAY.

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Zylet®
loteprednol etabonate 0.5% and tobramycin 0.3% ophthalmic suspension

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

Zylet® (loteprednol etabonate 0.5% and tobramycin 0.3% ophthalmic suspension)

Initial U.S. Approval: 2004

DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

Apply one or two drops of Zylet into the conjunctival sac of the affected eye every four to six hours. During the initial 24 to 48 hours, the dosing may be increased, to every one to two hours. Frequency should be decreased gradually as warranted by improvement in clinical signs. Care should be taken not to discontinue therapy prematurely.

2.2 Prescription Guideline

Not more than 20 mL should be prescribed initially and the prescription should not be refilled without further evaluation [*see Warnings and Precautions (5.3)*].

CONTRAINDICATIONS

4.1 Nonbacterial Etiology

Zylet, as with other steroid anti-infective ophthalmic combination drugs, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

WARNINGS AND PRECAUTIONS

5.1 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.

5.2 Cataracts

Use of corticosteroids may result in posterior subcapsular cataract formation.

5.3 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 a slit lamp biomicroscopy and, where appropriate, fluorescein staining.

5.4 Bacterial Infections

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

5.5 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).

5.6 Fungal Infections

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

5.7 Aminoglycoside Hypersensitivity

Sensitivity to topically applied aminoglycosides may occur in some patients. If hypersensitivity develops with this product, discontinue use and institute appropriate therapy.

ADVERSE REACTIONS

Adverse reactions have occurred with steroid/anti-infective combination drugs which can be attributed to the steroid component, the anti-infective component, or the combination.

Zylet:

In a 42 day safety study comparing Zylet to placebo, ocular adverse reactions included injection (approximately 20%) and superficial punctate keratitis (approximately 15%). Increased intraocular pressure was reported in 10% (Zylet) and 4% (placebo) of subjects. Nine percent (9%) of Zylet subjects reported burning and stinging upon instillation.

Ocular reactions reported with an incidence less than 4% include vision disorders, discharge, itching, lacrimation disorder, photophobia, corneal deposits, ocular discomfort, eyelid disorder, and other unspecified eye disorders.

The incidence of non-ocular reactions reported in approximately 14% of subjects was headache; all other non-ocular reactions had an incidence of less than 5%.

Loteprednol etabonate ophthalmic suspension 0.2% - 0.5%:

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

In a summation of controlled, randomized studies of individuals treated for 28 days or longer with loteprednol etabonate, the incidence of significant elevation of intraocular pressure (≥10 mm Hg) was 2% (15/901) among patients receiving loteprednol etabonate, 7% (11/164) among patients receiving 1% prednisolone acetate and 0.5% (3/583) among patients receiving placebo.

Tobramycin ophthalmic solution 0.3%:

The most frequent adverse reactions to topical tobramycin are hypersensitivity and localized ocular toxicity, including lid itching and swelling and conjunctival erythema. These reactions occur in less than 4% of patients. Similar reactions may occur with the topical use of other aminoglycoside antibiotics.

Secondary Infection:

The development of secondary infection has occurred after use of combinations containing steroids and antimicrobials. Fungal infections of the cornea are particularly prone to develop coincidentally with long-term applications of steroids.

The possibility of fungal invasion must be considered in any persistent corneal ulceration where steroid treatment has been used.

Secondary bacterial ocular infection following suppression of host responses also occurs.

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects: Pregnancy Category C. Loteprednol etabonate has been shown to be embryotoxic (delayed ossification) and teratogenic (increased incidence of meningocele, abnormal left common carotid artery, and limb fixtures) when administered orally to rabbits during organogenesis at a dose of 3 mg/kg/day (35 times the maximum daily clinical dose), a dose which caused no maternal toxicity. The no-observed-effect-level (NOEL) for these effects was 0.5 mg/kg/day (6 times the maximum daily clinical dose). Oral treatment of rats during organogenesis resulted in teratogenicity (absent innominate artery at ≥5 mg/kg/day doses, and cleft palate and umbilical hernia at ≥50 mg/kg/day) and embryotoxicity (increased post-implantation losses at 100 mg/kg/day and decreased fetal body weight and skeletal ossification with ≥50 mg/kg/day). Treatment of rats at 0.5 mg/kg/day (6 times the maximum daily clinical dose) during organogenesis did not result in any reproductive toxicity. Loteprednol etabonate was maternally toxic (significantly reduced body weight gain during treatment) when administered to pregnant rats during organogenesis at doses of ≥5 mg/kg/day.

Oral exposure of female rats to 50 mg/kg/day of loteprednol etabonate from the start of the fetal period through the end of lactation, a maternally toxic treatment regimen (significantly decreased body weight gain), gave rise to decreased growth and survival and retarded development in the offspring during lactation; the NOEL for these effects was 5 mg/kg/day. Loteprednol etabonate had no effect on the duration of gestation or parturition when administered orally to pregnant rats at doses up to 50 mg/kg/day during the fetal period.

Reproductive studies have been performed in rats and rabbits with tobramycin at doses up to 100 mg/kg/day parenterally and have revealed no evidence of impaired fertility or harm to the fetus. There are no adequate and well controlled studies in pregnant women. Zylet should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemic steroids that appear in human milk could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when Zylet is administered to a nursing woman.

8.4 Pediatric Use

Two trials were conducted to evaluate the safety and efficacy of Zylet® (loteprednol etabonate and tobramycin ophthalmic suspension) in pediatric subjects age zero to six years; one was in subjects with lid inflammation and the other was in subjects with blepharoconjunctivitis.

In the lid inflammation trial, Zylet with warm compresses did not demonstrate efficacy compared to vehicle with warm compresses. Patients received warm compress lid treatment plus Zylet or vehicle for 14 days. The majority of patients in both treatment groups showed reduced lid inflammation.

In the blepharoconjunctivitis trial, Zylet did not demonstrate efficacy compared to vehicle, loteprednol etabonate ophthalmic suspension, or tobramycin ophthalmic solution. There was no difference between treatment groups in mean change from baseline blepharoconjunctivitis score at Day 15.

There were no differences in safety assessments between the treatment groups in either trial.

8.5 Geriatric Use

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

NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate or tobramycin.

Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma TK assay, a chromosome aberration test in human lymphocytes, or in an *in vivo* mouse micronucleus assay.

Oral treatment of male and female rats at 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (500 and 250 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender. No impairment of fertility was noted in studies of subcutaneous tobramycin in rats at 100 mg/kg/day (1700 times the maximum daily clinical dose).

PATIENT COUNSELING INFORMATION

This product is sterile when packaged. Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the suspension. If pain develops, redness, itching or inflammation becomes aggravated, the patient should be advised to consult a physician. As with all ophthalmic preparations containing benzalkonium chloride, patients should be advised not to wear soft contact lenses when using Zylet.

MANUFACTURER INFORMATION

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Based on 9007705-9004405 Revised 08/2013 US/ZYL/15/0014

The IRIS Registry: The First 18 Months

Christopher Kent, Senior Editor

Ophthalmology's large-scale data registry is showing signs of promise. Here, those involved discuss its benefits and potential pitfalls.

A few years ago, the American Academy of Ophthalmology decided to undertake a huge project that could have a great impact on the field of ophthalmology: a registry that would collect enormous amounts of real-time data from practicing ophthalmologists across the country. Such registries in other medical specialties have already proven to be powerful tools for improving outcomes and shedding light on the safety and efficacy of specific techniques and tools. Extending those advantages to the field of ophthalmology seemed both advantageous and—given the current nature of insurance company evaluation and government regulation—a way of maintaining some control over how ophthalmologists are judged.

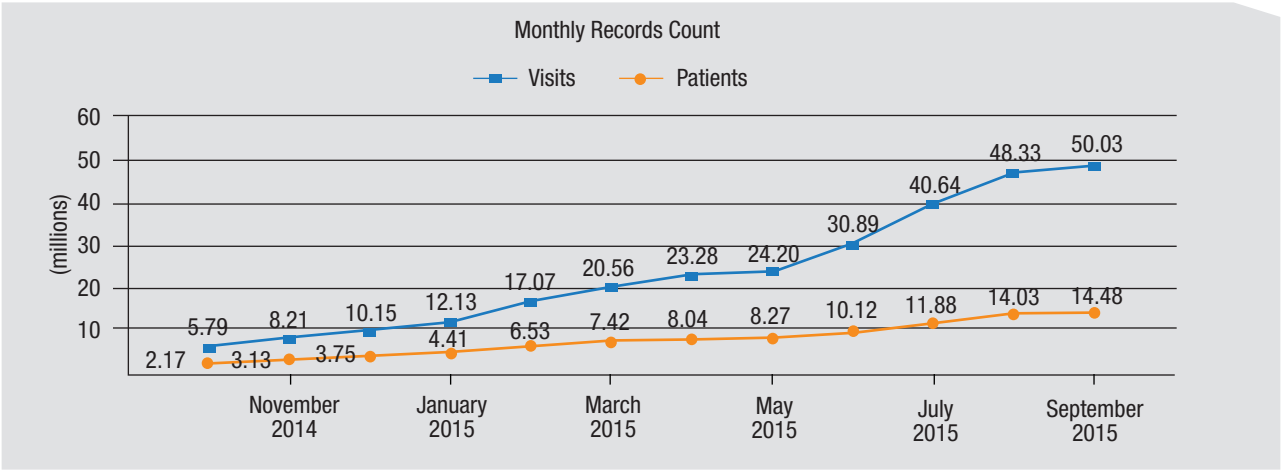
"We started planning this project in February 2012," explains William L. Rich III, MD, American Academy of Ophthalmology's medical director of health policy and chairman of the executive committee of the IRIS Registry. "We solicited the software vendor and received funding from the board in late 2012. We developed our quality measures and started implementing the software in 2013. Finally, we launched the registry in April 2014, with the goal of serving the needs of 2,200 physicians and 8 million patients by the year 2017.

"We surpassed that goal very quickly," he continues. "We now have data from 10,800 ophthalmologists covering more than 15.3 million patients and more than 54 million office visits. I believe this demonstrates the perceived value of the IRIS Registry by the membership. And it's worth noting that the registry isn't supported by any commercial money. All of the funding has come from the Academy's reserves; it's the greatest expenditure in our 100-year history."

Dr. Rich says they've already begun assessing the validity of some of the data. "We looked at the data from the first 636,000 cataract surgeries submitted to the IRIS Registry and compared it to the data from a very structured cataract surgery registry in Sweden," he says. "Our outcomes numbers were within about 2 percent of theirs."

Of course, any large-scale effort like this—especially one involving mass data collection and electronic movement of information—raises a host of questions. Here, Dr. Rich and Cynthia Mattox, MD, FACS, (vice chair of the Department of Ophthalmology at Tufts University School of Medicine, director of the New England Eye Center Glaucoma & Cataract Service, and chair of the Task Force on Quality Measure Development for the IRIS

Total IRIS Registry Data Over Time



In 2016 the Registry projects that the number of participating EHR-integrated doctors will reach 10,140 and the number of patient visits will reach 85.48M. The goal for 2017 is 48 million patients. If that goal is reached, patient visits should approach 152 million.

Registry) discuss the potential benefits of the IRIS Registry and address the concerns that some surgeons have expressed.

Regulatory Requirements

"Right now, the main role of the IRIS Registry is to help doctors comply with Physician Quality Reporting System requirements and the Meaningful Use Clinical Quality Measures," says Dr. Mattox. "By reporting data through either a cataract measure group or the Registry, doctors are successfully meeting the requirements for the PQRS. That's only going to get more important as we go forward with the new program that was created in the 2015 Sustainable Growth Rate reform bill—the Medicare Access and Children's Health Insurance Program Reauthorization Act legislation, or MACRA—which makes things even more complex. As a matter of practice economics, being a participant in the IRIS Registry makes things so much easier. It's almost impossible to participate in these programs just by reporting on claims anymore."

"Between 9 and 11 percent of ophthalmologists in the United States are likely to incur penalties relating to not using an electronic health records system in a meaningful way, PQRS and the value-based modifier, based on 2015 data," notes Dr. Rich. "For a specialty that gets the largest percentage of its revenue from Medicare, that's a big impact. Being part of the IRIS Registry gives the physicians who are using an EHR a chance to meet all those regulatory requirements. Last year we successfully helped 6,000 ophthalmologists manage their reporting to the federal government. We anticipated 8,000 for 2015 and that goal has been exceeded. We're now up to 90 percent of the ophthalmologists currently using EHRs."

"For this to work most efficiently, you have to be using an EHR that's been connected through the IRIS Registry," notes Dr. Mattox. "In order to allow the IRIS Registry to capture the data required for PQRS, an extraction software tool connects to your EHR and locates the data needed for the measures. Fortunately, most of the background work that makes this possible has already been done by the IRIS Registry, working with the EHR vendors to map where those pieces of data lie within their databases. About 36 popular EHRs are already mapped for this purpose.

"Of course, there are individual variations in each doctor's practice," she continues. "One doctor might document a certain type of data in a certain location; another doctor might document the information somewhere else. For that reason, every participating practice has an IRIS Registry client account manager who works with the doctors to figure out where the data is located within the EHR record. The fact that the IRIS Registry has already done 90 percent of the background work of mapping with the EHR vendors makes it much more efficient to get this working."

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that can accrue from assembling this type of large-scale data is being able to compare yourself to the rest of the profession—or to compare the doctors within your own practice. "As surgeons, we think we do a good job, but we can still improve by comparing ourselves to our peers and learning from one another," says Dr. Rich. "When you receive your PQRS results from the federal government, the data is 18 months old. Whatever it says about you, it's so old that you can't really act on it. As a result, no one pays much attention to it. With the IRIS Registry, about a month after you do a procedure you're going to be able to compare your results to a database with more than a million cataracts. That's pretty powerful, and doctors are already taking advantage of it.

"Basically, physicians are very competitive people," he continues. "They compete in college, in medical school, during internships and residencies. Their success rate is always being noted and intensely scrutinized, even during their training. So physicians are kind of used to being measured. Eventually, I think pretty much all ophthalmologists will be a part of this. If you really want to improve as a doctor, it's nice to be able to compare yourself to a big benchmark. A registry lets you do that."

Dr. Mattox says that once the system is set up, the doctor can get a report of activity within the practice on a dashboard that's refreshed every month. "Whoever in the practice has administrative privileges for the reports can look at the information and identify areas that might need to be improved, and also look at the practice's or doctor's comparison to benchmarks," she explains. "One really amazing feature is the ability to drill down into the information to the actual patient level, where the doctor can review any issue that is identified. Other custom reports can also be generated within the IRIS Registry dashboard.

"If there's any problem with the data," she adds, "it may be that the information is not being picked up in a particular location. The client account manager can help to fix that. Sometimes it's just that a doctor is not remembering to document something, even though he's doing it. That can prompt a conversation with the doctor to put the necessary documentation in the record."

"In terms of comparing the doctors within a practice, when you're in a big group—my practice has 12 doctors, for example—you probably have no idea how each of you does in comparison to the others," says Dr. Rich. "IRIS will let you make that comparison. Of course, the only person that has access to that information is your practice and you. I know of one practice that did this and discovered that one member of the group, a well-established surgeon with a good reputation, had a complication rate four times higher than the rest of the practice. I don't know what the group decided to do with that information, but I'm sure they were glad to be aware of it. Of course, this type of information will create some interesting challenges, but they are challenges worth addressing."

Improving Outcomes

"One of the goals for the IRIS Registry is to help physicians meet federal regulatory requirements for better outcomes," notes Dr. Rich. "If you ask the question, 'Do registries really improve outcomes?' the answer is that they definitely do. That's been shown incontrovertibly by our peers at the Society of Thoracic Surgery and the American College of Cardiology, both of which have long-standing registries. Or, look at our peers in Sweden. Since they implemented their registry the

The IRIS Registry: A User's Perspective

"As far as I know, our practice was one of the first to implement the IRIS Registry," says John M. Haley, MD, in private practice in Dallas for near 40 years, and a member of the American Academy of Ophthalmology Health Policy Committee. "Start-up was remarkably easy. IRIS is hooked up to your EHR system with help from your IT people. There's a required mapping process where you communicate with the IRIS group and let them know specifically where you document PRQS measures, such as the presence or absence of DME, in your EHR. All of the measures must be mapped for each doctor, unless everyone in your practice does things exactly the same way. This sounds complicated, but it all goes quickly and easily. Once you're set up, the IRIS computers work behind the scenes at night; they extract that DME information from your records and give you a check that indicates that you performed the evaluation.

"Progress in your practice can easily be followed on your personal dashboard," he continues. "Any problems that occur can be addressed by IRIS before there's any risk of failing your PQRS evaluation. You can also evaluate all the partners in your practice using various parameters, although in our practice this has been limited to the PQRS measures. We're now able to bring all partners up to one standard quickly and easily, thanks to the IRIS monitoring.

"Outcome comparison will be important in the future," he adds. "And, there's no other practical way to comply with all the quality measures that will determine our bonuses and penalties. Data will be king in the future, and IRIS will allow collection of that data for clinical studies, as well as personal outcomes that determine quality. Using the IRIS Registry is a no-brainer."

—CK

***Richard Lindstrom**, MD*
Ophthalmologist and noted refractive and cataract surgeon.
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complication rates in cataract surgery have steadily and continually gone down, both in low-volume and high-volume hospitals. So there's no doubt about it."

"Having access to this kind of database definitely raises the bar," agrees Dr. Mattox. "And in the future, we hope to learn new things about patient care that can be identified within the IRIS Registry data. The time it will take to do this will be far shorter than the time it takes to complete a controlled clinical trial, which can be years. Of course, there will always be a role for randomized clinical trials, but it's a different mindset. Clinical trials target very specific questions looking for very specific answers. In the IRIS Registry, the sheer volume of data should reveal answers that we may not even have been looking for.

"The first phase of using a registry like the IRIS Registry is measuring and benchmarking and making sure that your practice is up to snuff," she adds. "But the second phase is taking the data to another level, where we identify serious deficiencies or risk factors that can push care in a different direction."

Simplifying Clinical Trials

Dr. Rich notes that registry data may help researchers conduct large clinical trials for much less cost than traditional methods. "If you look at the cost of clinical trials in the United States, even a small trial like the Comparison of Age-Related Macular Degeneration Treatments Trial costs more than $10 million over a period of three years," he says. "Some trials cost more than $100 million. Our society really can't afford to spend that kind of money. Registry data may provide a way to solve that problem.

"Researchers at the National Heart Lung Blood Institute, which is part of the National Institutes of Health, compared the cost of a standard clinical trial of a cardiac stent to the cost of using registry data," he continues. "They did the comparison study in Denmark, even though it was funded by the United States and all of the data analysis was done over here. There were two arms of the trial; one looked at the cost of a typical randomization of patients; the other looked at the cost of randomization using the Denmark registry. They found that the cost of using the registry was about $50 per patient. That was less than 5 percent of the cost of the other approach.[1] So it's likely that the IRIS registry data will be able to provide the same kind of cost relief in some clinical trials done over here."

Dr. Mattox notes that using the IRIS data for clinical trials is still down the road a ways. "However, this will be a huge gold mine for something like that," she says. "This is real-world longitudinal clinical data from many, many patients—more than 14.2 million unique patients have been captured in IRIS as of early September. Not only could you pull patients from the registry in order to do clinical comparative-effectiveness research, you'll be able to stratify risk because we'll have all the associated diagnoses, medications and everything else that you can extract from an electronic record. Already there are interesting analyses being performed on the data, but this is in its infancy. Eventually, this will be an amazing, powerful benefit."

Comparative Rates of Endophthalmitis (April 2014 – May 2015)

Drug	Injections	Endophthalmitis rate
Avastin	478,381	0.12%
Lucentis	245,381	0.09%
Eylea	103,390	0.12%

One of the ways in which registry data can be used is as a means to resolve questions that may impact public policy. Questions regarding the relative risk of endophthalmitis when injecting Avastin, a compounded drug, versus noncompounded drugs such as Lucentis and Eylea were put to rest after looking at the accumulated data for those types of injections.

Other Potential Benefits

Dr. Rich notes several additional ways ophthalmology may benefit from the existence of the IRIS Registry:

• ***Impacting public policy.*** Dr. Rich points out that this kind of "big" data can have a serious impact on public policy—and already has in some instances. "In April of this year there was a major debate taking place in Washington, D.C., about when and how compounded drugs, such as anti-VEGF agents, should be injected into the body," he says. "A committee was formed to make recommendations to the FDA. One member of the committee was associated with a company whose profits might be affected if the injection of non-approved compounded drugs were encouraged. That person basically said that no one in the United States should have a non-FDA approved drug injected into the eye because of the risk of endophthalmitis, despite the safety data from the CATT trial, which suggested that there was equal safety whether the drug was compounded or not.

"In response, George Williams, MD, who is the secretary for federal affairs in the Academy, asked Dr. Flora Lum, AAO vice president of Quality and Data Science, if the IRIS Registry had produced any data relevant to this question," he continues. "A few days later, Dr. Williams was able to show the committee the data from 827,000 consecutive injections of an anti-VEGF agent into the eye, comparing the endophthalmitis rates between Lucentis, Avastin and Eylea. The difference was 0.03 percent between the drugs. That ended the

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ID	MEASURE	PERFORMANCE
IRIS 1	Primary Open Angle Glaucoma (POAG): Optic Nerve Evaluation	94.17% (Registry Benchmark: 79.42%)
IRIS 2	Diabetic Retinopathy: Documentation of Presence or Absence of Macular Edema and Level of Severity of Retinopathy	13.72% (Registry Benchmark: 38.91%)
IRIS 3	Diabetic Retinopathy: Communication with the Physician Managing Ongoing Diabetes Care	0.00% (Registry Benchmark: 27.17%)
IRIS 4	Cataracts: 20/40 or Better Visual Acuity within 90 Days Following Cataract Surgery	79.51% (Registry Benchmark: 86.28%)
IRIS 5	Complications within 30 Days Following Cataract Surgery Requiring Additional Surgical Procedures	0.00% (Registry Benchmark: 0.62%)
IRIS 6	Diabetes: Eye Exam	80.92% (Registry Benchmark: 87.05%)
IRIS 14	Preventive Care and Screening Tobacco Use: Screening and Cessation Intervention	87.96% (Registry Benchmark: 82.20%)

The IRIS Registry allows a practice to compare itself to benchmarks (above). The small vertical lines represent benchmarks; the bar shows the practice's current score. Green indicates surpassing the benchmark; red indicates falling short. A different screen (right) shows performance over time. At this practice, the short feedback cycle—about four weeks—has resulted in steady improvement in this measure.

debate. In the past, addressing a question like this with this level of data would have been nearly impossible."

• ***Monitoring the safety and efficacy of drugs and devices.*** "Remember Vioxx?" asks Dr. Rich. "It took years to figure out the correlation between Vioxx and cardiac events. The FDA is currently attempting this type of monitoring using what they call a 'Mini-Sentinel Initiative' where they look at big data from many sources. We think that's going to play a huge role in the surveillance of ophthalmic devices in the future. Currently, about 60 percent of Class III devices have mandated post-market surveillance by the FDA, but only 6 percent are being monitored by independent registries. The rest are commercial registries formed by the industry. The FDA would certainly prefer a more independent source for that kind of data, so I think there's a huge opportunity for societies like ours to get involved in device and drug surveillance. That's one of our plans at the Academy—to develop a practice-based research network that can do both research and device surveillance."

• ***Monitoring public health.*** "Previously, we never really had a large database to look at ophthalmic disease in the United States," notes Dr. Rich. "We're now becoming involved with multiple large public-health comparative-effectiveness applications, including an eye disease surveillance project backed by the Centers for Disease Control and Prevention. The IRIS data would be the backbone for those applications."

• ***Creating common standards.*** Dr. Rich says the registry is also hoping to find common ground with the American Board of Ophthalmology. "Becoming board-certified can be laborious," he notes. "We're working with the ABO to find ways that board certification can utilize some of the data that's already being extracted, to minimize the need for picking up charts and filling out forms. We also want to help ensure that the things being measured are meaningful for the board, the profession and the public, which is not necessarily the case now. Ophthalmology boards are appropriately independent from the specialties, and our goals are somewhat different from theirs. Their goal is to protect the public good by developing standards; our goal is to educate and improve the performance of physicians. But if we all used the same metrics for measurement, that would make a lot of sense."

What if the Data Is Hacked?

"The prospect of the database being hacked is a little scary," admits Dr. Rich. "However, in contrast to major companies like Target or Blue Cross, there hasn't been a data breach in any registry, even though a number of them have been around for sev-

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- 22%* vs 7% on Day 8; 41%* vs 11% on Day 15[1]

Nearly 2x as many cataract patients achieved zero pain on postoperative Days 8 and 15 vs placebo
- 58%* vs 27% on Day 8; 63%* vs 35% on Day 15[1]

WHEN TREATING ENDOGENOUS ANTERIOR UVEITIS, DUREZOL® EMULSION WAS NONINFERIOR TO PRED FORTE^ (DUREZOL® EMULSION 4X DAILY VS PRED FORTE^ 8X DAILY)[1]

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*Pooled data from placebo-controlled trials in patients undergoing cataract surgery; $P<0.01$ vs placebo.
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INDICATIONS AND USAGE:
DUREZOL® Emulsion is a topical corticosteroid that is indicated for:
- The treatment of inflammation and pain associated with ocular surgery.
- The treatment of endogenous anterior uveitis.

Dosage and Administration
- For the treatment of inflammation and pain associated with ocular surgery instill one drop into the conjunctival sac of the affected eye 4 times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period, followed by 2 times daily for a week and then a taper based on the response.
- For the treatment of endogenous anterior uveitis, instill one drop into the conjunctival sac of the affected eye 4 times daily for 14 days followed by tapering as clinically indicated.

IMPORTANT SAFETY INFORMATION
Contraindications: DUREZOL® Emulsion, as with other ophthalmic corticosteroids, is contraindicated in most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

Warnings and Precautions
- Intraocular pressure (IOP) increase—Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. If this product is used for 10 days or longer, IOP 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 beyond 28 days should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.
- Bacterial infections—Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.
- Viral infections—Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).
- Fungal infections—Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use.
- Contact lens wear—DUREZOL® Emulsion should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of DUREZOL® Emulsion. The preservative in DUREZOL® Emulsion may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of DUREZOL® Emulsion.

Most Common Adverse Reactions
- Post Operative Ocular Inflammation and Pain—Ocular adverse reactions occurring in 5-15% of subjects included corneal edema, ciliary and conjunctival hyperemia, eye pain, photophobia, posterior capsule opacification, anterior chamber cells, anterior chamber flare, conjunctival edema, and blepharitis.
- In the endogenous anterior uveitis studies, the most common adverse reactions occurring in 5-10% of subjects included blurred vision, eye irritation, eye pain, headache, increased IOP, iritis, limbal and conjunctival hyperemia, punctate keratitis, and uveitis.

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

For more resources for eye care professionals, visit MYALCON.COM/DUREZOL.

References: 1. DUREZOL (difluprednate ophthalmic emulsion) [package insert]. Fort Worth, TX: Alcon Laboratories, Inc; Revised May 2013. **2.** Korenfeld MS, Silverstein SM, Cooke DL, Vogel R, Crockett RS; Difluprednate Ophthalmic Emulsion 0.05% (Durezol) Study Group. Difluprednate ophthalmic emulsion 0.05% for postoperative inflammation and pain. *J Cataract Refract Surg.* 2009;35(1):26-34. **3.** Fingertip Formulary, November 2014 (estimate derived from information used under license from Fingertip Formulary, LLC, which expressly reserves all rights, including rights of copying, distribution and republication). **4.** WellCare. Medication Guide: 2014 WellCare Classic. WellCare website. https://www.wellcarepdp.com/medication_guide/default. Accessed November 14, 2014. **5.** WellCare. Medication Guide: 2015 WellCare Classic and Simple. WellCare website. https://www.wellcarepdp.com/medication_guide/default. Accessed November 14, 2014. **6.** Humana. Drug guides for Medicare plans 2014. Humana website. https://www.humana.com/medicare/products-and-services/pharmacy/rx-tools/medicare-drug-list/2014-print. Updated October 30, 2014. Accessed November 14, 2014. **7.** Humana. Drug guides for Medicare plans 2015. https://www.humana.com/medicare/products-and-services/pharmacy/rx-tools/medicare-drug-list/2015-print. Updated September 5, 2014. Accessed November 14, 2014.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE
Ocular Surgery
DUREZOL® (difluprednate ophthalmic emulsion) 0.05%, a topical corticosteroid, is indicated for the treatment of inflammation and pain associated with ocular surgery.
Endogenous Anterior Uveitis
DUREZOL® Emulsion is also indicated for the treatment of endogenous anterior uveitis.

DOSAGE AND ADMINISTRATION
Ocular Surgery
Instill one drop into the conjunctival sac of the affected eye 4 times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period, followed by 2 times daily for a week and then a taper based on the response.

Endogenous Anterior Uveitis
Instill one drop into the conjunctival sac of the affected eye 4 times daily for 14 days followed by tapering as clinically indicated.

DOSAGE FORMS AND STRENGTHS
DUREZOL® Emulsion contains 0.05% difluprednate as a sterile preserved emulsion for topical ophthalmic administration.

CONTRAINDICATIONS
The use of DUREZOL® Emulsion, as with other ophthalmic corticosteroids, is contraindicated in most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal disease of ocular structures.

WARNINGS AND PRECAUTIONS
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 beyond 28 days should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

Bacterial Infections
Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

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

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

Topical Ophthalmic Use Only
DUREZOL® Emulsion is not indicated for intraocular administration.

Contact Lens Wear
DUREZOL® Emulsion should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of DUREZOL® Emulsion. The preservative in DUREZOL® Emulsion may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of DUREZOL® Emulsion.

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

Ocular Surgery
Ocular adverse reactions occurring in 5-15% of subjects in clinical studies with DUREZOL® Emulsion included corneal edema, ciliary and conjunctival hyperemia, eye pain, photophobia, posterior capsule opacification, anterior chamber cells, anterior chamber flare, conjunctival edema, and blepharitis. Other ocular adverse reactions occurring in 1-5% of subjects included reduced visual acuity, punctate keratitis, eye inflammation, and iritis. Ocular adverse reactions occurring in < 1% of subjects included application site discomfort or irritation, corneal pigmentation and striae, episcleritis, eye pruritus, eyelid irritation and crusting, foreign body sensation, increased lacrimation, macular edema, sclera hyperemia, and uveitis. Most of these reactions may have been the consequence of the surgical procedure.

Endogenous Anterior Uveitis
A total of 200 subjects participated in the clinical trials for endogenous anterior uveitis, of which 106 were exposed to DUREZOL® Emulsion. The most common adverse reactions of those exposed to DUREZOL® Emulsion occurring in 5-10% of subjects included blurred vision, eye irritation, eye pain, headache, increased IOP, iritis, limbal and conjunctival hyperemia, punctate keratitis, and uveitis. Adverse reactions occurring in 2-5% of subjects included anterior chamber flare, corneal edema, dry eye, iridocyclitis, photophobia, and reduced visual acuity.

USE IN SPECIFIC POPULATIONS
Pregnancy
Teratogenic Effects
Pregnancy Category C. Difluprednate has been shown to be embryotoxic (decrease in embryonic body weight and a delay in embryonic ossification) and teratogenic (cleft palate and skeletal) anomalies when administered subcutaneously to rabbits during organogenesis at a dose of 1–10 mcg/kg/day. The no-observed-effect-level (NOEL) for these effects was 1 mcg/kg/day, and 10 mcg/kg/day was considered to be a teratogenic dose that was concurrently found in the toxic dose range for fetuses and pregnant females. Treatment of rats with 10 mcg/kg/day subcutaneously during organogenesis did not result in any reproductive toxicity, nor was it maternally toxic. At 100 mcg/kg/day after subcutaneous administration in rats, there was a decrease in fetal weights and delay in ossification, and effects on weight gain in the pregnant females. It is difficult to extrapolate these doses of difluprednate to maximum daily human doses of DUREZOL® Emulsion, since DUREZOL® Emulsion is administered topically with minimal systemic absorption, and difluprednate blood levels were not measured in the reproductive animal studies. However, since use of difluprednate during human pregnancy has not been evaluated and cannot rule out the possibility of harm, DUREZOL® Emulsion should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus.

Nursing Mothers
It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when DUREZOL® Emulsion is administered to a nursing woman.

Pediatric Use
DUREZOL® Emulsion was evaluated in a 3-month, multicenter, double-masked, trial in 79 pediatric patients (39 DUREZOL® Emulsion; 40 prednisolone acetate) 0 to 3 years of age for the treatment of inflammation following cataract surgery. A similar safety profile was observed in pediatric patients comparing DUREZOL® Emulsion to prednisolone acetate ophthalmic suspension, 1%.

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, and Impairment of Fertility
Difluprednate was not genotoxic *in vitro* in the Ames test, and in cultured mammalian cells CHL/IU (a fibroblastic cell line derived from the lungs of newborn female Chinese hamsters). An *in vivo* micronucleus test of difluprednate in mice was also negative. Treatment of male and female rats with subcutaneous difluprednate up to 10 mcg/kg/day prior to and during mating did not impair fertility in either gender. Long term studies have not been conducted to evaluate the carcinogenic potential of difluprednate.

Animal Toxicology and/or Pharmacology
In multiple studies performed in rodents and non-rodents, subchronic and chronic toxicity tests of difluprednate showed systemic effects such as suppression of body weight gain; a decrease in lymphocyte count; atrophy of the lymphatic glands and adrenal gland; and for local effects, thinning of the skin; all of which were due to the pharmacologic action of the molecule and are well known glucocorticosteroid effects. Most, if not all of these effects were reversible after drug withdrawal. The NOEL for the subchronic and chronic toxicity tests were consistent between species and ranged from 1–1.25 mcg/kg/day.

PATIENT COUNSELING INFORMATION
Risk of Contamination
This product is sterile when packaged. Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the emulsion.
Use of the same bottle for both eyes is not recommended with topical eye drops that are used in association with surgery.

Risk of Secondary Infection
If pain develops, or if redness, itching, or inflammation becomes aggravated, the patient should be advised to consult a physician.

Contact Lens Wear
DUREZOL® Emulsion should not be instilled while wearing contact lenses. Patients should be advised to remove contact lenses prior to instillation of DUREZOL® Emulsion. The preservative in DUREZOL® Emulsion may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of DUREZOL® Emulsion.

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U.S. Patent 6,114,319

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Can Comparisons Be Fair?

How surgeons may be compared to other surgeons is a sore point for many physicians. "We've been very careful and cognizant of that along the way, in terms of how comparisons are going to be made," says Cynthia Mattox, MD, FACS, chair of the Task Force on Quality Measure Development for the IRIS Registry. "I would say this: Right now, any profiling done by private payers is all about simply comparing ophthalmologists to other ophthalmologists. There's no stratification of subspecialists, taking into account that a retina specialist is going to have higher costs than a comprehensive ophthalmologist. There's no differentiation between ophthalmologists who do surgery and those who don't do surgery. In other words, private payers are not using the correct peer groups for comparison. That's a big problem: garbage in, garbage out.

"In contrast," she continues, "something as sophisticated as the IRIS Registry is going to allow us to compare all the retinal specialists, or all the doctors who do a similar number of trabeculectomies, across the country. We're not there yet, but this is the future. And you'll get a much more robust comparison of your results or the makeup of the patients within your practice—how many patients are severely afflicted with diabetes compared to other practices, for example. The risk stratification and profiling and meaningful comparisons that can be done using a big database like the IRIS Registry is leaps and bounds beyond what is currently happening in private-payer situations today. This will be far better than what we have now."

Dr. Mattox notes that what is being measured also makes a big difference, and payers are pushing "quality" measurement on ophthalmologists without involving the physicians. "This type of registry, where we design the measures that are of interest to us and look at the questions of interest to us, makes much more sense," she says. "This will allow us to make proposals to the policy makers, saying, 'Look, this is something that's important that needs to be changed.' They would never identify these things using their systems.

"There are always people who are concerned that they will be targeted in some way as a result of this kind of comparison," she adds. "But in reality, I think the IRIS Registry is going to prove to payers that we are providing exceptional care. We'll be able to demonstrate that the people who are taking on those more difficult cases have a reason to be more costly providers, just based on their patient demographics and severity. That's where we're headed. We want this to help members, not harm them."

—CK

eral years. They all use the highest degree of security available, although of course that's not a guarantee."

Dr. Rich says the data would be of limited use to a hacker. "The data is extracted from your computer at night," he explains. "It goes into the cloud where the medical part is separated from the patient's personal information. Those things are linked for Medicare and Medicaid use, but not for the IRIS Registry. So a patient or physician's personal information isn't linked to the medical data.

"As we know, anything can be hacked," he continues. "It's something everyone worries about. But hacking your IRIS information from the cloud would have about the same impact as if someone got the information from hacking your credit card database; they would not have access to the linked data on your health. So someone with that data wouldn't be able to discriminate against you if you have cancer, if you're a candidate for a job and might have exorbitant costs to insure. Right now, I don't think we're of much interest to hackers."

Dr. Mattox notes that preventing hackers from accessing the registry is a technical issue beyond the expertise of many of the ophthalmologists running it. "FIGmd is the IRIS Registry vendor," she notes. "Their company has more experience with registries and database-capture than any other company. As I understand it, all of the identifiers and demographics are kept in a completely different server from all of the clinical information," she says. "So, everything on the clinical side of the aggregate data is de-identified. Within your own practice, if you're given the rights to look at others in your practice, you can see each physician's data. However, even doing that requires access permission. From practice to practice or region to region, the setup is much different. You won't be able to look at the data from Dr. X's practice down the street."

Dr. Rich adds that the size of this type of data collection is relative. "This qualifies as 'big data,' but not really, really big data, like the type the NSA collects when monitoring people's phone calls," he says. "For medicine this is big, but we're not talking about high-speed collection of unbelievable volumes of billions of data inputs like the security agencies use."

Could the Data Be Biased?

Some surgeons wonder whether the statistical data captured by the IRIS Registry might be slanted as a result of coming from mostly EHR-using, self-selected practices. Dr. Rich says the quantity of data is so large that he doesn't think this will be an issue. "For example, we're going to have data about a couple million intravitreal injections and cataracts," he says. "Furthermore, we've looked carefully at who's participating in IRIS. The spread of practice sizes

and mix of specialties among the participants is the same as in the general membership.

"Of course," he continues, "using or not using EHR will be a delineating factor, but it's not clear that that alone will affect the data in any significant way. About 50 percent of ophthalmologists are now using EHR, and the number keeps growing. Some subspecialties, such as pediatric ophthalmologists, may not gain much by implementing EHR, and older ophthalmologists who are near retirement probably won't want to make a huge change like that. However, of the doctors who are using EHR, 90 percent are on IRIS now. And we think that will increase in the next two years."

Dr. Mattox notes that even if your practice doesn't use electronic records, it's still possible to participate. "It's extremely difficult to report on the required nine measures for PQRS without an electronic records system," she admits. "However, in 2014 about 700 doctors who don't use EHR participated in PQRS by allowing the IRIS Registry to report data for the cataract measure group. This requires reporting on a specific set of measures, but you only have to report them for 20 of your uncomplicated cataract patients. The patients need to be Medicare patients, but you can include nine Medicare Advantage patients. For 2016, we also have approval for a diabetic retinopathy measure group reporting option."

Other Concerns

• ***Will the data create legal liability if you have a bad outcome?*** "There hasn't been an issue yet with discoverability," says Dr. Rich. "Going back 20 years or more, there has not been a successful subpoena of a registry chart. Personal charts, yes—those are obviously discoverable. But no one should have access to someone's comparative effectiveness. I don't know the rate of endophthalmitis or dropped nuclei of the surgeon down the street. Only he or she knows that, as well as those who are also in that practice. Your comparative success in doing a procedure, no matter what device, drug or approach you use, is not legally discoverable. The IRIS database is not public unless we make it public. It's owned by the Academy and its members."

• ***Won't this affect workflow in the office?*** Dr. Rich says it will not. "The Academy formed a registry in 1995 called NEON, the National Eye Outcomes Network," he explains. "To submit data you had to use a piece of paper, like the SAT test; you filled in little boxes and darkened the circles. NEON was a disaster because it interfered with workflow. Our practice was a beta site, and my staff begged me to stop. With the IRIS Registry, a piece of software sitting on top of your server pulls out the day's data at night and loads it into the registry. There's no staff work. The fact that it doesn't affect workflow is a huge benefit."

• ***Could this kind of data cause protocols to become overly restricted?*** Some surgeons are concerned that once massive amounts of data indicate that one method produces the best results, insurance companies may refuse to reimburse any alternative options—unless, perhaps, the surgeon completes extensive paperwork explaining the reasons for not using the preferred approach.

Dr. Rich believes this is unlikely to become a problem. "As long as you get good results and cause no injuries and follow the norms, I don't think that's possible," he says. "However, if you have a patient with wet macular degeneration and you want to treat that patient with a hot laser like we did in the '80s and '90s, while everyone else is now using anti-VEGF drugs, well, you shouldn't be doing that. If you're caught, you'll have a legal problem. But preferring one device or approach over another? I just don't see that, as long as your outcomes are reasonable."

Dr. Mattox agrees. "We have randomized controlled trials comparing procedures now, and nobody's using the results to tell us what to do," she points out. "You could argue that the Tube vs. Trabeculectomy trial might cause payers to refuse to pay for trabeculectomy. That isn't happening."

• ***Measuring outcomes would provide more meaningful data than comparing doctors' completion of processes.*** Insurers tend to measure whether doctors' are completing the steps in a process instead of measuring treatment outcomes. Dr. Mattox says the IRIS Registry is working toward measuring both. "Most of the PQRS measures are still process measures," she says. "Those ask: If a patient has a particular condition, are you doing X, Y and Z? In contrast, an outcome measure asks how well your patients are doing after your treatment. There's a big push toward outcome measures, but we don't want to get rid of the process measures; they are ophthalmology-specific, and there are practice gaps that relate to them that we need to pay attention to.

"The IRIS Registry is now designated as a clinical-quality data registry, which allows us to develop our own homegrown quality outcome measures," she continues. "At this point we have 18 approved subspecialty quality measures that are outcome measures. Those outcome measures are optional right now, but it's possible to choose two outcome measures in order to be a successful participant in the PQRS program in the future."

Dr. Mattox says measuring outcomes is the direction in which the IRIS Registry is moving. "The ones that are approved are just our first go-round, trying to identify some mea-

sures that are easily measured with the data that we know is captured by EHR," she says. "Eventually they'll be revised and improved. We'll have more information in the database that we can pull from to identify the next phase of measures."

The Wave of the Future?

"The Society of Thoracic Surgeons and the American College of Cardiology were the real pioneers in the creation of medical registries," notes Dr. Rich. "Today, everyone is realizing that this is a good thing. Medical specialties want to educate their members and improve quality of care, and most of them have decided that this is the best way to do it. In the past two years, they've seen the success that the pioneering specialties have had. As a result, registries are proliferating right now. I think soon almost all specialists will have a registry. If they haven't set one up already, they're in development or negotiations to do it. I don't think there's much downside to participating.

"Right now we're the largest registry in the United States, and I'm pretty sure in the world," he adds. "It's been a lot of work, but we've been surprised at the level of acceptance. The vendor we're working with has had to hire triple the number of staff to handle the uptake. It's an exciting time."

Dr. Mattox notes that this is just the beginning. "The measures we've developed are rather coarse, and there will be criticism of that," she says. "But I feel strongly that as we move forward and learn more about data collection and analysis, we'll be able to refine the measures and identify information that really moves the needle. Right now this is a work in progress. We encourage doctors who have ideas about what we should be measuring, or how we should be measuring it, to get involved and help us."

Dr. Mattox notes that some fear about unintended consequences surrounding a project like this is to be expected. "However, I think most of that fear is unfounded," she says. "Whatever we can do to control our own destiny as a profession is better than waiting for our destiny to be determined by people who don't know anything about ophthalmology. That's what's happening now. We're changing the conversation, and that's a good thing." REVIEW

1. Lauer MS, D'Agostino RB Sr. The randomized registry trial--the next disruptive technology in clinical research? N Engl J Med 2013;369:17:1579-81.

How Not to Fail Your Clinical Trial

Walter Bethke, Managing Editor

Veteran researchers tell you how to be prepared if you become a clinical trial investigator.

Ophthalmologists say that taking part in a clinical trial can be very rewarding, since it allows you to be on the cutting edge of the latest therapies and interact with your fellow ophthalmologists as you advance the field together. However, physicians and support staff who have been through a clinical trial process say there are many things to learn that differ greatly from how you carry out your everyday clinic. Sometimes you may have to learn an entirely new process, while other times you have to engage in a more intense version of a process that you already perform. In any case, veteran clinical investigators say it pays to go in with your eyes open. If you're thinking about embarking on the rewarding, challenging road of a clinical trial, here are tips and key issues to consider beforehand that will help you hit the ground running.

Staff Matters

Physicians who have conducted clinical trials say that the volume of documentation, organization and attention to detail involved in running a trial put new demands on your current staff, and almost certainly will require you to hire someone new, as well.

"Such tasks as fulfilling regulatory requirements, documenting things systematically, making sure everything is done by the book, ensuring that [Institutional Review Board] approval is secured correctly, making sure the patient has signed all the consent forms, ensuring the informed consent is properly documented, seeing to it that everything is dated and timed properly and that all personnel are correctly certified—that involves a tremendous amount of paperwork and is really a skillset unto itself," declares Sunir Garg, MD, an associate professor of ophthalmology at the Sidney Kimmel Medical College at Thomas Jefferson University. Dr. Garg has had experience as a principal investigator in several clinical trials in retina. "If an ophthalmologist were new to clinical trials, having a clinical trials coordinator or research personnel with some experience with research and regulatory documents isn't just helpful—it's critical," he says. "Each patient who comes in for the trial will fill two three-ring binders by the end of the study. If you try to do it all by yourself out of the gate, it will be very hard to do.

"Ideally, this clinical coordinator would start off with experience," Dr. Garg continues. "A person with strong leadership ability and clinical and regulatory experience can help train other good techs to become skilled

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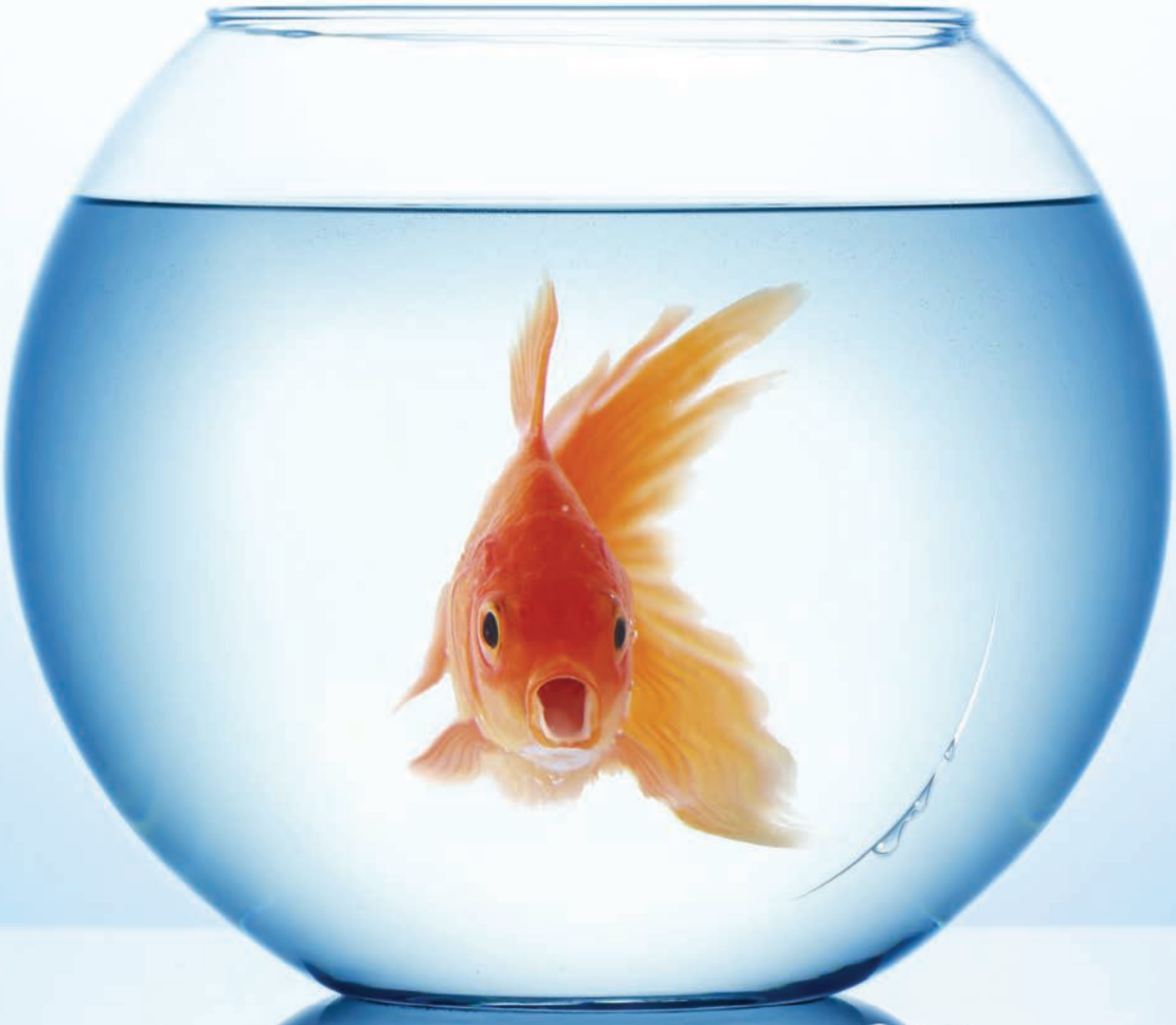

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research associates, as well. If you don't have someone who's been through the trial process before, many large metro areas have companies or individuals with clinical trial experience who are available as consultants. You can hire a consultant to get things up and running and he or she can then serve as a mentor to help train current members of your staff."

BethAnn Hibbert, clinical study coordinator for The Cornea & Laser Eye Institute in Teaneck, N.J., says first-time clinical investigators are also often caught flat-footed in terms of general staff training. "Another thing that's critical in terms of your documentation is staff training in good clinical practices that ensure subjects' safety and data integrity," she says. "It's important to understand that any staff involved in research that involves human subjects needs to undergo training. This training is sometimes available through your IRB but it can also be done online, as well. The service we use is the online Collaborative Institutional Training Initiative at the University of Miami. Additionally, this staff training needs to be updated every two to three years to ensure and document that all your staff involved with trials are adequately trained in subject protection. This training is important, and it's one of those things that may not be noted for physicians when they get into research, since some sponsors assume your staff has this training and may not make it known that it's needed."

This staff training touches on such things as the management of the informed consent process and protecting the privacy of subjects in terms of how their records are kept on-site. "The staff should have a working knowledge of the protocol, including any procedures that are going to be performed, the study's purpose, risks and benefits and subject selection criteria," says Mrs. Hibbert, who adds a tip for practices embarking on clinical trials: "What we do here is keep a kind of cheat sheet for each of the studies in which we're participating. These sheets have a breakdown of the inclusion/exclusion criteria and the diagnostic tests that are required at each visit, to ensure that we didn't overlook anything and to reinforce the staff training in the protocol, because sometimes it's a lot of detail to keep in your head."

Robert MacLaren, FRCOphth, FRCS

Gene therapy subject Richard Chandler discusses the details of his upcoming operation with surgeon Robert MacLaren at the University of Oxford.

Even though the physician may be used to anticipating problems and taking corrective action in the day-to-day clinic, experts say being in a clinical trial requires even more on this front. "If some of your study staff aren't experienced in performing clinical trials, it can help to simply develop a really strong manual of standard operating procedures that breaks down every aspect of the study," says Mrs. Hibbert. "It's kind of like a bible for you to follow. It covers everything, from the process of informed consent and the maintenance of the regulatory files to the process of reporting adverse events."

Though ophthalmologists may feel their staff is capable in a standard clinic, they have to drill deeper and make personnel decisions with a different set of criteria in mind when they get into a trial and have to assign staffing duties. "For the research staff, I'd choose some of the better, more detail-oriented techs," advises Dr. Garg. "Choose some folks who are maybe more curious in terms of new treatments and treatment options, because patients will bring up a lot of questions regarding the trial or diseases in general. Even after subjects have been in a trial for 18 months, they will sometimes ask, 'Why am I in this trial again?' Having a staff that's able to field such questions is helpful, not only for keeping patients motivated but also to free up the doctor so he can focus on patient care in the regular practice and not just in the research unit."

Patient Discussions

Doctors and trial experts say that many of the patient discussions before and during a clinical trial are different from those in the everyday clinic. The ophthalmologist has to have a different approach and thought process, because patients can be coming at the trial from different points of view, depending on their disease state and the efficacy of their current medications.

Robert MacLaren, FRCOphth, FRCS, professor of ophthalmology at the University of Oxford in the United Kingdom, is currently researching stem-cell therapy for retinal disease, an

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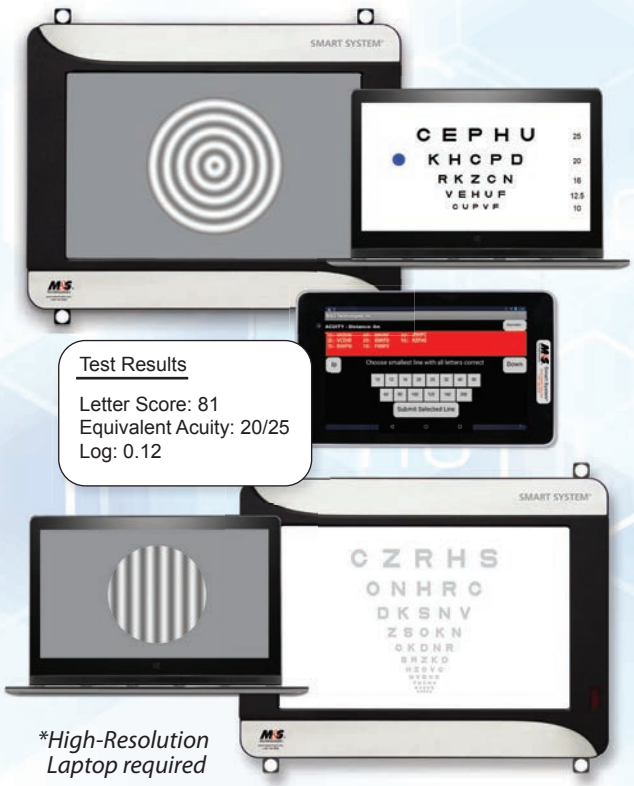

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electronic retinal implant and a new intraocular lens. He says it's important not to lose sight of the patient's perspective when embarking on a trial. "The patients are very important because you need to have the right people," he says. "If you're dealing with patients with incurable disease, which, unfortunately, I am on a daily basis, they are very keen to do almost anything to help, but can sometimes misinterpret 'trial' for 'treatment.' It's very important to remind patients at every stage of the trial that they're taking part in a clinical trial with unknown risks. It's not a treatment. Sometimes, we actually won't recruit a patient because even though he really wants to be in the trial, he doesn't understand what we're trying to achieve with it. He assumes it's actually a treatment."

Dr. Garg says you have to adjust your expectations as to who can enter a trial, because they're not always the same as who you'd treat in your office. "Whenever we're evaluating a patient for possible inclusion in a trial, such as a macular degeneration trial, I might think off-the-cuff, 'I have a million patients with macular degeneration, and it would be super easy to enroll any number of patients in a study,' " he says. "However, the studies often have specific inclusion/exclusion criteria, and when you begin to think about your patients in terms of those criteria, the number of patients who qualify for a study may be fewer than you originally thought. That's one difference between regular practice and a trial.

"A second difference is the time involved," Dr. Garg continues. "When you're in a really busy clinic and are two hours behind schedule, many times your general bias is to treat someone fast and get him on his way so you don't fall further behind. But when you're involved with a research trial, the discussion about the trial, getting patients interested in it, talking to them about potential pros and cons—that all takes time. In the middle of a busy day it can be hard to be motivated to have that discussion. However, if you're invested in the clinical trial process, that's the kind of conversation you need to have, because if you're not willing to take the time to discuss with patients why they might be interested in doing something different from the standard, they're simply not going to be interested in the trial."


Sunir Garg, MD

Be prepared for extensive, time-consuming testing in a clinical trial, experts say.

Physicians say motivation can be an issue for some patients, since they may not see the need to enter a trial. "If the patient has a disease from which he knows he's going to go blind, and you're known to be doing research in that field to try and find a treatment, he's going to be the most helpful and accommodating person you could ever want in a clinical trial," says Dr. MacLaren. "But if he has a condition that causes a problem with his eyesight but you're actually investigating him for some other reason, or he has no obvious benefit from what you're doing in the trial, then he won't be nearly as motivated. This is understandable, given the commitment he has to make. However, in such a case, there may be an indirect benefit to the patient that he may not be aware of, so you may wish to give him more information about that. For instance, in a glaucoma clinic, patients may be perfectly happy with the drop that they're on, but you want them to come in and try a new one in a study. They may not like this, and in response you can say, 'Well, the time may come in a few years when you've become tolerant or intolerant to your current drop, and we might need to change them round or add one to your current drop. By getting these new drops approved with the trial, it might help you indirectly later on.' They need to be aware of that possibility."

Mrs. Hibbert says the clinical trial informed consent process that these patient conversations comprise is much more involved than the consents doctors might be used to. "Something that's not necessarily obvious to a practice starting out in clinical trials is the need to document the whole informed consent process," she says. "With a clinical trial, it's not sufficient to just have an informed consent document that's signed; you also have to document the process that surrounds the signing. When you're in research, if you're subjected to an investigation by the FDA or a sponsor, the informed consent documentation is the first thing they look at. In practice, after a subject has had the opportunity to review a consent document, we'll document the discussion of the consent. A tip we learned from an internal audit is to have the subject read through the consent and then ask him, 'Why do you want to participate in this study?' and then document key parts of the discussion that follows. You want to document that the subject truly understands the nature of the research and that he has realistic expectations of what participation would provide for him."

Jumping Through the Hoops

As Dr. Garg alluded to in his discussion of the need for a clinical coordinator, one of the most pronounced differences between everyday practice and a clinical trial is the vast amount of contemporaneous documentation that's required. When this documentation is coupled with the rigorous regimentation of clinical trial patients'

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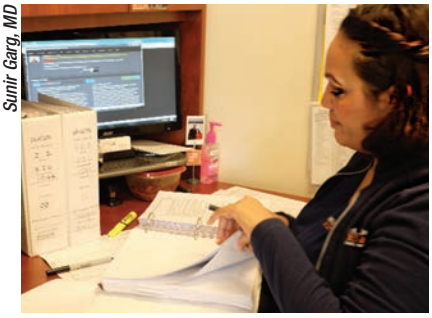
exams—which can last hours—the ophthalmologist is forced to adjust his approach to his daily schedule. Here are the key areas to be aware of:

• ***Regimented visits.*** "There are so many differences between a well-run clinical trial and just taking care of patients in terms of the amount of documentation and structure that are required," says Doug Koch, MD, professor and chair of ophthalmology at Baylor College of Medicine in Houston. "It affects everything, from scheduling to testing to patient questionnaires and so on, that it requires a very different mindset, and not a mindset that's always oriented toward the best patient care and certainly not toward efficiency. For instance, in a normal clinic protocol, if a patient is doing great one-day postop, you might just have him come back in four weeks. But what if the trial protocol requires patients to come back at two weeks? What do you do with that? A protocol may also require best-corrected acuity refraction for near, medium and distance, performed in various lighting conditions which you need to gauge, and performed by the same person each time, with a certain type of eye chart. That's way out of bounds for what a good-quality private practice situation—or any kind of private care—for a patient would entail.

"It's ultimately oriented toward patient care because you're trying to create new science, but it's a very different system for a practice," Dr. Koch continues. "However, if the trial starts cutting into efficiency and the care you're giving to other patients, everyone will start to bail on it psychologically and physically. You have to have a good system so you can fit the trial into your schedules and still retain the initial enthusiasm throughout the trial."

Teaneck, N.J., cornea specialist Peter Hersh, who has participated in a number of clinical trials and is currently the medical monitor for Avedro's U.S. cross-linking studies,



Sumir Garg, MD

It helps to have a trial coordinator to manage a study's heavy documentation.

says you may need to set aside an exam room that's specially prepared for your clinical study, as well as arrange for special staffing needs. "In refractive surgery studies, the patients require multiple refractions, masked refractions by masked observers who haven't seen the patient before and corneal topography," he says. "A lot of measurement needs to be done at each visit, so these tend to be lengthy visits. You need study personnel who know the patient and study personnel who don't know the patient, if you're dealing with masked observer requirements. At our site, our optometrist will do the masked refractions because he's otherwise not involved with the trial.

"Often, you'll need to dedicate a specific exam room with specific lighting conditions so you have reproducible tests," Dr. Hersh continues. "You can't take patients from one exam room to another because the lighting conditions can change from room to room."

Norfolk, Va., ophthalmologist Elizabeth Yeu, an assistant professor of ophthalmology at Eastern Virginia Medical School, says the extra testing required for trial patients may require you to re-evaluate your scheduling. "Setting aside a block of time for clinical trial patients can work," she says. "Also, you can have them come in on your clinical coordinator's schedule, so you can just go in and do your part. In one study, we had trial patients come in on a Saturday morning to enable us to complete all the exams at once."

Dr. MacLaren says, in some cases, you may need to dust off your negotiator hat. "I'm always negotiating with commercial sponsors and asking them to stop doing all of these tests," he says. "They always tend to overcook it because they don't realize how difficult it is to run everything on the ground. I joke with my staff that they overload the patients with so many investigations that when they leave the clinic someone here realizes he never checked the patient's visual acuity. It's always better to do fewer tests, generate test readings that are more reliable and have more motivated patients than to overload patients and your staff."

Also, since extra staff usually needs to be on hand to perform all the necessary tests on trial patients, if such a patient cancels his appointment it deserves special attention. "Trial patients will have a time window when they can come in for a follow-up visit," says Dr. Hersh. "You need to train your front-desk staff to make sure these patients get in within that window. They can't just cancel an appointment and reschedule it whenever; the front desk needs to be able to recognize that this is a study patient that has a limited window, and the patient needs to be contacted and an appropriate exam date needs to be set up. Essentially, the entire office needs to buy into this and understand that these subjects are different from our standard patients."

• ***Extensive documentation.*** In addition to the obvious need to document patient exam results, the ancillary documentation requirements might surprise the first-timer. "Any investigational product on-site has to be carefully monitored," explains Mrs. Hibbert. "Early on, we weren't aware that we had to document the fact that we were maintaining temperature logs for trial drugs. You can't just write that the drug's temperature range is normal, you need trackable records of the temperature showing that it's been maintained throughout the day.

Shipments of products have to be carefully logged, and any shipping invoices that come with the product have to be retained in the regulatory binder. You have to document your staff's training, and any changes in study staff and the fact that they were trained also need to be documented. This way, if you have to go back and look at something in the binder, the whole process reads like a story."

• ***Adverse event reporting.*** Physicians say ferreting out adverse events and properly reporting them can be a challenge at first. "Understanding how adverse events are reported is quite complicated," says Dr. MacLaren, who notes that this particular function took the most getting used to when he did his first clinical study. "You have a certain amount of time to report an adverse event, and requirements regarding who you report them to. If you have an adverse event, you need to know quickly what to do. That's probably one of the most complicated parts of the process: knowing what to do if a patient suddenly reports an adverse event or gets admitted to hospital.

"You have to report all adverse events," Dr. MacLaren continues, "because you don't know if that particular adverse event is related to the drug or not. The only way you can tell that is by repeatedly seeing more adverse events that are similar coming up amongst study patients. A good example is ciprofloxacin. No one could have assumed that someone straining his Achilles tendon was due to him taking an antibiotic. But it was only when several instances of Achilles tendon injuries occurred that clinicians realized that this was something that was related to the drug. It's now a known adverse reaction to ciprofloxacin. In ophthalmology, we really don't have such an issue—but you never know. So you document it."

Mrs. Hibbert says you sometimes have to fish for an adverse event that might turn out to be relevant. "You and your staff have to be of the mindset to ask the subject, 'How are you feeling? Has anything changed since you were here last?' " she says. "The subject won't necessarily report something to you because he might not think it's related to the treatment, so you have to prompt him. Ask about patients' general health and any medication that might be new. These may prompt red flags for reportable events."

In the end, Dr. MacLaren says proper preparation, mentally and in your facility, can make the most of the clinical trial experience. "There are those patients who have no treatment available for their disease," he says. "They are going blind and you can offer them a trial that may help them preserve their vision, and this is a tremendous opportunity for them to get involved with. First, however, you have to be motivated by the research and the notion of understanding the disease better and helping your patients. Research is a long-term treatment, not a short-term one, so you need to ask yourself: Do you really want to do this?" REVIEW

Treatment Options with Amniotic Membrane

Michelle Stephenson, Contributing Editor

AM can be used successfully as either a graft or a bandage.

Amniotic membrane has been used in ophthalmology for two decades for the treatment of a number of conditions, such as cicatricial pemphigoid and Stevens-Johnson syndrome; pterygium; persistent epithelial defects with ulceration; conjunctival surface reconstruction; and ocular surface reconstruction in patients with chemical and thermal burns. The membrane comprises three layers: epithelium; basement membrane; and stroma. AM has anti-inflammatory and anti-microbial properties and low immunogenicity, which can be beneficial to the eye. The possibility of freezing and preserving sections of the membrane has further expanded its clinical use.

"Its usage is increasing and can be divided into two categories," says Scheffer Tseng, MD, PhD, medical director of the Ocular Surface Center in Miami. "It can be used as a surgical graft, where the tissue is integrated into the host, and it can be used as a biological bandage. When used as a bandage, the tissue will not be integrated into the host. Instead, it will just be placed as a temporary dressing."

When used as a graft, amniotic membrane provides the scaffold for re-epithelialization. "In other words, it is the foundation that skin can grow onto in cases where tissue has been lost for whatever reason," says Darren Gregory, MD, an associate professor of ophthalmology at the University of Colorado School of Medicine. "It also provides an anti-inflammatory and anti-scarring effect that minimizes the buildup of scar tissue. The hope is to generate new tissue growth rather than just filling in the injured areas with scar tissue, because scar tissue can inhibit proper lid movement and movement of tears across the eye."

The anti-inflammatory effect is especially important in cases of chemical burn or in patients with Stevens-Johnson syndrome. "In these cases, there is often intense inflammation that lasts two to three weeks," Dr. Gregory says. "After it subsides, we can see that a lot of skin has been lost on the surface of the eye, and those areas fill in with scar tissue. Once that scarring has set in, it's nearly impossible to get rid of and is a real challenge for patients and doctors."

When used as a graft, AM is typically glued or sutured in place, and epithelium is expected to grow over it. When it is used as a bandage, the epithelium is expected to grow in underneath it rather than over the top. As healing progresses, the membrane gets sloughed off like a scab. When used as a bandage, it tends to degrade over the course of seven to 14 days.

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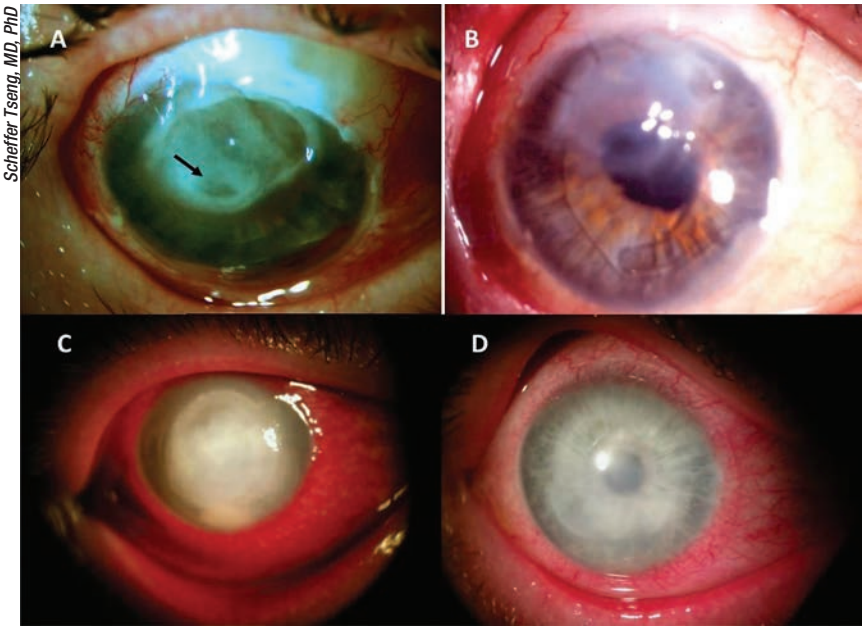

Scheffer Tseng, MD, PhD

Figure 1. Amniotic membrane can be used as a graft (A & C are before placement, and B & D are after) or bandage via Prokera. The top panel is an eye suffering from corneal ulcer and descemetocele (arrow) following a glaucoma shunt procedure and pseudomonas infection. After multiple layers of cryopreserved AM, the eye regained vision of 20/70 seven months later. The bottom panel is an eye developing infective keratitis following photorefractive keratectomy for myopia with a large corneal epithelial defect, stromal infiltration and hypopyon despite topical fortified antibiotics. Prokera was placed to reduce inflammation and promote healing to regain 20/50 vision in two months.

Uses

"When amniotic membrane was first used in ophthalmology in the late '90s and became commercially available, people were trying it for everything under the sun," Dr. Gregory says. "I use it with some regularity because it does help with Stevens-Johnson syndrome. It is being used more and more in cases where there is a non-healing epithelial defect on the cornea, which can happen for a variety of reasons, but is usually either associated with corneal stem cell failure or a neurotrophic ulcer where the cornea has lost sensation because of a neurosurgical procedure, damage to the nerves from viruses, or a tumor that has damaged the trigeminal nerve, which provides sensation to the cornea."

It has been shown to be successful in treating a variety of conditions. For example, in a study conducted in Italy with 12 years of follow-up, 5,349 surgical procedures were successfully performed using amniotic membrane patches.[1] Conditions treated were corneal ulcers including neurotrophic keratitis (2,430); keratitis/endophthalmitis (363); pterygium (343); post-keratoplasty, glaucoma or cataract (339); chemical trauma (332); bullous keratopathy (265); neoplasm of the ocular surface (239); reconstruction of the conjunctiva and fornix (154); corneal degeneration (123); recurrent epithelial erosion (109); primary and secondary limbal stem cell deficiency (78); mucous membrane pemphigoid (59); dystrophy (58); mechanical trauma (25); chronic Stevens-Johnson syndrome or Lyell's syndrome (20); reconstruction of the anophthalmic cavity (17); physical trauma (16); eyelid reconstruction (11); dysfunctional tear syndrome (9); and other (359).

The success or failure of the treatment was established with one year of postoperative follow-up. Success was determined based on the scope of surgery and the presence of one or more of the following criteria: resolution of inflammation; relief of symptoms; restoration of regular and stable corneal epithelium; and restoration of the structural integrity of the eye.

Partial success was defined as attainment of only two of the above criteria. Failure was defined as the absence of all of the above criteria. Conditions with a 100 percent success rate included: corneal ulcers including neurotrophic keratitis; post-keratoplasty, glaucoma or cataract; bullous keratopathy; corneal degeneration; dystrophy; mechanical trauma; reconstruction of the anophthalmic cavity; eyelid reconstruction; and dysfunctional tear syndrome.

AM treatment failed in the following conditions: mucous membrane pemphigoid (79 percent); chronic Stevens-Johnson or Lyell's syndrome (62 percent); other (54 percent); reconstruction of the conjunctiva and fornix (47 percent); neoplasia of the ocular surface (33 percent); primary and secondary limbal stem cell deficiency (32 percent); physical trauma (30 percent); chemical trauma (24 percent); pterygium (8 percent); and recurrent epithelial erosions (5 percent).

The study found that the therapeutic effects after treatment were variable and were related to the type of pathological condition treated. According to the study results, "The best results were obtained when the membrane was used to control inflammation and pain. In general, a higher success rate was attained when membrane transplantation was performed for its key therapeutic indication, i.e., persistent epithelial defect with stromal ulceration in patients with functional limbal stem cell deficiency. In such cases, the procedure was able to promote re-epithelialization in the majority of the pa-

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tients and the restoration of a stable corneal epithelium in ulcers caused by different pathological conditions."

The amniotic membrane was successfully incorporated into the corneal tissue in some patients, and membrane fragments remained visible for several days after surgery. In these cases, the membrane displayed its scaffold-like properties, as mentioned above, and provided a healthy and intact basal membrane on which the patient's cells were able to proliferate.

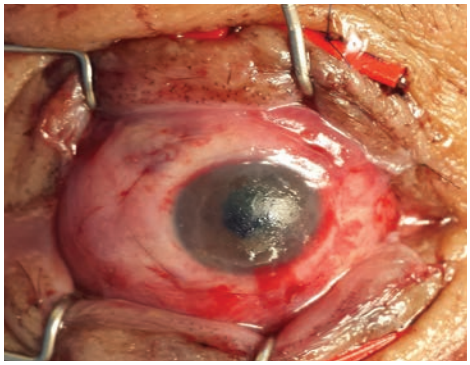

Figure 2. Cryopreserved amniotic membrane covering the entire ocular surface in acute toxic epidermal necrolysis with severe eye inflammation and epithelial sloughing.

Thomas John, MD, in practice in Chicago, says AM is now the standard of care for the treatment of acute Stevens-Johnson syndrome. Additionally, he has found that amniotic membrane in the treatment of acute toxic epidermal necrolysis preserves normal ocular and eyelid surfaces and may prevent blindness. Dr. John along with his co-authors published the first two cases of toxic epidermal necrolysis that were treated with amniotic membrane transplantation and described the surgical techniques involved.[2] The first was a 6-year-old boy with severe toxic epidermal necrolysis that developed after being treated with trimethoprim and sulfamethoxazole for chronic otitis media. In this patient, both eyes and eyelids were affected. He underwent bilateral lysis of symblepharon and all adhesions. He then underwent bilateral amniotic membrane transplantation to the entire ocular surface, except the cornea. Because of the patient's loss of eyelid skin, transplantation of amniotic membrane was performed on all four eyelids, and transplantation of strips of amniotic membrane at the eyelid margins was required. Thirteen years after bilateral ocular surgery, there was no symblepharon, good ocular surface wetting, and 20/20 uncorrected bilateral vision.

The second patient was an 8-year-old girl with severe toxic epidermal necrolysis associated with mycoplasma pneumonia. She had bilateral, diffuse keratoconjunctivitis, diffuse corneal epithelial defects and bilateral symblepharon. Bilateral amniotic membrane transplantation was performed using a symblepharon ring in the left eye. In this case, amniotic membrane transplantation protected both ocular surfaces and prevented conjunctival contracture without adhesion of the eyelids to the ocular surface. Central vision was preserved, and there was minimal peripheral corneal vascularization and mild conjunctival scarring of the tarsal conjunctival surface 34 months postoperatively.

"In these cases, if you don't use amniotic membrane in the first 10 to 14 days, the eye can be potentially lost over time," Dr. John says. "It also works well to treat corneal perforation and for other corneal restoration procedures, and it can be easily performed in most cases under topical anesthesia."

However, it should be noted that, although it can be used to treat the conditions noted above, it is not ideal for all cases. According to Dr. Gregory, although AM is commonly used for pterygium surgery, he does not use it in primary cases of pterygium excision. The benefit of amniotic membrane in these patients is that it is a shorter procedure and is less technically demanding for the surgeon. The trade-off is that the recurrence rate is higher when AM is used.

A recently published study identified risk factors for reproliferation of pterygial tissue after excision and graft surgery.[3] The study included 130 eyes, and recurrence was observed in 20 eyes. The study found that age younger than 40 years and AM graft instead of conjunctival autograft were statistically significant risk factors for recurrence. Additionally, the study found that intraoperative mitomycin C application decreased the rate of recurrence.

Cryopresered vs. Dehydration

Several processing methods are used to preserve the membranes for in-office use. While fresh amniotic membrane has been shown to be effective in clinical applications, its use presents a significant risk of disease transmission. For this reason, processing methods that preserve its biological effectiveness while ensuring safety are important. One method is cryopreservation, which involves quickly freezing the tissue. It was "developed to maintain the structural integrity of the extracellular matrix and the endogenous biochemical functions of the native amniotic membrane and umbilical cord tissues."[4] In comparison, dehydration is a much harsher process and has been shown to cause protein denaturation, loss of function and irreparable damage to the ultrastructure and material properties of the tissue.

Dr. Tseng and his colleagues recently evaluated how these two different processing methods affect the structural integrity and biological composition of key signaling molecules within amniotic membrane and umbilical cord tissues.[4] In this study, they directly compared cryopreserved amniotic membrane and umbilical cord tissues with dehydrated amniotic membrane/chorion tissue using biochemical and functional assays including histological and histochemical staining, bichincho-

ninic acid, agarose gel electrophoresis, western blot, ELISA and proliferation and cell death assays. The researchers found that cryopreservation retains the native architecture of the amniotic membrane/umbilical cord extracellular matrix and maintains the quantity and activity of key biological signals present in fresh amniotic membrane/umbilical cord, including high molecular weight hyaluronic acid, heavy chain-HA complex and pentraxin 3. The dehydrated tissues were found to be structurally compromised and almost completely lacked these crucial components.

Cryopreserved tissue requires refrigeration and has a limited shelf-life. "If it is in a bone freezer where it is -70°, it can be kept for up to two years, but some specialized freezers are required," says Dr. Gregory. "Then, there is the freeze-dried or dehydrated form, which doesn't require any specialized refrigeration. It can just be kept on the shelf and used as needed. You just rehydrate it. The concern with this form is whether it really retains all of the hyaluronic acid with a heavy side-chain protein that provides the anti-inflammatory effect. The sense is that the dehydrated form doesn't retain as much anti-inflammatory effect."

Dr. John calls the future of amniotic membrane transplantation bright. "In terms of the indications, amniotic membrane covers a huge area that encompasses the cornea, conjunctiva and the eyelids," he says. "Patients, especially those being implanted with a premium intraocular lens, have high expectations, including a high quality of vision, fewer corneal aberrations and faster visual recovery. An optimal visual outcome depends on the ocular surface. Ocular surface health has really come to the forefront in ophthalmology in recent times, and amniotic membrane, especially an in-office Prokera type of device, is one way to augment and improve the ocular surface along with appropriate tear substitutes before performing cataract surgery with premium IOL or refractive surgery, especially in patients who have severe dry eye or ocular surface-compromising conditions." REVIEW

Dr. Gregory has no financial interest in any companies that produce AM. Drs. Tseng and John have a financial interest in Bio-Tissue Inc.

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Endothelial Regeneration: Help Is on the Way

William C. Stewart, MD, Las Vegas, Lindsay A. Nelson, Goose Creek, S.C., and David D. Eveleth, PhD, San Diego

New therapies may replace corneal transplantation as the treatment of choice for patients with endothelial cell dystrophy or dysfunction.

Corneal endothelial disease is a serious sight-threatening and debilitating condition. The corneal endothelium is a single layer of delicate cells on the inner aspect of the cornea. Although their complete function probably remains unknown, their major role in the eye appears to be to maintain a dry cornea, relative to surrounding tissues, which allows for the cornea's transparency and useful visual function.

Typically, a healthy cornea has about 3,000 endothelial cells/mm^2 in the central area.[1] CECs, or corneal endothelial cells, unfortunately, are lost with age. This natural reduction rarely presents a clinical problem unless the loss of cells is unusually aggressive, such as in Fuchs' dystrophy, or there is excess cell loss that might occur with trauma, typically surgical.

As endothelial cell loss worsens, the remaining cells can typically spread and cover the exposed portions of the overlying cornea to maintain visual function. However, if the cell density decreases to about 400 cells/mm^2 then insufficient cells may be available to effectively keep the cornea dry.[2] Corneal edema then may occur, with associated visual loss. In addition, epithelial edema may occur, resulting in a painful, debilitating foreign body sensation. Unfortunately, CECs do not naturally regenerate. When lost, they are gone forever.

The only routine treatment available for edema resulting from endothelial cell loss is corneal transplantation. While this procedure may be effective in regaining some measure of sight and relieving pain the post-surgical follow-up process is long and difficult, with some patients not achieving their best vision for some time after transplant. Further, ultimate graft failure may occur necessitating re-grafting.

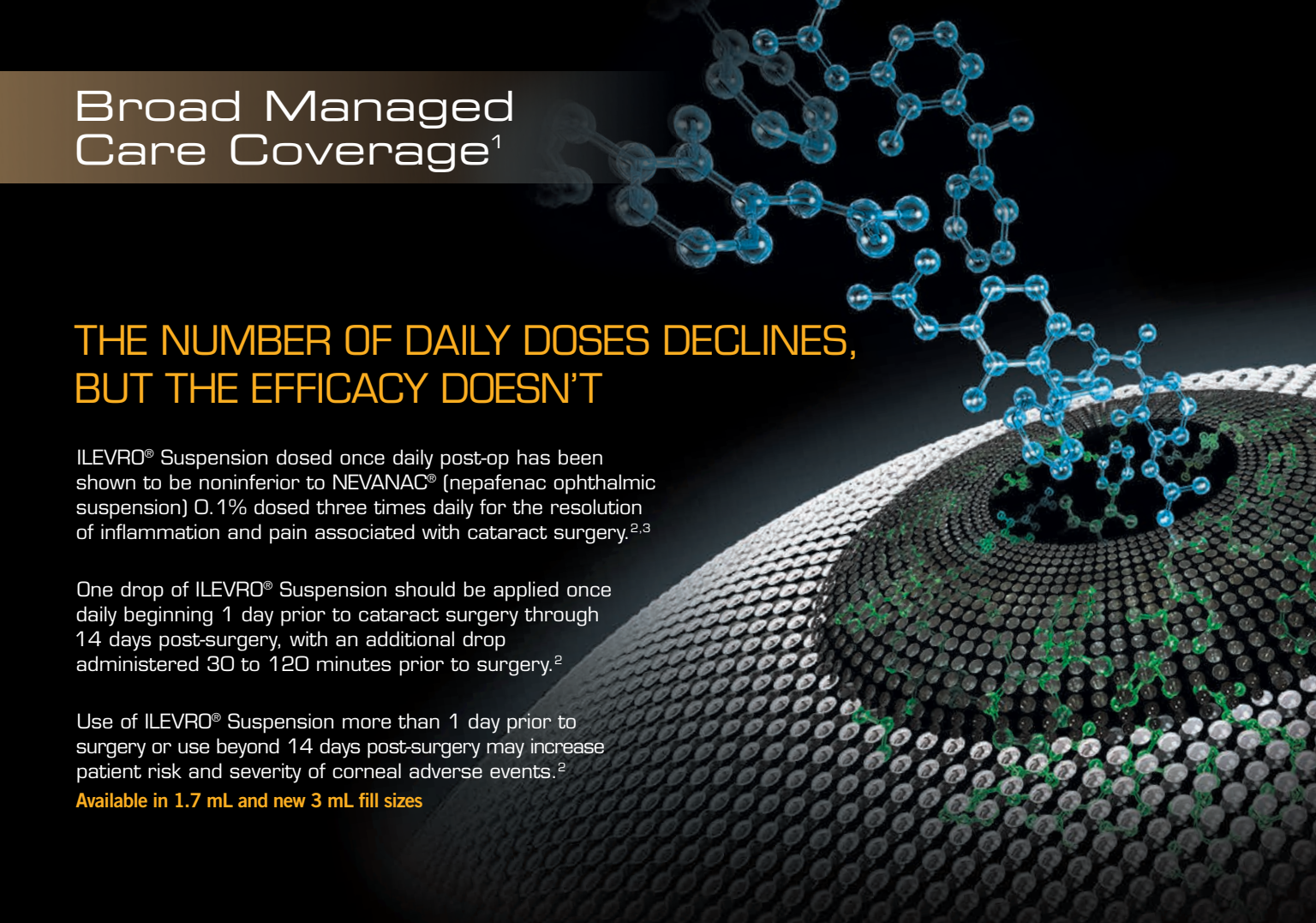
Survey data accumulated by Dr. William C. Stewart (internal data, PRN PharmaFarm, LLC) has noted that ophthalmologists perceive a need for a corneal regeneration product not just for Fuchs' dystrophy, but also for endothelial cell loss associated with age and with surgical cell loss in complicated cases *(See Table, next page).*

To date, no pharmaceutical therapy has been approved by the Food and Drug Administration to treat this condition, either by preventing CEC loss or by regenerating the CECs to avoid transplant surgery. Fortunately, several ophthalmic start-up and mid-size companies have potential pharmaceutical therapies in development that when available could greatly help patients and change how corneal failure is treated.

The purpose of this article is to dis-

This article has no commercial sponsorship.

Broad Managed Care Coverage[1]



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One drop of ILEVRO® Suspension should be applied once daily beginning 1 day prior to cataract surgery through 14 days post-surgery, with an additional drop administered 30 to 120 minutes prior to surgery.[2]

Use of ILEVRO® Suspension more than 1 day prior to surgery or use beyond 14 days post-surgery may increase patient risk and severity of corneal adverse events.[2]

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INDICATIONS AND USAGE

ILEVRO® Suspension is a nonsteroidal, anti-inflammatory prodrug indicated for the treatment of pain and inflammation associated with cataract surgery.

IMPORTANT SAFETY INFORMATION

Contraindications

ILEVRO® Suspension is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formula or to other NSAIDs.

Warnings and Precautions

- Increased Bleeding Time – With some nonsteroidal anti-inflammatory drugs including ILEVRO® Suspension there exists the potential for increased bleeding time. Ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphema) in conjunction with ocular surgery.
- Delayed Healing – Topical nonsteroidal anti-inflammatory drugs (NSAIDs) including ILEVRO® Suspension may slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- Corneal Effects – Use of topical NSAIDs may result in keratitis. In some patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use.

  Patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

  Use more than 1 day prior to surgery or use beyond 14 days post-surgery may increase patient risk and severity of corneal adverse events.
- Contact Lens Wear – ILEVRO® Suspension should not be administered while using contact lenses.

Adverse Reactions

The most frequently reported ocular adverse reactions following cataract surgery occurring in approximately 5 to 10% of patients were capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation.

For additional information about ILEVRO® Suspension, please refer to the brief summary of prescribing information on adjacent page.

References: 1. Formulary data provided by Pinsonault Associates, LLC, PathfinderRx, June 2014. **2.** ILEVRO® Suspension prescribing information. **3.** NEVANAC® Suspension prescribing information.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE
ILEVRO® Suspension is indicated for the treatment of pain and inflammation associated with cataract surgery.

DOSAGE AND ADMINISTRATION
Recommended Dosing
One drop of ILEVRO® Suspension should be applied to the affected eye one-time-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. An additional drop should be administered 30 to 120 minutes prior to surgery.

Use with Other Topical Ophthalmic Medications
ILEVRO® Suspension may be administered in conjunction with other topical ophthalmic medications such as beta-blockers, carbonic anhydrase inhibitors, alpha-agonists, cycloplegics, and mydriatics. If more than one topical ophthalmic medication is being used, the medicines must be administered at least 5 minutes apart.

CONTRAINDICATIONS
ILEVRO® Suspension is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formula or to other NSAIDs.

WARNINGS AND PRECAUTIONS
Increased Bleeding Time
With some nonsteroidal anti-inflammatory drugs including ILEVRO® Suspension, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery. It is recommended that ILEVRO® Suspension be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Delayed Healing
Topical nonsteroidal anti-inflammatory drugs (NSAIDs) including ILEVRO® Suspension, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Corneal Effects
Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs including ILEVRO® Suspension and should be closely monitored for corneal health. Postmarketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Postmarketing experience with topical NSAIDs also suggests that use more than 1 day prior to surgery or use beyond 14 days post surgery may increase patient risk and severity of corneal adverse events.

Contact Lens Wear
ILEVRO® Suspension should not be administered while using contact lenses.

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

Ocular Adverse Reactions
The most frequently reported ocular adverse reactions following cataract surgery were capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation. These events occurred in approximately 5 to 10% of patients.

Other ocular adverse reactions occurring at an incidence of approximately 1 to 5% included conjunctival edema, corneal edema, dry eye, lid margin crusting, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, photophobia, tearing and vitreous detachment.

Some of these events may be the consequence of the cataract surgical procedure.

Non-Ocular Adverse Reactions
Non-ocular adverse reactions reported at an incidence of 1 to 4% included headache, hypertension, nausea/vomiting, and sinusitis.

USE IN SPECIFIC POPULATIONS
Pregnancy
Teratogenic Effects.
Pregnancy Category C: Reproduction studies performed with nepafenac in rabbits and rats at oral doses up to 10 mg/kg/day have revealed no evidence of teratogenicity due to nepafenac, despite the induction of maternal toxicity. At this dose, the animal plasma exposure to nepafenac and amfenac was approximately 70 and 630 times human plasma exposure at the recommended human topical ophthalmic dose for rats and 20 and 180 times human plasma exposure for rabbits, respectively. In rats, maternally toxic doses ≥10 mg/kg were associated with dystocia, increased postimplantation loss, reduced fetal weights and growth, and reduced fetal survival.

Nepafenac has been shown to cross the placental barrier in rats. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ILEVRO® Suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic Effects.
Because of the known effects of prostaglandin biosynthesis inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of ILEVRO® Suspension during late pregnancy should be avoided.

Nursing Mothers
ILEVRO® Suspension is excreted in the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ILEVRO® Suspension is administered to a nursing woman.

Pediatric Use
The safety and effectiveness of ILEVRO® Suspension in pediatric patients below the age of 10 years 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
Nepafenac has not been evaluated in long-term carcinogenicity studies. Increased chromosomal aberrations were observed in Chinese hamster ovary cells exposed *in vitro* to nepafenac suspension. Nepafenac was not mutagenic in the Ames assay or in the mouse lymphoma forward mutation assay. Oral doses up to 5,000 mg/kg did not result in an increase in the formation of micronucleated polychromatic erythrocytes *in vivo* in the mouse micronucleus assay in the bone marrow of mice. Nepafenac did not impair fertility when administered orally to male and female rats at 3 mg/kg.

PATIENT COUNSELING INFORMATION
Slow or Delayed Healing
Patients should be informed of the possibility that slow or delayed healing may occur while using nonsteroidal anti-inflammatory drugs (NSAIDs).

Avoiding Contamination of the Product
Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Use of the same bottle for both eyes is not recommended with topical eye drops that are used in association with surgery.

Contact Lens Wear
ILEVRO® Suspension should not be administered while wearing contact lenses.

Intercurrent Ocular Conditions
Patients should be advised that if they develop an intercurrent ocular condition (e.g., trauma, or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multi-dose container.

Concomitant Topical Ocular Therapy
If more than one topical ophthalmic medication is being used, the medicines must be administered at least 5 minutes apart.

Shake Well Before Use
Patients should be instructed to shake well before each use. U.S. Patent Nos. 5,475,034; 6,403,609; and 7,169,767.

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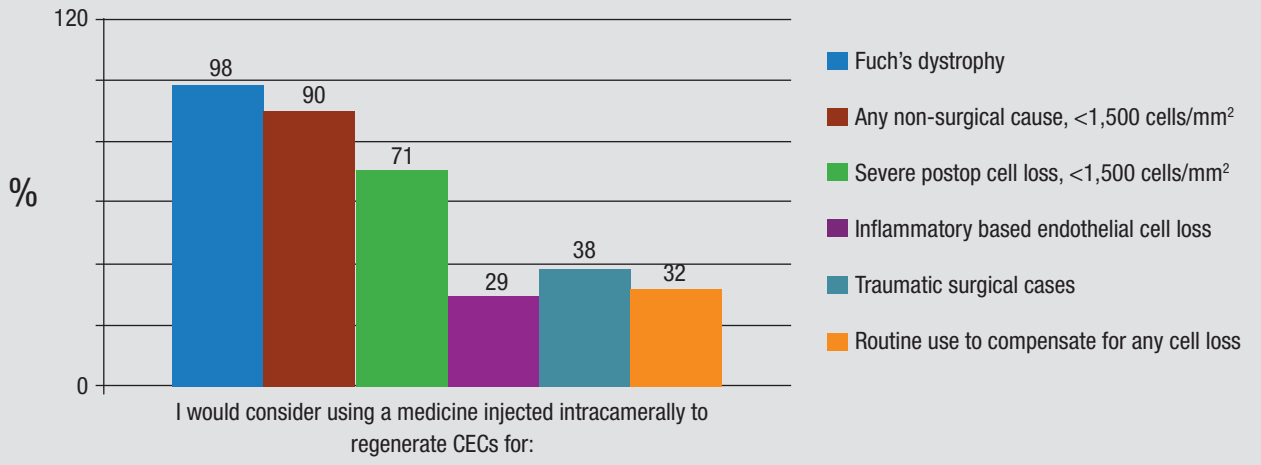
U.S. Ophthalmologists' Potential Clinical Use of an Injectable Corneal Regeneration Product (n=56)



cuss in brief the current status of the development of new pharmaceutical products to treat corneal endothelial degeneration.

Engineered FGF–1 (Trefoil)

• ***Background.*** Engineered fibroblast growth factor (eFGF, Trefoil Therapeutics LLC, San Diego) is a biologic derivative of the FGF hormone that occurs naturally in the body. There are 22 different naturally occurring FGFs. They have been developed for prior indications by several different companies including:

• Kepivance (palifermin, FGF-7) is approved in the United States to treat mucositis (manufactured by Swedish Orphan Biovitrum AB, Stockholm, Sweden).

• The wild type FGF-1 was clinically tested in dermal wound healing by Merck.[3]

• Fiblast Spray (trafermin, FGF-2) is approved in Japan and China for wound healing and clinical trials are ongoing for indications in periodontis and bone fractures.

• FGF-2 has been clinically tested as an eye drop.[4]

Recently, Michael Blaber, PhD, working from his laboratory at Florida State University, engineered a series of new FGF-1s (eFGF-1) for the indication of both wound healing and corneal endothelial regeneration.

• ***Mechanism.*** FGF-1, also known as acidic FGF (aFGF), is a potent and broad-spectrum mitogenic, chemotactic and survival factor for a variety of cells that can promote repair and regeneration of damaged tissues. FGFs function by binding to high affinity transmembrane FGF receptors.

Engineered FGF-1 possesses the following potential clinical advantages:

• increased potency for stimulation of CEC proliferation;

• enhanced stability; and

• prolonged tissue binding, even to dystrophic tissue.

• ***Efficacy.*** In *in vitro* experiments using rabbit and human CECs, eFGF-1 stimulated proliferation with EC50's up to 100-fold lower than unmodified (wild type) FGF-1. Preliminary studies have confirmed the ability of eFGF-1 to accelerate corneal endothelial regeneration in the cryogenic injury model in the rabbit *(See Figure 1, p. 78)*.

Further research is ongoing to better quantitate the efficacy of eFGF-1 and to determine proper dosing levels (internal data, Trefoil Inc.).

• ***Adverse events***. Hypothetical adverse events based on the pharmacology of eFGF-1 include angiogenesis and elevation of intraocular pressure due to proliferation within the trabecular meshwork. To date these effects have not been observed in any of the *in vivo* ocular dosing development programs.

Stem-Cell-Based Regeneration

• ***Background.*** JCR Pharmaceuticals Co. (Hyogo, Japan) has developed a novel platform based on human mesenchymal stem cells (MSCs) which has progressed to the clinical study phase for at least one indication. MSCs developed by JCR are produced from bone marrow aspirates collected from healthy donors. These cells may be administered to patients without donor-recipient human leukocyte antigen (internal data, JCR Pharmaceuticals).

In addition, JCR is cooperating with the Japanese government to develop a medicine using culture-expanded human corneal endothelium to regenerate this tissue layer. In this project, gene recombinant technology is used to cultivate the CECs. As such, this technique may be useful for the early treatment of patients who otherwise would need a corneal transplant (internal data, JCR Pharmaceuticals).

• ***Safety.*** No safety issues have

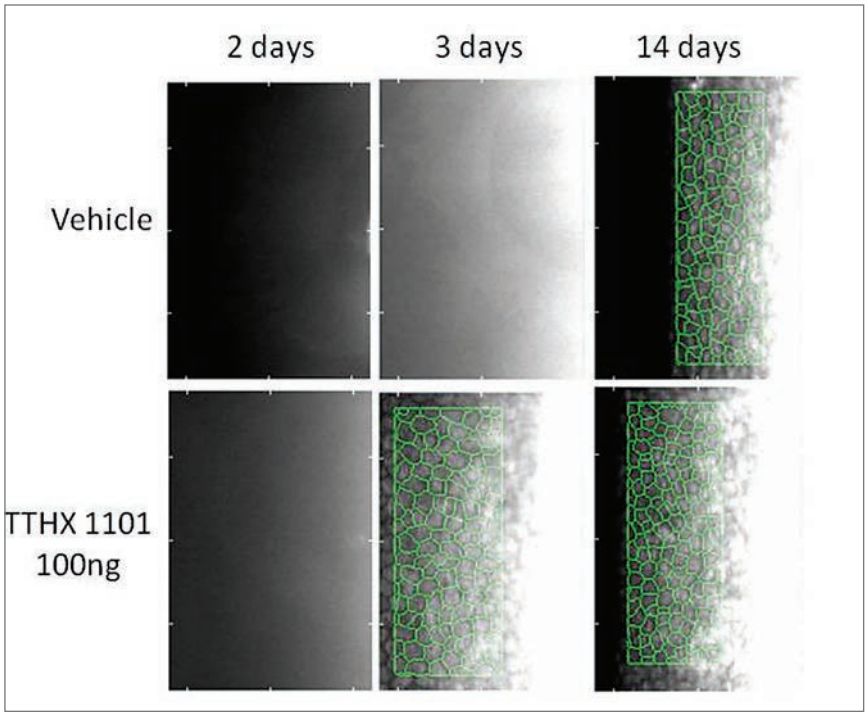


Figure 1. Rabbits were subjected to corneal cryogenic injury and treated with a single intracameral injection of eFGF-1 TTHX 1101 one hour post-injury. Contralateral eyes were treated with vehicle only. Monitoring of endothelial regeneration via specular microscopy showsaccelerated regeneration of the endothelium in treated animals.

been noted to our knowledge directly from transplanting stem cells to regenerate CECs. However, generally, stem cells may possess features similar to cancer cells including: long duration; relative apoptosis resistance; and replicative capacity for extended periods of time. In addition, similar growth regulators and control mechanisms are involved in cancer and stem cell maintenance. Therefore, stem cells potentially may undergo malignant transformation which is often believed to be a key obstacle to their safe use.[5]

ROCK Inhibitors

• ***Background.*** A completely different therapeutic strategy from JRC is exemplified by a new study testing Rho-associated kinase inhibitors, or ROCK inhibitors, as stimulators of CECs.[6] Although the mechanism has not been clearly established, this approach may inhibit endogenous pathways that limit CEC growth by altering cell adhesion and attenuating cell-contact growth inhibition.

In addition, apoptosis may play an important role in the pathological condition of corneal endothelium, such as in Fuchs' dystrophy or post-keratoplasty. ROCK inhibitors might suppress CEC apoptosis caused by myosin light chain phosphorylation.

• ***Safety.*** Safety issues related to the use of ROCK inhibitors to regenerate CECs are unknown. From ongoing clinical trials with topical formulations for glaucoma the major adverse events of most, if not all, ROCK inhibitors are ocular hyperemia and inflammation. This effect most likely results because of their vasodilator activity. *(Asada K, et al. IOVS 2002;55:ARVO E-Abstract 2052) (Kakutani K, et al. IOVS 2002;55:ARVO E-Abstract 2055) (Kusakabe A, et al. IOVS 2002;55:ARVO E-Abstract 2058)*

Magnetic Cell Technologies

• ***Background.*** Emmetrope Ophthalmics Inc. (Key Biscayne, Fla.) has developed a method for identifying, isolating and/or enriching human CECs. This method comprises a positive selection process in which a cell population containing human CECs is selectively bound with either a positive or negative affinity reagent relative to cells other than human CECs (e.g., corneal keratocytes, etc.)[7]

• ***Efficacy.*** Initial data has shown positive efficacy results. Twenty-two rabbit corneas underwent central endothelial debridement. *(Kunzevitzky NJ, et al. IOVS 2002;55:ARVO E-Abstract 2040)* Eyes treated with human CEC recovered faster than controls (treated with balanced saline solution+). At 28 days, the thickness of human CEC-injected corneas was comparable to that of the intact contralateral eye while control corneas remained thicker. Histology with immunofluorescence showed clumps of donor cells repopulating the stripped endothelial regions. This pilot study revealed that injection of magnetic human CECs may be a safe therapy for the treatment of corneal endothelial dysfunction.

• ***Safety.*** No acute inflammatory response was observed in any of the treated corneas. Cancer is the prevailing safety issue associated with stem cells and this adverse event is described more in detail under JCR Pharmaceuticals, above.

Inflammation Modulators

A number of studies have demonstrated that classical antioxidants can mitigate CEC loss under conditions of stress, even in cells from

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Fuchs' dystrophy subjects.

• ***Sulforaphane*** (unsponsored). Sulforaphane (SFN), a naturally occurring isothiocyanate found in cruciferous vegetables, has been shown to activate endogenous anti-oxidative protective pathways.

Interestingly, SFN acts on a specific pathway (the Nrf2) that is known to be down-regulated in Fuchs' dystrophy. Treatment of *ex vivo* corneas from Fuchs' dystrophy subjects with SFN prior to peroxide exposure normalized the antioxidant response, suggesting that this or similar compounds may be a potential treatment for prevention of CEC loss.

• ***Efficacy.*** A study published in 2013 examined the effects of SFN in Fuchs' dystrophy. After pretreatment with SFN, oxidative stress was induced with tert-Butyl hydroperoxide (tBHP) in *ex vivo* Fuchs' dystrophy specimens.[8] Pretreatment with SFN decreased CEC apoptosis by 55 percent in the unstressed group and by 43 percent in tBHP-treated specimens. These results suggest that targeting Nrf2-ARE pathway may arrest degenerative cell loss seen in Fuchs' dystrophy.[8]

RTA 408

Reata Pharmaceuticals Inc., (Irving, Texas) is developing several novel classes of drugs with transcriptional activity called antioxidant inflammation modulators (AIMs), which also activate the biological transcription factor Nrf2. This protein controls the body's production of hundreds of antioxidative and cytoprotective molecules and is associated with protection against a broad range of diseases involving inflammation and oxidative stress (internal data, Reata Pharmaceuticals).

RTA 408 is a member of the synthetic oleanane triterpenoid class of compounds known to potently activate the cytoprotective transcription factor Nrf2. This factor is known to be down-regulated in Fuchs' dystrophy. Reata's product RTA 408 has been formulated into a sterile ophthalmic suspension and is being developed for prevention of corneal endothelial cell loss due to cataract surgery.

• ***Efficacy.*** In a series of preclinical studies, a topically applied suspension of RTA 408 was effective in inducing antioxidative gene expression in the corneal epithelium and endothelium as well as reducing markers of postoperative inflammation.[9]

Reata has initiated a Phase II clinical trial (GUARD) to evaluate the effects of RTA 408 ophthalmic suspension for the prevention of corneal endothelial cell loss in cataract surgery patients (NCT02128113).[10] No results from this study are publicly available. The potential safety concerns regarding Nrf2 activation are unknown.

New pharmaceutical therapies for corneal degeneration promise to transform the routine treatment of corneal endothelial cell loss by providing treatment that could either block the degeneration of the endothelial cell or cause regeneration of the cellular layer. Such therapies have the potential to replace corneal transplantation as the treatment of choice for patients with endothelial cell dystrophy or dysfunction.

These therapies would provide better vision for patients by removing the need for corrections of astigmatism that follows surgery. These promising treatments are still early in development but include: engineered fibroblast growth factor; corneal stem cells; ROCK inhibitors; and antioxidant inflammation modulators.

Much research is still required to develop efficacy and safety data to satisfy the FDA regarding the commercialization of these products. In addition, final formulations need to be developed consistent with regulatory requirements. However, early indications are that these products hold much promise for helping an important segment of suffering ophthalmic patients. The goal of being able to maintain normal vision in this important group of corneal patients is coming closer. REVIEW

Dr. Stewart is CEO and medical director of PRN Pharmaceutical Research Network LLC, an international ophthalmic clinical study management and consulting firm, as well as PRN PharmaFarm LLC, which specializes in financing new ophthalmic start-up companies to assist towards product commercialization. Ms. Nelson is a research coordinator for both companies. Dr Eveleth is CEO of Trefoil Therapeutics, LLC.. Dr. Stewart is a consultant for Trefoil Therapeutics and Ms. Nelson has no financial interest. For information, visit prnorb.com *or* prnorb.blogspot.com*, or contact Dr. Stewart at (843) 606-0776; e-mail: info@prnorb.com.*

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AAAHC Study Assays Key Cataract Metrics

Kris Kilgore, RN, BSN, Grand Rapids, Mich.

A national survey of ambulatory surgery centers describes trends in surgery time, staffing and more.

Since its inception in 1999, the Accreditation Association for Ambulatory Health Care Institute for Quality Improvement has sought to develop standards to advance and promote patient safety, quality and value in the ambulatory setting. The association promotes a voluntary, peer-based, consultative and educational survey process to advance patient care.

One such survey is the "Cataract Extraction with Lens Insertion" study. From January to June 2015, 79 ambulatory surgery centers nationally participated and submitted information on 2,127 cases. These organizations perform from 92 to 8,000 procedures each year, for a total of 163,568 cataract procedures performed annually.

As a nurse administrator of a busy ophthalmic physician-owned ambulatory surgery center, I have used this report to glean insights that influence our quality improvement and operational initiatives. In the data from the report, our organization was able to benchmark with 78 other organizations in the areas of perioperative times; types of anesthesia administered and who monitors the patient; the average staffing per procedure and hourly wages; and the types of lenses used and cost of each lens inserted.

Perioperative Times

The study provides pre-procedure times, procedure times and discharge times for cataract extraction with lens insertion procedures. These times, for the most part, are within control of the organization and can significantly affect patient satisfaction and operational efficiency.

The range for pre-procedure times was 41 to 151 minutes, with a median and an average of 82 minutes. The organization with the shortest pre-procedure time attributes its efficiency to a few strategies, including dilating patients soon after they arrive in a private room adjacent to the reception area used by its nurses to begin the dilation process.

Patient discharge times ranged from 7 to 49 minutes, with a median and an average of 20 minutes. In addition to having adequate staffing, the organization with the shortest discharge time attributed its efficiency to using topical anesthesia with minimal sedation, having consistent discharge instructions for all surgeons, keeping patients in street clothes for the procedure and streamlining paperwork.

Our organization designs a QI Study on any area where we are out of the average or median range and adapt the best practices to fit our organization.

We perform a re-measurement after the corrective actions have been given time to be implemented and tested. The one area where we have noticed the most improvement is in the area of recovery. By adapting the best practices, we have been able to discharge our patients five minutes sooner than before our QI Study was conducted.

Anesthesia Usage

The study defines the types of anesthesia used, who administers the anesthesia and who monitors the patient, which are all important safety issues for patients. This information allows an organization to determine if the type of anesthesia used affects the procedure and discharge time from the facility.

The study indicated that the average procedure time was lowest when IV sedation was used along with a peribulbar block. This method reduced procedure time to a 10 minute average (average procedure time for all cases was 13 minutes). It was also noted in the study that in 51 percent of the cases anesthesia was administered and monitored by CRNAs, while 41 percent of the cases had anesthesia administered by an anesthesiologist, who then monitored the patient 36 percent of the time. This information is beneficial in providing patient education when discussing the different anesthesia types and provider qualifications.

Staffing

In an effort to monitor case costs, staffing plays a large role in the cost of each procedure. The AAAHC Institute "Cataract Extraction with Lens Insertion" study, dated July to December 2014, provides information on staffing levels and the mix of staff and hourly wages for various professional staff.

The median staffing for a cataract procedure is four RNs, one CRNA,

one LPN/LVN and two technicians. The median hourly wage for each as is follows:

- RN - $30/hour
- CRNA - $100/hour
- LPN/LVN - $22/hour
- Technician - $20/hour

The study supports the need for cross-training and a staff mix that places the appropriately qualified and educated person in each job. It also allows the opportunity to benchmark hourly wages between your organization and that of the participants. All of these factors enable an organization to provide quality patient care in a cost-conscious environment.

Lens Usage and Cost

Finally, another measure that helps control cost while maintaining a high level of patient satisfaction is choosing the correct lens for each patient.

The most common lens used was an acrylic model SN60WF, with a median price of $134. Fifty-five percent of organizations reported receiving a rebate on the lenses they use, 63 percent consign lenses and 36 percent consign and buy lenses.

This information is useful to an organization when meeting with vendors and negotiating pricing and consignments for the lenses it stocks and uses.

Quality Improvement

The overall purpose of this study is quality improvement. The measures in it are tools which providers can use to assess their care, and the report shares best practices from organizations that report exceptional results. REVIEW

Ms. Kilgore is the administrative director at Grand Rapids Ophthalmology Surgical Care Center, and a member of the AAAHC. For information or to receive the full study text, email info@aaahc.org.

Protecting Your EHR From Security Breaches

Michelle Stephenson, Contributing Editor

How to keep your records secure and what to do in case of a breach.

Just like any other database containing demographic information about a large number of people, electronic health records are a target for hackers, and they may become more of a target in the future as their use increases.

Michael Chiang, MD, past chair of the American Academy of Ophthalmology's Medical Information Technology Committee, says EHR adoption is increasing dramatically. "We surveyed the AAO membership in 2008, and about 12 percent of ophthalmologists were using EHRs," he says. "In 2012, we repeated that survey, and the adoption rate went up to 34 percent. Now in 2015, my guess is that it's at least 50 percent to 60 percent. The point is that, in a relatively short amount of time, there has been a dramatic shift in terms of how doctors are handling their records. EHRs make medical data far more accessible than ever before, but one downside is that there are more potential risks from security breaches. Stores like Target have had tens of millions of customers' credit card data compromised, which was done using nothing more sophisticated than off-the-shelf malware." Dr. Chiang is currently a professor of ophthalmology and medical informatics at the Casey Eye Institute at Oregon Health & Science University.

He notes that ophthalmologists really need to take this risk seriously because security is a shared responsibility. "Most of us use information systems that are sold to us by vendors, and it is ultimately our responsibility to make sure vendors are managing these risks appropriately and that we and our staff are using these systems properly," he says.

Mary Ann Fitzhugh, vice president of marketing at Compulink Business Systems, agrees. "This is a really important issue for private practices, and our experience is that they aren't nearly as vigilant as they need to be or are not taking the steps they need to protect themselves," she says. "Now that patient data are online, the genie is out of the bottle, and providers need to be aware of who is accessing patient

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information and what they're doing when they access it. They also need to ensure that those who don't have authorized access don't get access. And, this security mindfulness needs to occur at several levels, including not only the strong built-in features we provide in the software but also the devices (phone, tablets, wireless access, office PCs) that staff members are using to access the EHR. Their EHR vendor can assist with some of these issues, but doctors need to stay on top of other issues, such as the security of the PC or device they are using to access their EHR software."

Anthem's Experience

On January 29, Anthem, the nation's second-largest health insurance company, detected the breach of a database containing records for 80 million customers and employees. On February 4, Anthem began notifying affected individuals. Anthem was then named as a defendant in six separate class action lawsuits filed in federal courts in Alabama, California, Georgia and Indiana.

According to Anthem, "Cyber attackers executed a very sophisticated attack to gain unauthorized access to one of our parent company's IT systems and have obtained personal information relating to consumers and Anthem Blue Cross and Blue Shield employees who are currently covered, or who have received coverage in the past. The information accessed includes names, birthdays, social security numbers, street addresses, email addresses and employment information, including income data. No credit card information was compromised, nor is there evidence at this time that medical information such as claims, test results or diagnostic codes were targeted or obtained. As soon as we learned about the attack, we immediately made every effort to close the security vulnerability, contacted the FBI and began fully cooperating with their investigation. Our parent company has also retained Mandiant, one of the world's leading cybersecurity firms, to evaluate our systems and identify solutions based on the evolving landscape."

For those whose information was accessed, Anthem provided credit monitoring and identity protection services free of charge.

Because no actual medical information appears to have been stolen, the breach would not come under the rules of the 1996 Health Insurance Portability and Accountability Act, which governs the confidentiality and security of medical information.

What Can Vendors Do?

EHR vendors are taking steps to help protect their clients. According to Ms. Fitzhugh, features within the software can secure patient data and protect against threat. Compulink's system includes the following:

- Multiple levels of access controls to specify access rights to patient data.
- Automatic audit logging, which tracks, records, and reports on activities, such as which users have accessed a patient record and what changes they made to that record. "Our audit logs also monitor when protected health information is exported out of our software, such as through printing, or imported into our software," she says.
- Support data encryption and authentication protocols to ensure the highest levels of data integrity are maintained and to control access to electronic protected health information.
- Automatic log-off, where the software will "time out" user access to patient records after a pre-determined time of inactivity.
- Support for "hashing," where upon receipt of electronically exchanged information by the software from another source, we verify that information has not been altered, she says.

"We also have taken steps to help our clients secure physical access to their EHR systems. We offer Advantage Cloud, a state-of-the-art hosted solution. This solution allows the client full access to the software, while we maintain the network, software and hardware in our secure and HIPAA-compliant data center. All connections to our Cloud solution are encrypted."

If clients wish to install the software on their own servers at the practice, Compulink's IT support group advises them on the security measures they need to take, including installing antivirus software and making full use of the security features of the operating system. "We also routinely send security bulletins to our clients of industry-wide security attacks like the infamous CryptoLocker Virus," says Ms. Fitzhugh.

CryptoLocker is a virus that only affects Windows PCs, and it holds the files on your computer hostage. You are required to pay a fee or lose everything on your hard drive. The virus arrives in the form of an email from a logistics company, like FedEx or UPS, and users are tricked into opening it. It causes your computer files to be inaccessible. If your files are not backed up, your only option is to pay the "ransom" within 100 hours. If you don't pay, then you lose all of your files. Ransom amounts typically range from $100 to $700.

What Can You Do?

According to Jim Messier, vice president of sales and marketing, Medflow Inc., the safety of the data depends on the type of security that you have in place. If you have a client server product that sits in your office, someone can come in and pick up the box and walk away with it. "If you have this type of product, you should have encryption, so that if someone were to take the server, he wouldn't be able to get anything important from it," he says. "On the cloud version of the product,

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there are multiple layers of protection for information. First and foremost, you need an electronic certificate from any device that would access the cloud. So, one limitation is that you wouldn't be able to access your records from the admiral's club at the airport using their internet computers. The device itself has to be authenticated to the application on the cloud. Of course, you have the user credentials as the second layer of protection."

Additionally, data that resides in the cloud is also encrypted so that if someone breaches the protection that is in place and obtains information, it would not be recognizable or downloadable in human-readable format. "It is important to make sure that the vendor has some type of encryption program in place," says Mr. Messier. "If it is a cloud product, it should be with a tier-4 type of hosting company, and the hosting companies themselves are held to a high degree of scrutiny with regard to what they employ for protection within their data center itself. Even with encryption programs, the federal government has been breached."

Unfortunately, nothing is 100 percent safe. "There are a lot of clever, malicious people out there," says Mr. Messier. "You can track who has accessed your data through an audit log. Any good software will have an audit log, which will tell you every access point to the server and to patients' charts. It will tell you the date, time, what was accessed and who accessed it. If someone tried to access something that he didn't have roles and permissions for, then that would typically be noted in an audit log, and the manager of the system would be able to see that and either identify that as an internal member of the organization or someone from the outside."

Whether the manager is someone inside the office or from a third party typically depends on the size of the practice. If the practice has its own IT staff, then this is something that the IT staff would be tending to on a regular basis. "If you are working with a vendor, that might be provided as part of your software maintenance support," says Mr. Messier. "If I'm responsible for hosting that information, then that's part of my software license agreement that I'm providing you with that kind of security. If it's a client server product within your walls, then it would be up to the practice to look at the audit log regularly or have a third-party IT company looking at it. Cloud-based systems have more layers of protection than in-office systems."

The Wilmer Eye Institute in Baltimore has begun using two-factor authentication to authenticate users of the systems, so users must have their user name, password and something else. Michael V. Boland, MD, PhD, associate professor of ophthalmology and director of Wilmer's information technology, explains: "For example, they will send you a code on your cell phone to increase the likelihood that users are who they claim. For smaller practices, it is challenging because you are expected to do all of the same things with a smaller budget and a smaller staff. Trying to go it alone in terms of security becomes risky for those small practices because you are not necessarily going to have the best quality security staff. That's why outsourcing your data storage to someone else may be a reasonable thing to do.

"It is increasingly complicated to handle security on your own, so the key message is that you need to get expert help," he says. "You can't really do it on your own anymore. You can outsource it to a contractor who will help secure servers that are located at your practice or you can outsource all of your data storage and server needs. It has become sufficiently complicated that it is not a good idea for a small practice to try to do this on its own."

Dr. Chiang points out another issue: keeping passwords secure. "It is very important that all of these systems have passwords, and that all staff members are setting appropriate passwords and using them securely," he says. "In other words, make sure they are not writing passwords down on Post-it notes or sharing their passwords with others. The recommendation is to use strong passwords, which means that they are a mixture of characters, upper and lowercase letters and numbers. Don't use anything that can be easily guessed like the name of your children, your birthdate or words like 'password.' There really should be a different password for every system. Studies have shown that when you don't use strong passwords, it is easier for people to hack into your system. One tip is to either spell words backwards or to use password management software, some of which can be downloaded for free. Password management software will store your passwords and can automatically assign strong passwords."

What to Do After a Breach

There are typically two types of breaches. One involves copying data, while the other is deleting data from your system. "A breach can cause a worm or bug in the database," Mr. Messier says. "There are forensic companies out there that do that kind of work, and they may or may not be able to recover your data. Most of these breaches that you hear about are just basically taking copies of the information and not deleting it."

According to Dr. Boland, if you know that there has been a breach, you are required to report it. "That doesn't necessarily mean that you are going to be fined or penalized, because these things happen. You are expected to have all of the policies and procedures in place to show that you did everything you could to protect your patients' information. As is the case with other 'bad outcomes,' coming clean is an important strategy," he says. REVIEW

Classic beta blocker adjunctive therapy for the right patient at the right time[3]

The concomitant use of two topical beta-adrenergic blocking agents is not recommended[4,5]

Indications and Usage

ISTALOL® (timolol maleate ophthalmic solution) is a non-selective beta-adrenergic receptor blocking agent indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

Preservative-free TIMOPTIC® (timolol maleate ophthalmic solution) in OCUDOSE® (dispenser) is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma. It may be used when a patient is sensitive to the preservative in TIMOPTIC (timolol maleate ophthalmic solution), benzalkonium chloride, or when use of a preservative-free topical medication is advisable.

Important Safety Information for Istalol® and Timoptic® in Ocudose®

- Both ISTALOL® (timolol maleate ophthalmic solution) and TIMOPTIC® (timolol maleate ophthalmic solution) in OCUDOSE® (dispenser) are contraindicated in patients with: bronchial asthma; a history of bronchial asthma; severe chronic obstructive pulmonary disease; sinus bradycardia; second or third degree atrioventricular block; overt cardiac failure; cardiogenic shock; hypersensitivity to any component of the product.
- **The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. Severe respiratory reactions and cardiac reaction, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate.**
- Patients with a history of atopy or severe anaphylactic reactions to a variety of allergens may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.
- Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.
- Beta-adrenergic blocking agents may mask signs and symptoms of acute hypoglycemia or certain clinical signs of hyperthyroidism. Patients subject to spontaneous hypoglycemia, or diabetic patients receiving either insulin or oral hypoglycemic agents, or patients suspected of developing thyrotoxicosis, should be managed carefully, with caution.
- In patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta adrenergic receptor blocking agents because these agents impair the ability of the heart to respond to beta-adrenergically mediated reflex stimuli.
- The most frequently reported adverse reactions have been burning and stinging upon instillation. This was seen in 38% of patients treated with ISTALOL and in approximately one in eight patients treated with TIMOPTIC in OCUDOSE. Additional reactions reported with ISTALOL at a frequency of 4 to 10% include: blurred vision, cataract, conjunctival injection, headache, hypertension, infection, itching and decreased visual acuity.

Please see Brief Summary of Prescribing Information for ISTALOL and TIMOPTIC in OCUDOSE on the following pages.

For the patients who need incremental IOP reduction in a preservative free form[6]

Preservative-Free

TIMOPTIC® in OCUDOSE®
(TIMOLOL MALEATE 0.5% OPHTHALMIC SOLUTION) (DISPENSER)

For the patients who need incremental IOP reduction in a once a day form[6]

Istalol®
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BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use TIMOPTIC® 0.25% AND 0.5% (timolol maleate ophthalmic solution) in OCUDOSE® (DISPENSER) safely and effectively. See full prescribing information for TIMOPTIC in OCUDOSE.

PRESERVATIVE-FREE STERILE OPHTHALMIC SOLUTION
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TIMOPTIC® 0.25% AND 0.5% (TIMOLOL MALEATE OPHTHALMIC SOLUTION)

in OCUDOSE® (DISPENSER)

INDICATIONS AND USAGE

Preservative-free TIMOPTIC in OCUDOSE is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

Preservative-free TIMOPTIC in OCUDOSE may be used when a patient is sensitive to the preservative in TIMOPTIC (timolol maleate ophthalmic solution), benzalkonium chloride, or when use of a preservative-free topical medication is advisable.

CONTRAINDICATIONS

Preservative-free TIMOPTIC in OCUDOSE is contraindicated in patients with (1) bronchial asthma; (2) a history of bronchial asthma; (3) severe chronic obstructive pulmonary disease (see WARNINGS); (4) sinus bradycardia; (5) second or third degree atrioventricular block; (6) overt cardiac failure (see WARNINGS); (7) cardiogenic shock; or (8) hypersensitivity to any component of this product.

WARNINGS

As with many topically applied ophthalmic drugs, this drug is absorbed systemically.

The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate (see CONTRAINDICATIONS).

Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, Preservative-free TIMOPTIC in OCUDOSE should be discontinued.

Obstructive Pulmonary Disease: Patients with chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease (other than bronchial asthma or a history of bronchial asthma, in which TIMOPTIC in OCUDOSE is contraindicated [see CONTRAINDICATIONS]) should, in general, not receive beta-blockers, including Preservativefree TIMOPTIC in OCUDOSE.

Major Surgery: The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

Diabetes Mellitus: Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis: Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm.

PRECAUTIONS

General: Because of potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with Preservative-free TIMOPTIC in OCUDOSE, alternative therapy should be considered.

Choroidal detachment after filtration procedures has been reported with the administration of aqueous suppressant therapy (e.g. timolol).

Angle-closure glaucoma: In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil. Timolol maleate has little or no effect on the pupil. TIMOPTIC in OCUDOSE should not be used alone in the treatment of angle-closure glaucoma.

Anaphylaxis: While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

Information for Patients: Patients should be instructed about the use of Preservative-free TIMOPTIC in OCUDOSE.

Since sterility cannot be maintained after the individual unit is opened, patients should be instructed to use the product immediately after opening, and to discard the individual unit and any remaining contents immediately after use.

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, or cardiac failure should be advised not to take this product. (See CONTRAINDICATIONS.)

Drug Interactions: Although TIMOPTIC (timolol maleate ophthalmic solution) used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with TIMOPTIC (timolol maleate ophthalmic solution) and epinephrine has been reported occasionally.

Beta-adrenergic blocking agents: Patients who are receiving a beta-adrenergic blocking agent orally and Preservative-free TIMOPTIC in OCUDOSE should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Calcium antagonists: Caution should be used in the coadministration of beta-adrenergic blocking agents, such as Preservative-free TIMOPTIC in OCUDOSE, and oral or intravenous calcium antagonists, because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, coadministration should be avoided.

Catecholamine-depleting drugs: Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

Digitalis and calcium antagonists: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

CYP2D6 inhibitors: Potentiated systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g., quinidine, SSRIs) and timolol.

Clonidine: Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate.

Injectable epinephrine: (See PRECAUTIONS, *General, Anaphylaxis*)

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year oral study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (approximately 42,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Similar differences were not observed in rats administered oral doses equivalent to approximately 14,000 times the maximum recommended human ophthalmic dose.

In a lifetime oral study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day (approximately 71,000 times the systemic exposure following the maximum recommended human ophthalmic dose), but not at 5 or 50 mg/kg/day (approximately 700 or 7,000 times, respectively, the systemic exposure following the maximum recommended human ophthalmic dose). In a subsequent study in female mice, in which post-mortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin.

Timolol maleate was devoid of mutagenic potential when tested *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 mcg/mL). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 mcg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats demonstrated no adverse effect on male or female fertility at doses up to 21,000 times the systemic exposure following the maximum recommended human ophthalmic dose.

Pregnancy: *Teratogenic Effects* — Pregnancy Category C. Teratogenicity studies with timolol in mice, rats and rabbits at oral doses up to 50 mg/kg/day (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose, in this case without apparent maternotoxicity.

There are no adequate and well-controlled studies in pregnant women. Preservative-free TIMOPTIC in OCUDOSE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Timolol maleate has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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

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

ADVERSE REACTIONS

The most frequently reported adverse experiences have been burning and stinging upon instillation (approximately one in eight patients).

The following additional adverse experiences have been reported less frequently with ocular administration of this or other timolol maleate formulations:

BODY AS A WHOLE: Headache, asthenia/fatigue, and chest pain.
CARDIOVASCULAR: Bradycardia, arrhythmia, hypotension, hypertension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, worsening of angina pectoris, palpitation, cardiac arrest, pulmonary edema, edema, claudication, Raynaud's phenomenon, and cold hands and feet.
DIGESTIVE: Nausea, diarrhea, dyspepsia, anorexia, and dry mouth.
IMMUNOLOGIC: Systemic lupus erythematosus.
NERVOUS SYSTEM/PSYCHIATRIC: Dizziness, increase in signs and symptoms of myasthenia gravis, paresthesia, somnolence, insomnia, nightmares, behavioral changes and psychic disturbances including depression, confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss.
SKIN: Alopecia and psoriasiform rash or exacerbation of psoriasis.
HYPERSENSITIVITY: Signs and symptoms of systemic allergic reactions including anaphylaxis, angioedema, urticaria, and localized and generalized rash.
RESPIRATORY: Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnea, nasal congestion, cough and upper respiratory infections.
ENDOCRINE: Masked symptoms of hypoglycemia in diabetic patients (see WARNINGS).
SPECIAL SENSES: Signs and symptoms of ocular irritation including conjunctivitis, blepharitis, keratitis, ocular pain, discharge (e.g., crusting), foreign body sensation, itching and tearing, and dry eyes; ptosis; decreased corneal sensitivity; cystoid macular edema; visual disturbances including refractive changes and diplopia; pseudopemphigoid; choroidal detachment following filtration surgery (see PRECAUTIONS, *General*); and tinnitus.
UROGENITAL: Retroperitoneal fibrosis, decreased libido, impotence, and Peyronie's disease.

The following additional adverse effects have been reported in clinical experience with ORAL timolol maleate or other ORAL beta blocking agents, and may be considered potential effects of ophthalmic timolol maleate: *Allergic:* Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress; *Body as a Whole:* Extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular:* Worsening of arterial insufficiency, vasodilatation; *Digestive:* Gastrointestinal pain, hepatomegaly, vomiting, mesenteric arterial thrombosis, ischemic colitis; *Hematologic:* Nonthrombocytopenic purpura; thrombocytopenic purpura; agranulocytosis; *Endocrine:* Hyperglycemia, hypoglycemia; *Skin:* Pruritus, skin irritation, increased pigmentation, sweating; *Musculoskeletal:* Arthralgia; *Nervous System/Psychiatric:* Vertigo, local weakness, diminished concentration, reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Respiratory:* Rales, bronchial obstruction; *Urogenital:* Urination difficulties.

OVERDOSAGE

There have been reports of inadvertent overdosage with Ophthalmic Solution TIMOPTIC (timolol maleate ophthalmic solution) resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest (see also ADVERSE REACTIONS).

Overdosage has been reported with Tablets BLOCADREN* (timolol maleate tablets). A 30 year old female ingested 650 mg of BLOCADREN (maximum recommended oral daily dose is 60 mg) and experienced second and third degree heart block. She recovered without treatment but approximately two months later developed irregular heartbeat, hypertension, dizziness, tinnitus, faintness, increased pulse rate, and borderline first degree heart block.

An *in vitro* hemodialysis study, using ^{14}C timolol added to human plasma or whole blood, showed that timolol was readily dialyzed from these fluids; however, a study of patients with renal failure showed that timolol did not dialyze readily.

DOSAGE AND ADMINISTRATION

Preservative-free TIMOPTIC in OCUDOSE is a sterile solution that does not contain a preservative. The solution from one individual unit is to be used immediately after opening for administration to one or both eyes. Since sterility cannot be guaranteed after the individual unit is opened, the remaining contents should be discarded immediately after administration.

Preservative-free TIMOPTIC in OCUDOSE is available in concentrations of 0.25 and 0.5 percent. The usual starting dose is one drop of 0.25 percent Preservative-free TIMOPTIC in OCUDOSE in the affected eye(s) administered twice a day. Apply enough gentle pressure on the individual container to obtain a single drop of solution. If the clinical response is not adequate, the dosage may be changed to one drop of 0.5 percent solution in the affected eye(s) administered twice a day.

Since in some patients the pressure-lowering response to Preservative-free TIMOPTIC in OCUDOSE may require a few weeks to stabilize, evaluation should include a determination of intraocular pressure after approximately 4 weeks of treatment with Preservative-free TIMOPTIC in OCUDOSE.

If the intraocular pressure is maintained at satisfactory levels, the dosage schedule may be changed to one drop once a day in the affected eye(s). Because of diurnal variations in intraocular pressure, satisfactory response to the once-a-day dose is best determined by measuring the intraocular pressure at different times during the day.

Dosages above one drop of 0.5 percent TIMOPTIC (timolol maleate ophthalmic solution) twice a day generally have not been shown to produce further reduction in intraocular pressure. If the patient's intraocular pressure is still not at a satisfactory level on this regimen, concomitant therapy with other agent(s) for lowering intraocular pressure can be instituted taking into consideration that the preparation(s) used concomitantly may contain one or more preservatives. The concomitant use of two topical beta-adrenergic blocking agents is not recommended. (See PRECAUTIONS, *Drug Interactions, Beta-adrenergic blocking agents.*)

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use ISTALOL® (timolol maleate ophthalmic solution) 0.5% safely and effectively. See full prescribing information for ISTALOL.

Istalol® (timolol maleate ophthalmic solution) 0.5%

Initial U.S. Approval: 1978

STERILE

INDICATIONS AND USAGE

Istalol (timolol maleate ophthalmic solution) 0.5% is a non-selective beta-adrenergic receptor blocking agent indicated in the treatment of elevated intraocular pressure (IOP) in patients with ocular hypertension or open-angle glaucoma.

CONTRAINDICATIONS

4.1 Asthma, COPD: Istalol is contraindicated in patients with bronchial asthma; a history of bronchial asthma; severe chronic obstructive pulmonary disease (see **WARNINGS AND PRECAUTIONS, 5.1, 5.3**).

4.2 Sinus Bradycardia, AV Block, Cardiac Failure, Cardiogenic Shock: Istalol is contraindicated in patients with sinus bradycardia; second or third degree atrioventricular block; overt cardiac failure (see **WARNINGS AND PRECAUTIONS, 5.2**); cardiogenic shock.

4.3 Hypersensitivity Reactions: Istalol is contraindicated in patients who have exhibited a hypersensitivity reaction to any component of this product in the past.

WARNINGS AND PRECAUTIONS

5.1 Potentiation of Respiratory Reactions Including Asthma: Istalol contains timolol maleate; and although administered topically, it can be absorbed systemically. Therefore, the same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate (see **CONTRAINDICATIONS, 4.1**).

5.2 Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition of beta-adrenergic receptor blockade may precipitate more severe failure. In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, Istalol should be discontinued (see also **CONTRAINDICATIONS, 4.2**).

5.3 Obstructive Pulmonary Disease: Patients with chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease [other than bronchial asthma or a history of bronchial asthma in which Istalol is contraindicated (see **CONTRAINDICATIONS, 4.2**)] should, in general, not receive beta-blocking agents, including Istalol.

5.4 Increased Reactivity to Allergens: While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

5.5 Potentiation of Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

5.6 Masking of Hypoglycemic Symptoms in Patients with Diabetes Mellitus: Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

5.7 Masking of Thyrotoxicosis: Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm.

5.8 Contamination of Topical Ophthalmic Products After Use: There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface (see **PATIENT COUNSELING INFORMATION, 17**).

5.9 Impairment of Beta-adrenergically Mediated Reflexes During Surgery: The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

5.10 Angle-Closure Glaucoma: In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This may require constricting the pupil. Timolol maleate has little or no effect on the pupil. Istalol should not be used alone in the treatment of angle-closure glaucoma.

5.11 Cerebrovascular Insufficiency: Because of potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with Istalol, alternative therapy should be considered.

5.12 Choroidal Detachment: Choroidal detachment after filtration procedures has been reported with the administration of aqueous suppressant therapy (e.g. timolol).

ADVERSE REACTIONS

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

The most frequently reported adverse reactions have been burning and stinging upon instillation in 38% of patients treated with Istalol. Additional reactions reported with Istalol at a frequency of 4 to 10% include: blurred vision, cataract, conjunctival injection, headache, hypertension, infection, itching and decreased visual acuity. The following additional adverse reactions have been reported less frequently with ocular administration of this or other timolol maleate formulations.

Timolol (Ocular Administration): *Body as a whole:* Asthenia/fatigue and chest pain; *Cardiovascular:* Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, worsening of angina pectoris, palpitation, cardiac arrest, pulmonary edema, edema, claudication, Raynaud's phenomenon and cold hands and feet; *Digestive:* Nausea, diarrhea, dyspepsia, anorexia, and dry mouth; *Immunologic:* Systemic lupus erythematosus; *Nervous System/Psychiatric:* Dizziness, increase in signs and symptoms of myasthenia gravis, paresthesia, somnolence, insomnia, nightmares, behavioral changes and psychic disturbances including depression, confusion, hallucinations, anxiety, disorientation, nervousness and memory loss; *Skin:* Alopecia and psoriasiform rash or exacerbation of psoriasis; *Hypersensitivity:* Signs and symptoms of systemic allergic reactions, including angioedema, urticaria, and localized and generalized rash; *Respiratory:* Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnea, nasal congestion, cough and upper respiratory infections; *Endocrine:* Masked symptoms of hypoglycemia in diabetic patients (see **WARNINGS AND PRECAUTIONS, 5.6**); *Special Senses:* Signs and symptoms of ocular irritation including conjunctivitis, blepharitis, keratitis, ocular pain, discharge (e.g., crusting), foreign body sensation, itching and tearing, and dry eyes; ptosis, decreased corneal sensitivity; cystoid macular edema; visual disturbances including refractive changes and diplopia; pseudopemphigoid; choroidal detachment following filtration surgery (see **WARNINGS AND PRECAUTIONS, 5.12**); *Urogenital:* Retroperitoneal fibrosis, decreased libido, impotence, and Peyronie's disease.

6.2 Postmarketing Experience

Oral Timolol/Oral Beta-blockers: The following additional adverse effects have been reported in clinical experience with ORAL timolol maleate or other ORAL beta-blocking agents and may be considered potential effects of ophthalmic timolol maleate: *Allergic:* Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress; *Body as a Whole:* Extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular:* Worsening of arterial insufficiency, vasodilatation; *Digestive:* Gastrointestinal pain, hepatomegaly, vomiting, mesenteric arterial thrombosis, ischemic colitis; *Hematologic:* Nonthrombocytopenic purpura; thrombocytopenic purpura, agranulocytosis; *Endocrine:* Hyperglycemia, hypoglycemia; *Skin:* Pruritus, skin irritation, increased pigmentation, sweating; *Musculoskeletal:* Arthralgia; *Nervous System/Psychiatric:* Vertigo, local weakness, diminished concentration, reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, emotional lability, slightly clouded sensorium and decreased performance on neuropsychometrics; *Respiratory:* Rales, bronchial obstruction; *Urogenital:* Urination difficulties.

DRUG INTERACTIONS

7.1 Beta-Adrenergic Blocking Agents: Patients who are receiving a beta-adrenergic blocking agent orally and Istalol® should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

7.2 Calcium Antagonists: Caution should be used in the co-administration of beta-adrenergic blocking agents, such as Istalol, and oral or intravenous calcium antagonists because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, co-administration should be avoided.

7.3 Catecholamine-Depleting Drugs: Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

7.4 Digitalis and Calcium Antagonists: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

7.5 CYP2D6 Inhibitors: Potentiated systemic beta-blockade (e.g., decreased heart rate) has been reported during combined treatment with CYP2D6 inhibitors (e.g., quinidine) and timolol.

7.6 Clonidine: Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate.

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C: Teratogenicity studies have been performed in animals. Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose, in this case without apparent maternotoxicity. There are no adequate and well-controlled studies in pregnant women. Istalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers: Timolol has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from Istalol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use: Safety and effectiveness 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.

OVERDOSAGE

There have been reports of inadvertent overdosage with Istalol resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest. An *in vitro* hemodialysis study, using ^{14}C timolol added to human plasma or whole blood, showed that timolol was readily dialyzed from these fluids; however, a study of patients with renal failure showed that timolol did not dialyze readily.

NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (approximately 42,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Similar differences were not observed in rats administered oral doses equivalent to approximately 14,000 times the maximum recommended human ophthalmic dose. In a lifetime oral study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day, (approximately 71,000 times the systemic exposure following the maximum recommended human ophthalmic dose), but not at 5 or 50 mg/kg/day (approximately 700 or 7,000, respectively, times the systemic exposure following the maximum recommended human ophthalmic dose). In a subsequent study in female mice, in which post-mortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day. The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin. Timolol maleate was devoid of mutagenic potential when tested *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 mcg/mL). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 mcg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test. Reproduction and fertility studies in rats demonstrated no adverse effect on male or female fertility at doses up to 21,000 times the systemic exposure following the maximum recommended human ophthalmic dose.

PATIENT COUNSELING INFORMATION

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, or cardiac failure should be advised not to take this product. (see **CONTRAINDICATIONS, 4.1, 4.2**) Patients should also be instructed that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions. (see **WARNINGS AND PRECAUTIONS 5.8**) Patients should also be advised that if they have ocular surgery or develop an intercurrent ocular condition (e.g., trauma or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five minutes apart. Patients should be advised that Istalol® contains benzalkonium chloride which may be absorbed by soft contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following Istalol® administration.

Rx Only

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Personalized Medicine: Impact on Retina Therapies

The power of genetically defined targets in the development of retinal therapies is beginning to bear fruit. Where it's headed next.

Thomas A. Ciulla, MD, MBA, Indianapolis

In his book, *The Creative Destruction of Medicine*, Eric Topol, the well-known physician-author, describes how wireless sensors in our bodies, imaging, information technology and genomics, will all converge to "digitize" each of us, and allow personalized medicine at a lower cost.[1] This disruptive convergence will "creatively destruct" medicine, because many common medical practices will become obsolete; for example, we may no longer mass screen for colon cancer or breast cancer, or mass treat for hyperlipidemia, but instead screen or treat those patients that are truly at risk based on their genetic profile. This is the basis behind personalized medicine, and this concept has arrived in retinal treatments.

Personalized medicine was born in 1997 when the Food and Drug Administration first approved a molecularly targeted treatment, IDEC Pharmaceutical's rituximab, a monoclonal antibody against protein CD20 found on B cells, for the treatment of CD20-positive B-cell non-Hodgkin's lymphoma. The following year marked the first time the FDA would grant simultaneous approval of targeted treatment, Genentech's Herceptin breast cancer therapy, with its companion diagnostic test, HercepTest, to identify eligible patients with increased human epidermal growth factor receptor 2 (HER2).

The era of personalized medicine in retinal disease was heralded by a landmark genetic finding. Throughout evolution, millions of mutations have accumulated in the human genome and approximately 12 million of these sites have been identified. These variations, known as Single Nucleotide Polymorphisms (SNPs), are single base changes in a DNA sequence that occur relatively frequently in the human population (>1 percent). Genome-wide association studies (GWAS) compare the entire genome from cases to that of controls to find associations between SNPs or other genetic variations and diseases. This approach differs from the candidate gene approach, in which variation in pre-specified candidate genes are compared to phenotypes. The first successful GWAS occurred in age-related macular degeneration and was published in 2005, assessing 116,204 SNPs in 96 AMD patients and 50 controls. This landmark study noted that a common variant in the complement factor H gene was strongly associated with AMD, with individuals homozygous for the risk allele possessing increased risk of AMD by a factor of 7.4[2]

The complement cascade of the immune system plays a role in AMD development. Complement is involved in drusen formation;[3-7] bioactive fragments of complement components (C3a and C5a) are found in drusen of patients with AMD, and may induce VEGF expression.[3] Normally, the complement cascade detects and destroys blood-borne bacteria. It can be activated via an antibody-dependent pathway (the "classical pathway"), or in an antibody-independent manner (the "alternate pathway"). C3 is central to both pathways; when activated, it leads to generation of membrane attack complex (MAC), which disrupts invading bacterial membranes. CFH is a natural inhibitor of C3 activation, controlling non-specific inflammation. Genetic variations in CFH can lead to less effective modulation of complement pathway activity and may lead to greater precipitation of complement protein found in drusen.[7]

This article has no commercial sponsorship.

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INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

- EYLEA® (aflibercept) Injection 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) in Patients with DME.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. 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.

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 floaters, intraocular pressure increased, and vitreous detachment.

Please see brief summary of full Prescribing Information on the following page.

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

TARGETED SCIENCE

REGENERON

05/2015
LEA-0760

EYLEA® (aflibercept) Injection For Intravitreal Injection

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

For complete details, see Full Prescribing Information.

1 INDICATIONS AND USAGE

EYLEA® (aflibercept) Injection 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) in Patients with DME.

2 DOSAGE AND ADMINISTRATION

2.1 Important Injection Instructions. For ophthalmic intravitreal injection. EYLEA must only be administered by a qualified physician.

2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD). The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.

2.3 Macular Edema Following Retinal Vein Occlusion (RVO). The recommended dose for EYLEA is (0.05 mL or 50 microliters) administered by intravitreal injection once every 4 weeks (monthly).

2.4 Diabetic Macular Edema (DME). The recommended dose for EYLEA is (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.

2.5 Diabetic Retinopathy (DR) in Patients with DME. The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.

2.6 Preparation for Administration. EYLEA should be inspected visually prior to administration. If particulates, cloudiness, or discoloration are visible, the vial must not be used. Using aseptic technique, the intravitreal injection should be performed with a 30-gauge x ½-inch injection needle. For complete preparation for administration instructions, see full prescribing information.

2.7 Injection Procedure. The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include surgical hand disinfection and the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a topical broad–spectrum microbicide should be given prior to the injection.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis needle should be available.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay (*see Patient Counseling Information*).

Each vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter, and injection needles should be changed before EYLEA is administered to the other eye. After injection, any unused product must be discarded.

3 DOSAGE FORMS AND STRENGTHS

Single-use, glass vial designed to provide 0.05 mL of 40 mg/mL solution (2 mg) for intravitreal injection.

4 CONTRAINDICATIONS

EYLEA is contraindicated in patients with

- Ocular or periocular infections
- Active intraocular inflammation
- Known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as severe intraocular inflammation

5 WARNINGS AND PRECAUTIONS

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

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

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

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in the *Warnings and Precautions* section of the labeling:

- Endophthalmitis and retinal detachments
- Increased intraocular pressure
- Thromboembolic events

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

A total of 2711 patients treated with EYLEA constituted the safety population in seven phase 3 studies. Among those, 2110 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, active-controlled clinical studies (VIEW1 and VIEW2) for 12 months.

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

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

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

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

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

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

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

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

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

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

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.

6.2 Immunogenicity. As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.

In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy. Pregnancy Category C. Aflibercept produced embryo-fetal toxicity when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days at subcutaneous doses ≥0.1 mg per kg. Adverse embryo-fetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was less than 0.1 mg per kg. Administration of the lowest dose assessed in rabbits (0.1 mg per kg) resulted in systemic exposure (AUC) that was approximately 10 times the systemic exposure observed in humans after an intravitreal dose of 2 mg. There are no adequate and well-controlled studies in pregnant women. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers. It is unknown whether aflibercept is excreted in human milk. Because many drugs are excreted in human milk, a risk to the breastfed child cannot be excluded. EYLEA is not recommended during breastfeeding. A decision must be made whether to discontinue nursing or to discontinue treatment with EYLEA, taking into account the importance of the drug to the mother.

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

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

17 PATIENT COUNSELING INFORMATION

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

REGENERON

Manufactured by:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

U.S. License Number 1760

Issue Date: March 2015
Initial U.S. Approval: 2011

Regeneron U.S. Patents 7,070,959; 7,303,746; 7,303,747; 7,306,799; 7,374,757; 7,374,758; 7,531,173; 7,608,261; 7,972,598; 8,029,791; 8,092,803; 8,647,842; and other pending patents.

LEA-0721

Regulatory and Payment Issues Surrounding Personalized Companion Diagnostic Testing

There are significant barriers to the development of companion diagnostic tests, which are so crucial to progress in personalized medicine. Although 30 percent of all drugs in Phase III testing rely on a biomarker to determine which patients respond to the drug, traditional payment models are misaligned with personalized medicine diagnostics on several levels.

First, existing coding and payment structures, often structured years ago, do not accurately describe novel companion diagnostic tests or their value. For example, if a CPT code already existed for a similar diagnostic test, it may be poorly aligned with the new diagnostic test or reimburse far too low to economically facilitate the test.

Second, the regulatory environment is poorly structured for integration of a complex and expensive companion diagnostic test into new treatment paradigms. For example, a diagnostic test must be Food and Drug Administration-approved before a new CPT code application can be completed, which is successful only 70 percent of the time, requiring 18 to 24 months, and oftentimes yielding only modest reimbursement. Consequently, the reimbursement is often not sufficient for the cost of the test.

Third, obtaining approval for a new diagnostic test is highly complex. Oversight of diagnostic tests and medications is handled by different agencies, which have historically been poorly integrated and involved a complex approval process. Medications are regulated by the Center for Drug Evaluation and Research, which reviews new drug applications (NDAs), and the Center for Biologics Evaluation and Research (CBER), which regulates biologic agents such as blood products, tissue-based products, therapeutic proteins and vaccines. Diagnostic tests are regulated by the Center for Devices and Radiological Health (CDRH), which is under the FDA, and the Centers for Medicare & Medicaid Services, which is autonomous from the FDA.

Fourth, for *in vitro* diagnostic products, there are two pathways leading to approval: the 510K pathway for class II, lower-risk devices; and the premarket approval pathway for higher-risk, class III devices. Most screening, diagnostic and prognostic diagnostic IVDs are class II, while IVDs to select patients for specific therapeutics are class III. Consequently, given these complex and differing pathways, it is difficult to time approval for a new therapeutic along with its companion diagnostic test.

Furthermore, it is unclear who is responsible for paying for the tests; the significant costs of these diagnostic tests can be borne by traditional payers, by patient advocacy or disease-state groups, as in the case of cystic fibrosis, or by the pharmaceutical companies who benefit from the successful use of their drug.

Finally, coverage decisions differ somewhat between CMS and private payers. For CMS, coding and payment processes are influenced by subspecialty societies, which often protect the interest of their constituents. For private payers, committees, familiar with therapeutics but not familiar with companion diagnostic tests, influence these decisions.

In the future, the simplest payment strategy for companion diagnostics is a bundled payment to the pharmaceutical company. Companion diagnostic tests influenced more than 60 percent of critical health-care treatment decisions in 2011, but accounted for only 2 percent of health-care spending worldwide. Since patient-specific chemotherapies, or similar agents that are often given over periods of time, can cost many multiples of the one-time companion diagnostic test, the pharmaceutical company may be in the best position to administrate the bundle payments and to address the appropriateness of competing companion diagnostic tests.

A payment bundle solves the misaligned payment model for companion diagnostic testing in several ways. First, the bundle itself creates value by directly linking the companion diagnostic test with the treatment, circumventing all of the time and labor-consuming issues surrounding billing, collection and payment. Second, by streamlining the reimbursement process, the bundle promotes testing and subsequent prompt and appropriate treatment, in the patient-specific manner of personalized medicine, enhancing the quality of care for patients. Third, the bundle would benefit both the pharmaceutical and companion diagnostic companies, as their products would be more readily adopted into clinical practice, enhancing the appropriate use of their products. Finally, this would further stimulate the companion diagnostic testing industry, enhancing personalized medicine systematically.

—T.A.C.

AMD has an exceedingly strong genetic contribution with about 15 SNPs accounting for most of the disease risk.[8-12] Commercially available tests assess a cheek swab for SNPs within the four major metabolic pathways involved in AMD pathogenesis: the complement cascade (CFH, CFI, CFB, C2, C3); oxygen metabolism (ARMS2); cholesterol metabolism (LIPC, APOE, CETP, ABCA1); and extracellular matrix (TIMP3, COL8A1). Algorithms incorporating these SNPs, along with non-genetic factors, such as age, smoking, fellow-eye status and body mass index, can assess a patient's risk for progression to advanced AMD.[13]

Using this approach, Carl Awh, MD, and associates recently reanalyzed data from the Age-Related Eye Disease Study to derive a personalized medicine approach to nutritional supplementation in AMD.[14,15] In the AREDS study, participants were randomly assigned to placebo or dietary supplementation with antioxidants (β-carotene, 15 mg; vitamin C, 500

mg; and vitamin E, 400 IU), zinc (80 mg as zinc oxide and copper 2 mg), and antioxidants and zinc combined. Of the 2,258 subjects with category 3 disease, 995 subjects had genetic information available, and both CFH and ARMS2 were assessed. The authors concluded, "In this analysis, patients with no CFH risk alleles and with one or two ARMS2 risk alleles derived maximum benefit from zinc-only supplementation. Patients with one or two CFH risk alleles and no ARMS2 risk alleles derived maximum benefit from antioxidant-only supplementation; treatment with zinc was associated with increased progression to advanced AMD. These recommendations could lead to improved outcomes through genotype-directed therapy."[14] This genotype-guided approach to nutritional supplementation generated some controversy, as other experts have pointed out that AREDS was not designed to assess this issue, and that this secondary statistical analysis may not be appropriate to warrant a change in current guidelines.[16,17] Nevertheless, this personalized medicine approach to nutritional supplementation represents an intriguing beginning, with more research to follow.

Genotype information involving complement risk alleles has been shown in one study to correlate with treatment response in geographic atrophy. In 129 subjects with geographic atrophy, Genentech/Roche's MAHALO study assessed lampalizumab, a monoclonal antibody fragment that inhibits the alternative complement pathway by binding to complement factor D. At month 18, a 20.4-percent reduction in geographic atrophy area progression was reported in the all-comer, lampalizumab monthly arm relative to the pooled, sham arm. However, in the complement factor I (CFI) positive subpopulation, there was an even greater, 44-percent reduction. Based on these positive Phase II results, Genentech/Roche has commenced Phase III Chroma/Spectri studies of lampalizumab in geographic atrophy and will incorporate genotype testing. Someday, treatment of geographic atrophy may involve a personalized medicine companion test for genotype-testing in order to select subpopulations of positive responders.

The ultimate form of personalized medicine in retinal disease involves genetically altering retinal cells. Gene therapy in the retina involves injecting viral vectors that transfect target cells with DNA to produce desired proteins. A common viral vector is the adeno-associated virus, which does not cause disease. Gene replacement has been studied most extensively in Leber's congenital amaurosis, an autosomal recessive retinal dystrophy characterized by severely decreased vision, nystagmus and severely extinguished electroretinogram within six months of birth. One group has extensively studied subretinal gene therapy in the RPE65 form of LCA using recombinant adeno-associated virus 2 (rAAV2) carrying the RPE65 gene. Visual function improved in all patients to different degrees, and cone and rod sensitivities increased significantly in the study eyes but not in the control eyes; however, photoreceptor degeneration continued to progress over the ensuing years, despite the improved visual acuity.[18-21]

In wet AMD, two approaches are currently being studied, an intravitreal injection and a subretinal injection of an AAV containing genes encoding anti-vascular endothelial growth factor therapies. The secreted extracellular domain of sFlt-1, a soluble isoform of the VEGF receptor 1, is a naturally occurring protein antagonist of VEGF. Genzyme is studying an intravitreal AAV2-sFlt-1 injection gene therapy for the treatment of wet AMD. Avalanche Biotech is studying single subretinal injection gene therapy for the treatment of wet AMD. AAV2-sFlt-1 consists of the AAV2 vector, which contains a gene encoding sFlt-1, to eliminate or limit the need for anti-VEGF injection therapy. Its recent 12-month Phase IIa study in wet AMD included 21 subjects in the treatment group and 11 subjects in the control group, all of whom received two initial monthly ranibizumab injections, followed by rescue ranibizumab injections based on pre-specified criteria. Treated subjects showed better results compared to control subjects in multiple criteria, including change in best corrected visual acuity, change in retinal thickness and number of rescue injections.

Currently, there are numerous trials assessing gene therapy in retinal disease including Leber's hereditary optic neuropathy; gyrate atrophy; choroidemia; X-linked retinoschisis; and Stargardt's disease. In the future, it is clear that personalized medicine will dramatically alter the treatment of retinal disorders. Eric Topol's prediction of the creative destruction of medicine may very well be realized in the retina specialist's clinic, in which genetic information will determine how best to treat the right patient, at the right time, with the right therapy, sometimes even altering the genetic makeup of the retina to obviate the need for repeated injection therapy. This approach may dramatically increase the quality of care while potentially lowering costs. REVIEW

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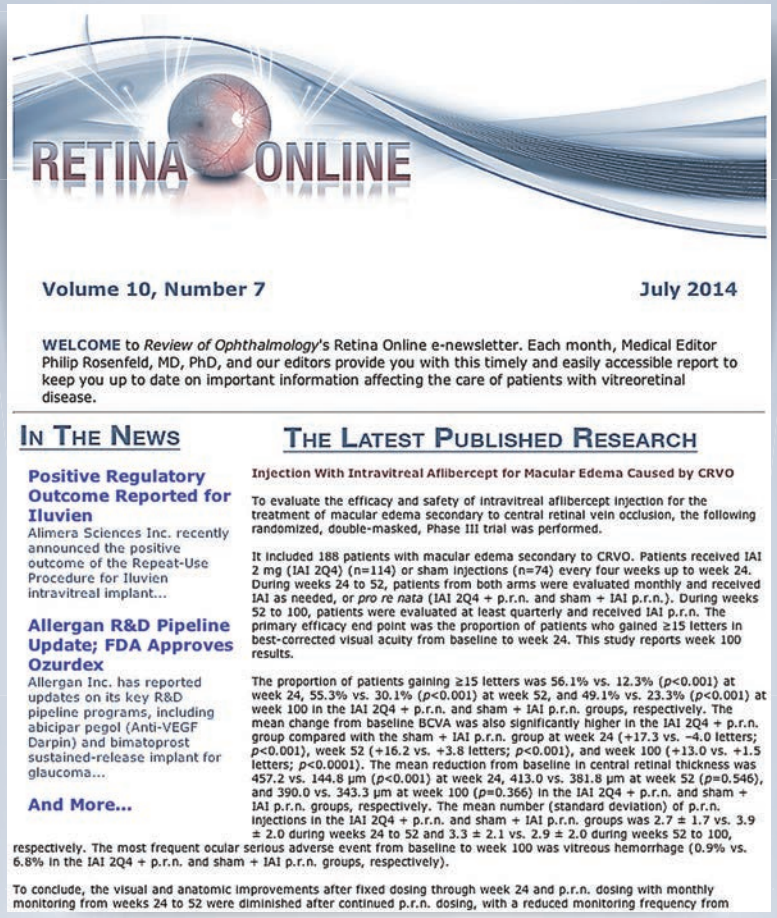
(continued on page 123)

RETINA ONLINE
E-NEWSLETTER



RETINA ONLINE

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WELCOME to *Review of Ophthalmology*'s Retina Online e-newsletter. Each month, Medical Editor Philip Rosenfeld, MD, PhD, and our editors provide you with this timely and easily accessible report to keep you up to date on important information affecting the care of patients with vitreoretinal disease.

IN THE NEWS

Positive Regulatory Outcome Reported for Iluvien
Alimera Sciences Inc. recently announced the positive outcome of the Repeat-Use Procedure for Iluvien intravitreal implant...

Allergan R&D Pipeline Update; FDA Approves Ozurdex
Allergan Inc. has reported updates on its key R&D pipeline programs, including abicipar pegol (Anti-VEGF Darpin) and bimatoprost sustained-release implant for glaucoma...

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THE LATEST PUBLISHED RESEARCH

Injection With Intravitreal Aflibercept for Macular Edema Caused by CRVO

To evaluate the efficacy and safety of intravitreal aflibercept injection for the treatment of macular edema secondary to central retinal vein occlusion, the following randomized, double-masked, Phase III trial was performed.

It included 188 patients with macular edema secondary to CRVO. Patients received IAI 2 mg (IAI 2Q4) (n=114) or sham injections (n=74) every four weeks up to week 24. During weeks 24 to 52, patients from both arms were evaluated monthly and received IAI as needed, or *pro re nata* (IAI 2Q4 + p.r.n. and sham + IAI p.r.n.). During weeks 52 to 100, patients were evaluated at least quarterly and received IAI p.r.n. The primary efficacy end point was the proportion of patients who gained ≥15 letters in best-corrected visual acuity from baseline to week 24. This study reports week 100 results.

The proportion of patients gaining ≥15 letters was 56.1% vs. 12.3% (p<0.001) at week 24, 55.3% vs. 30.1% (p<0.001) at week 52, and 49.1% vs. 23.3% (p<0.001) at week 100 in the IAI 2Q4 + p.r.n. and sham + IAI p.r.n. groups, respectively. The mean change from baseline BCVA was also significantly higher in the IAI 2Q4 + p.r.n. group compared with the sham + IAI p.r.n. group at week 24 (+17.3 vs. −4.0 letters; p<0.001), week 52 (+16.2 vs. +3.8 letters; p<0.001), and week 100 (+13.0 vs. +1.5 letters; p<0.0001). The mean reduction from baseline in central retinal thickness was 457.2 vs. 144.8 µm (p<0.001) at week 24, 413.0 vs. 381.8 µm at week 52 (p=0.546), and 390.0 vs. 343.3 µm at week 100 (p=0.366) in the IAI 2Q4 + p.r.n. and sham + IAI p.r.n. groups, respectively. The mean number (standard deviation) of p.r.n. injections in the IAI 2Q4 + p.r.n. and sham + IAI p.r.n. groups was 2.7 ± 1.7 vs. 3.9 ± 2.0 during weeks 24 to 52 and 3.3 ± 2.1 vs. 2.9 ± 2.0 during weeks 52 to 100, respectively. The most frequent ocular serious adverse event from baseline to week 100 was vitreous hemorrhage (0.9% vs. 6.8% in the IAI 2Q4 + p.r.n. and sham + IAI p.r.n. groups, respectively).

To conclude, the visual and anatomic improvements after fixed dosing through week 24 and p.r.n. dosing with monthly monitoring from weeks 24 to 52 were diminished after continued p.r.n. dosing, with a reduced monitoring frequency from

Once a month, Medical Editor Philip Rosenfeld, MD, PhD, and our editors provide you with timely information and easily accessible reports that keep you up to date on important information affecting the care of patients with vitreoretinal disease.

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Fellowship in A **Nutshell**

From patient preparation to surgical pearls, how to perform a **blepharoplasty like a master.**

By Rona Z. Silkiss, MD, FACS

Surgery requires discipline. Expectations for results are high for both patient and surgeon. Successful outcomes require not only the use of specific surgical techniques but also an understanding of the desires and aesthetics of the patient as mirrored against the potentially achievable and unachievable outcomes. For example, no surgeon, no matter how gifted, can turn an 88-year-old woman into her 28-year-old idealized self. This article will present specific techniques for patient expectation management and then pearls for the surgical techniques used in blepharoplasty.

Expectation Management

1. The preoperative evaluation is critical. An open conversation regarding the desires of the patient as compared to the "world of the possible" is critical for a successful procedure. With a mirror and Q-tip in hand, the likely outcome of a blepharoplasty, cosmetic or functional, is presented. Patients are encouraged to bring old photos and magazine images to the consultation. This serves as a platform to discuss what is probable versus impossible in outcome.

2. The patient is cautioned that more is less successful with respect to this procedure, and that a tight eyelid may lead to closure and dry-eye issues. If the patient refers to the subbrow tissue as excessive, she should be cautioned that you cannot lift an eyebrow by lifting the eyelid and any attempt to do so will "sew the eyelid to the eyebrow" leading to a nonfunctional and nonaesthetic result.

3. If the patient appears to be unsatisfiable at the time of the consultation, the surgeon does have the ability to say no and decline the opportunity to operate on the patient. Patients that are difficult in the preoperative period do not become easier to manage after surgery when the "honeymoon of good behavior" has ended. Given the damaging power of social media used as a weapon by hostile patients, judgment by the surgeon preoperatively of the appropriateness of the patient for a procedure is critical.

4. Establish an appropriate operating room environment. Our patients not only have high expectations for the procedure, they have high expectations for the process. As such, to the extent possible, a "Four Seasons" experience should be provided to the patient. This may involve private preoperative areas, kind and caring personnel, calming music in the operating suite, warm blankets, organized postoperative instructions, and even a get-well card from the operating room team!

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Surgical Procedures

1. Under intravenous sedation a 50:50 mixture of 2% Xylocaine with 1:100,000 epinephrine, 0.5% Marcaine with 1:200,000 epinephrine, NaHCO3 and hyaluronidase is injected into the lateral aspect of each upper lid with a 25 ga. 5/8-inch needle. A single injection point is used with the needle directed laterally. This lateral orientation is critical to patient safety in the event the patient moves her head suddenly. The circulating nurse may gently hold the patient's head to remind him not to move. Once a bleb of 1 cc is injected, the local solution is wiped across the eyelid from lateral to medial. This single point injection and wipe technique, "digital diffusion," allows for dissemination of the local solution without tissue distortion and decreases the risk of bruising by limiting the number of times the eyelid is injected.

2. The patient is prepped and draped in sterile fashion. The Betadine is wiped from the face to provide a clean surface. The undersurface of the chin is prepped in the event the patient's chin requires manual elevation during the course of the procedure. The head drape is secured making sure the brows are not elevated or under tension by the drape itself.

3. Attention is directed to lighting, table height and doctor position, ensuring that the illumination is bright and that the surgeon is comfortable without undue stress on her back or neck. The surgical tray is reviewed to ensure all equipment needed is available, additional local anesthetic is placed on the tray, and sutures are selected, opened and preloaded onto the needle holders. For an upper blepharoplasty a 5-0 silk suture on a P-1 and a 6-0 plain gut on a G-1 are used.

4. The patient is then marked with a fine-tip marking pen and caliper. Care is taken to note the position of the natural or desired lid fold crease. The initial marking is placed in the desired crease in the mid-pupillary line. The remainder of the lid crease incision is created by either following the natural and visible lid fold crease or marking the new crease in a gradual taper medially and laterally approximately 1 mm closer to the lid margin at each end point. The lateral aspect of the incision may extend approximately 1 mm less than the maximal lid crease height. Care is taken to provide maximal symmetry.

The enemy of good is the drive for perfection.

In a bilateral blepharoplasty, this marking is performed sequentially on the right and left eyelid. 0.5 Castroviejo forceps and Brown Adson forceps are used to delineate the skin to be excised via a pinch technique. Take care to ensure that there is no tension on the eyelid. If the eyelid does not close in the operating room, it will not close in the office. Once the amount of skin to be excised is determined, the marking pen is used to define the incision. Take care to ensure that the arc of the upper lid mark is the same height laterally and centrally. This ensures that the patient does not have residual temporal hooding after the procedure. Once the incisions have been delineated, the surgeon should stand back and compare the two incisions for symmetry. This should include both the extension and angle of the lateral incision as well as a visualization of the tissue that remains behind. The tissue remaining is more important for symmetry than the tissue removed.

5. A 5-0 silk suture on a P-1 needle is positioned in the central portion of the upper lid margin. The lid is placed on downward tension. Using a #15 Bard Parker blade the skin is incised. The cutting mode of cautery on blend and fulgurate at low levels is used to dissect the skin from the orbicularis. The orbicularis is left intact. This insures that the patient will have full blink function and not a skeletonized eyelid postoperatively. Additionally the plane between the skin and orbicularis is a bloodless plane.

6. If the patient requires diminution of the medial or central fat pad, a buttonhole incision is made through the medial preseptal orbicularis. A knuckle of orbital septum is incised. Pressure on the lid will prolapse both the medial and central preaponeurotic fat pads into the surgical field. The fat pads can be differentiated not only by location, but by the white coloration of the medial fat pad and more yellow coloration of the central fat pad. The pads are then trimmed as needed to achieve the desirable cosmetic contour.

7. The skin incisions are then closed with a running 6-0 plain gut or nylon suture. The medial end of the suture is clamped with a curved hemostat. A single, fine skin hook is placed at the lateral edge of the incision and allowed to dangle. This automatically aligns the wound edges and distributes the tension equally across the incision allowing accurate, rapid closure. The ends are tied and cut. A combination corticosteroid/antibiotic ointment is applied. Ice compresses are applied in recovery as they are applied in the operating room as attention is directed from one eyelid to the other. A video of this technique can be seen at: http://goo.gl/pRkv2v

Additional Considerations

1. Surgical expertise takes experience and practice. It takes a commitment to lifelong learning even when change is uncomfortable. Surgical expertise requires an open mind to change, but also a discerning intellect that keeps its own counsel regarding the viability of new ideas.

2. Blepharoplasty is a contour surgery, not a procedure designed to correct wrinkles.

3. Attempts to dramatically alter someone's underlying configuration may lead to a surgical appearance, rather than an attractive eyelid.

4. Surgery is subtractive. It does not correct overall deflation and volume loss, which are all signs of aging.

5. Surgical overcorrection may lead to changes that are similar to those of aging—skeletonization, loss of fullness, etc.

6. The enemy of good is the drive for perfection.

7. The best possible surgical outcome results from understanding your patient's goals and how they compare with realistic outcomes. Understanding the enduring characteristics of beauty and attractiveness and the value of restraint will guide the surgeon in the attempt to achieve optimal results. REVIEW

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Bring Them to Tears With Your Treatment

New compounds, especially those derived from hyaluronic acid, may change the game of dry-eye treatment.

Mark B. Abelson, MD, CM, FRCSC, FARVO, George Ousler, Lisa Smith, and Urmila Santanam, PhD
Andover, Mass.

Christian Nestell Bovee, a 19th century writer known for pithy epigrams, once wrote, "Tears are nature's lotion for the eyes. The eyes see better for being washed by them." However, as clinicians know, nature's lotion doesn't always appear for everyone, and it's striking how something as seemingly ordinary as tears, or the lack thereof, can be the bane of existence for so many individuals. To help these sufferers, clinicians and companies have provided compounds to replace what is lacking on the ocular surface, though these solutions only go so far; there are only a limited number of polymers that could be accepted as components of these products because the construction of a tear substitute must comply with the U.S. Food and Drug Administration monograph. Therefore, using a new component would first require proof of its efficacy, which is often a lengthy process. However, help is on the way, as studies are showing that hyaluronic acid and its modified forms can significantly increase the benefits of artificial tear products. In this month's column, we take a look at artificial tears, focusing on the ongoing refinement of formulations, active components, improved lubricants and the pursuit of an optimal ocular surface tear substitute.

The Scope of the Problem

Keratoconjunctivitis sicca or dry-eye disease is a condition affecting nearly 5 million Americans over the age of 50, the main causes of which are manifold. Dry-eye disease has often been oversimplified as being characterized by a deficiency of the tear film[1] that leads to ocular burning, stinging, foreign body sensation or blurred vision, since the use of replacement tear substitutes does account for the majority of the recommended therapies. It can vary in severity from mild discomfort to a more severe loss of visual function, pain and light sensitivity. The collected combination of one or more of these symptoms leads to a potentially profound lowering of quality of life. While Restasis is helpful in some patients by virtue of its anti-inflammatory effect, tear substitutes offer only periodic, short-lived relief.

Although we have learned a great deal about the pathophysiology of dry eye, its treatment still challenges us, and what we perhaps considered to be a simple shortage of ordinary tears is in fact a far more complex issue. Despite efforts to develop secretagogues, anti-inflammatories and other tear modulators, we still—surprisingly—rely on the symptomatic relief offered by tear substitutes as one of the primary means of dry-eye management.

Artificial Tears

While browsing through the aisles in a drug store, a patient is confronted with an abundance of over-the-counter artificial tear options *(See box, p. 105)*. Further options include non-preserved, single-use products. While preservative-containing products offer safety and a cost-saving benefit, preservative-free options avoid the potential for irritation and other adverse effects of preservatives and are more suitable for dry-eye patients who require a greater frequency of instillation (more than six times each day). Additional options

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include ointments—or products with a high viscosity that cause blurring and are typically used at nighttime—and those with a low viscosity that are used during the day. This usually means that most patients require two types of products, adding to the confusion. The vast assortment of available products often requires multiple rounds of trial and error before patients can find those best suited to them.

The first tear substitutes in modern times were saline-based isotonic or hypotonic solutions. These, unfortunately, had poor distribution over the ocular surface and low retention time, producing only momentary relief and requiring very frequent administration. Another group of tear substitutes included natural or synthetic polymers like methylcellulose derivatives, polyethylene glycol and polyvinyl alcohol which, due to their higher viscosity, contributed to a better retention time. A third group of tear substitutes included lipid emulsions that increased retention time, reduced evaporation from the ocular surface and improved the stability of the lipid layer.

Ingredients in artificial tear products have been shown to have different effects on comfort and on signs of dry eye. These effects, however, are mostly short-lived, providing relief from discomfort for a mere 10 or 20 minutes, and therefore requiring repeated instillations. One way to address this issue is by modulating drop viscosity, as a product with a higher viscosity will tend to have a longer retention time on the ocular surface. Conversely, if it's too viscous, a drop of it can cause blurring or lid-caking. A measure of the importance of this issue is reflected in the hundreds of patents issued in recent years covering manufacturing of tear substitutes within a specific viscosity range or with other specific physical properties relating to viscosity.[2] Refinements of drop formulations with the aim of achieving optimal viscosity are ongoing. Of these, hyaluronic acid-based products have been a focus in many dry-eye trials, and there's reason to believe they might be the best of the viscous additives. These should soon to be available by prescription or over-the-counter.

Let's take a deeper look into hyaluronic acid and its viscoelastic properties, and see how these properties can provide for positive outcomes in dry-eye treatment.

Over-the-Counter Tear Options

Artificial Tears (Akorn)	Oasis Tears (Oasis Medical)
Refresh Celluvisc (Allergan)	Opti-Free (Alcon)
Clear Eyes CLR (Prestige Brands Holdings Inc.)	Optive (Allergan)
GenTeal (Alcon)	Refresh Tears (Allergan)
Hypotears (Alcon Novartis)	Soothe (Bausch + Lomb)
Isopto Tears (Alcon)	Systane (Alcon)
Lacri-Lube S.O.P. (Allergan)	TheraTears (Akorn)
	Visine Tears (J&J)

Hyaluronic Acid

Hyaluronic acid is a naturally occurring polysaccharide that's ubiquitous in humans and other animals. What makes HA such an ideal lubricant is that it is amphipathic, with both hydrophobic and hydrophilic traits. This amphipathic nature yields a unique biological behavior. Hundreds of monosaccharide rings are linked to form a planar hydrophobic surface, acting like a long-chained fat molecule—energetically happiest when stacked and away from aqueous environments. At the same time, the sugars have acid side-chains projecting laterally, creating a hydrophilic edge stabilized by a crowd of adoring water molecules. The HA monomers are like ribbons in which the face of the ribbon is the hydrophobic domain, and its edges are the hydrophilic domain. This combination of features gives it its viscoelasticity, its capacity to retain water and its ability to occupy a large volume at a relatively low concentration. They also allow it to act as a selective permeability barrier where small molecules can diffuse through it at faster rates than larger molecules.[3]

Therapeutic uses of HA abound in many branches of science and medicine. HA is used for intra-articular injections to replace synovial fluid in patients with osteoarthritis, to control post-surgical adhesions and prevent scar formation, and to promote wound healing. It's better-tolerated than collagen injections when cross-linked preparations are injected into the skin to aesthetically treat wrinkles.[3] Three-dimensional tissue culture using HA-containing scaffolds enhances tissue growth and differentiation and is now the foundation of many types of tissue engineering and drug-delivery applications.[4,5] HA preparations are of course useful in ophthalmology due to the viscosity of HA, a property that helps conserve spatial orientations of ocular tissues during surgery.[3] These unique viscoelastic characteristics, as well as its tolerability and biodegradability, allow for numerous potential applications, including the use of HA as an active ingredient in tear substitutes. But is it inert or is it actually pharmacologically active?

The viscoelasticity of HA-based formulations allows for better tear

Table: HA and modified-HA Artificial Tear Products

Product (Company)	Active Ingredient	Notes	Status	ClinicalTrials.gov Identifier
Vismed (TRB Cemedica)	0.18% Sodium Hyaluronate	Preservative free	Phase III completed, marketed in U.K., Europe and Asia	NCT00599716
Vislube (TRB Cemedica)	0.18% SH solution	Preservative free	Marketed in Europe, Australia and Asia	NCT01363414
Hylabak or Hyabak (Spectrum Thea Pharmaceuticals)	0.15% Hyaluronic Acid or SH	Preservative free Phosphate free	Marketed in Russia, Lebanon, Argentina and Germany	-
Hyalein	0.1% SH	Active control in Phase III study	Phase III completed, marketed in Japan	NCT00885079
Opticalm (Omega Pharma)	0.2% SH	Also contains 0.2% Hypromellose	Marketed in Europe	-
Hylovis (TRB Cemedica)	0.18% SH solution	Preservative free	Marketed in Europe, Australia and Asia	-
Blink Tears (Abbott)	0.25% Polyethylene Glycol	HA listed as inactive ingredient	Approved; Phase IV completed	NCT01061268
Rejena (sponsor)	0.18% HA	Data considered weak	Not approved by FDA	NDA 22-358
JDE-001 (Jade Therapeutics)	Thiolated carboxy-methyl HA	Designed to improve tear-film stability	Pre-IND Stage	-
SI-614 Ophthalmic Solution (Seikagaku)	Modified HA	Possibly improves residence time and tear-film stability	Phase III ongoing	NCT02205840

stability, longer retention time and improvement of dry-eye symptoms, all of which have made it beneficial in the management of dry eye. A review of the positive outcomes brought on by different artificial tears showed increasing improvements in the percentage change in rose bengal scores of 25.9 ±18.4 with saline, 38 ±20.7 with polyacrylic acid and 41.8 ±16.3 with hyaluronic acid products.[6] A comparative study revealed that HA formulations provided superior ocular comfort relative to other viscous comfort agents like hydroxypropyl methylcellulose and carboxymethyl cellulose by enhancing tear-film stability, retaining tear volume and lubricating the ocular surface.[7] In a separate study, sodium hyaluronate was well-tolerated and improved moderate dry-eye symptoms more rapidly than carboxymethyl cellulose-based artificial tear formulations.[8]

The 0.1% concentration of HA has been the most extensively studied in artificial tears. Patients treated with 0.1% HA for four weeks had statistically significant relief from burning and improved rose bengal staining compared to those treated with 1.4% polyvinyl alcohol in a crossover study.[9] A 28-day treatment with 0.1% HA solution was also reported to reduce epithelial cell damage assessed by rose bengal staining, to improve Schirmer's scores and to decrease ocular burning and grittiness.[10] Instillation of 0.18% HA for periods of seven or 14 days was found to improve lissamine green staining and a global symptom frequency score.[11] Long-term use of 0.15% sodium hyaluronate-containing artificial tears has been shown to reduce ocular surface damage in dry-eye patients, with no treatment-related adverse events.[12] Recently, HA has been used as a combination product, or dual polymer (in conjunction with hydroxypropyl guar, a mucomimetic polymer). A study from Alcon Research showed that formulations combining HA and hydroxypropyl guar could provide synergistic benefits in improving ocular surface hydration and decreasing friction.[13] These HA products appear to function as more than just ocular lubricants, since they also exert pharmacological effects on the ocular surface.

While there are as yet no FDA-approved tear substitutes with HA-derived active ingredients, a host of

(continued on page 131)

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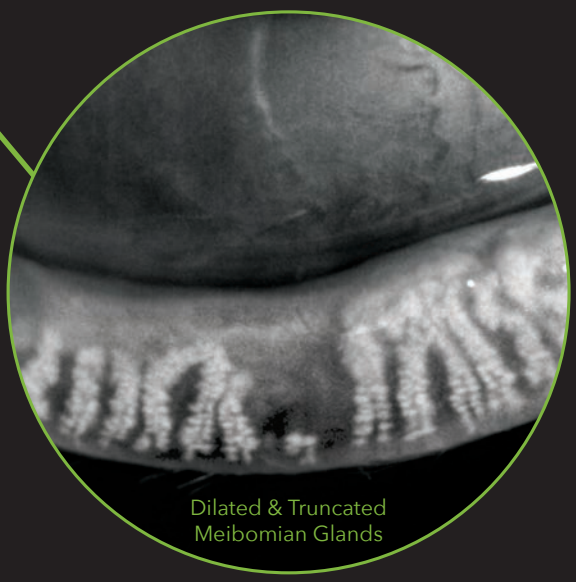

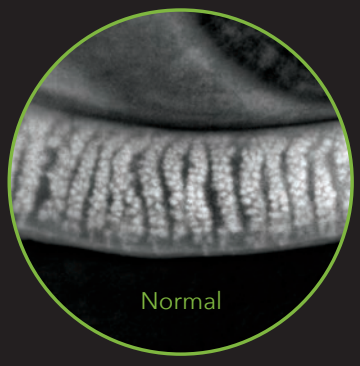

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Hone Your Surface Ablation Technique

Expert tips on how to get the best outcomes possible when a patient is a good candidate for surface ablation.

Walter Bethke, Managing Editor

Though LASIK is the most popular laser refractive surgery procedure, surgeons' concerns about ectasia and some patients' desire to avoid a flap have led to surface ablation retaining a healthy number of fans. And, as they do with other surgeries, surgeons are constantly analyzing their surface ablation techniques to see if they can improve them. Here, expert refractive surgeons outline aspects of their surface ablation protocols that they feel enhance their outcomes.

The Right Patient

Surgeons say that, depending on your readiness to perform surface ablation, patient inclusion criteria can vary.

William Wiley, MD, assistant clinical professor of ophthalmology at University Hospitals/Case Western University, says he's more apt to reserve surface ablation for certain patients. "I like surface ablation, but if I can do LASIK or—for a patient with high myopia—an ICL, I prefer to do either of those," he says. "The main reason I would do surface ablation would be for thinner corneas with milder prescriptions. Also, if a cornea is borderline suspicious for keratoconus, or the patient has slightly irregular topographies, I'd prefer not to perform vision correction. However, in some cases involving a highly motivated patient with just one thing that might be slightly suspicious, such as slight inferior steepening and a mild prescription, we'd discuss surface ablation. I would also discuss the risk of ectasia, and that the patient might need to be followed over time. We'd also plant the seed for the possibility of cross-linking for corneal strengthening after six months."

Austin, Texas, refractive surgeon Steven Dell says that, though dry-eye concerns might push some physicians in the direction of recommending surface ablation to certain patients, he doesn't subscribe to that notion. "We don't automatically do surface ablation in patients in whom we fear dry eye," he says. "I don't think dry eye is less common with PRK than it is with LASIK. In data on around 32,000 patients at [the U.K.'s] Optical Express, Dr. Steve Schallhorn found dry eye to be less common with LASIK than PRK postop. So, for us, the threat of dry eye isn't a reason to go to surface ablation in a patient who would otherwise be a candidate for LASIK."

All images: Elizabeth Hofmeister, MD

The Amoils brush can be useful when you need a large treatment area, surgeons say.

In an interesting juxtaposition from most surgeons' experience, in the U.S. Navy, PRK is actually more popular than LASIK, mainly because of patient choice. "Fifty-five percent of our procedures are PRK," says Capt. Elizabeth Hofmeister, MD, a refractive surgeon who practices at the Naval Medical Center in San Diego. "Forty-four percent are LASIK and just under 1 percent are ICL. We do a lot of surface ablation. It usually comes down to patient choice—they've done some research and heard the information in our informed consent process and they decide which procedure they want. Depending on what we find in

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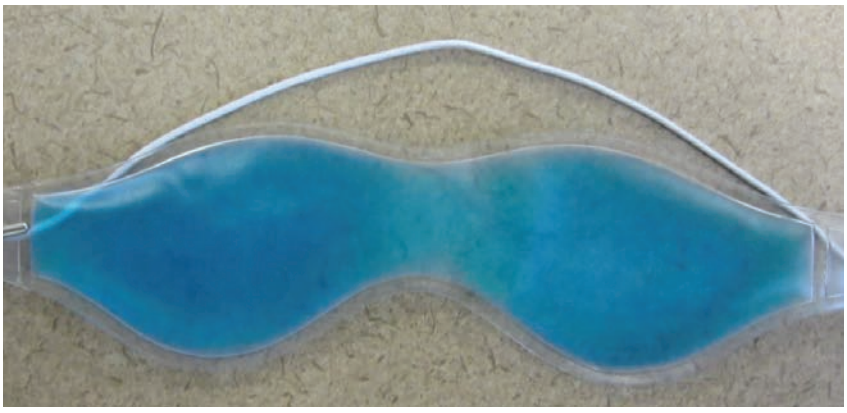
their preoperative exam, however, we may steer patients toward PRK. One big patient category that we steer toward PRK consists of individuals with corneal scars. If the scar is deep or prominent enough, we're concerned that that might be a place for vertical gas breakthrough during the creation of the femtosecond LASIK flap. Also, we operate on very young patients—in their early 20s—and we try to avoid performing any kind of corneal refractive surgery on anyone we think might have keratoconus. However, if they have questionable topography but it's not at the point where you could even make a diagnosis of forme fruste keratoconus, we'll steer them toward PRK. Otherwise, beyond those indications, it's up to the patient to decide."



An ice-pack mask placed over the eyes from time to time during the postop period following a surface ablation procedure can help reduce swelling and decrease postoperative pain until the eye has had a chance to recover.

Intraoperative Tips

Surgeons say you can have success with different methods of epithelial debridement to start the procedure.

Dr. Hofmeister says the Navy's centers have settled on debridement with a rotating brush. "Years back, we did studies on different methods of epithelial removal, and what we decided on as being the best, most reliable method was the rotating Amoils brush," she says. "It's rare that we'll do alcohol debridement, and we don't have the capability to do a laser epithelial removal that would get a large enough area of epithelium to incorporate the large-zone treatments we like to use—it would be limited to a 6-mm zone. We tend to use the 9-mm brush head for all our patients. We know that we might not quite need 9 mm for our myopes, but you definitely need it when treating a low hyperope."

Dr. Dell, however, gets the best results with alcohol debridement. "We place a well over the desired optical zone and irrigate some alcohol solution, 20% ethanol, onto the cornea for about 30 to 35 seconds," he explains. "The epithelium comes right off. Note that there will be a little bit of seepage of the alcohol beyond the confines of the well, so you'll end up with a slightly larger epithelial defect than the size of the well. For example, using a 7.5-mm well would result in an 8-mm defect. This is nice because it allows you to titrate the defect. If I'm treating a low prescription, such as less than a diopter of myopia, I really don't need a huge epithelial defect, so I can use a smaller well. Having a smaller defect speeds the healing process. The rationale behind this is that the so-called transition zone beyond the 6-mm optical zone isn't important when you have a very low correction and the difference between treated and untreated cornea isn't particularly significant.

"If you're treating a very high prescription, however," Dr. Dell continues, "you don't want an abrupt transition zone between treated cornea and untreated peripheral cornea. In those cases, the optical zone and the transition zone are both very important. In those cases, we'd tend to use a larger epithelial defect diameter. Whichever size well you use, after you remove the epithelium it's important that you wick away the alcohol and don't let it get on the conjunctiva, because it can be very irritating to the patient."

Dr. Wiley sometimes uses the laser scrape technique referred to by Dr. Hofmeister, but says, "We've seen some variable responses due to irregular epithelium in which the stroma is ablated along with the epithelium, causing unexpected outcomes or refractive surprises." He says he prefers to use the alcohol technique. Recently, however, he's been incorporating a new device from Israel's Orca Surgical called Epi Clear. The device is used for a procedure the company is billing as epithelial Bowman's keratectomy. "EBK preserves Bowman's membrane prior to laser ablation," Dr. Wiley explains. "Of course, when you laser the cornea you laser through Bowman's, but in the periphery Bowman's will still be intact. By preserving Bowman's there, it's thought that, when the epithelium regrows, it grows in more of a lamellar, regular fashion that could result in faster healing. We haven't done enough eyes to see if that theory is correct, but it looks promising. The way the Epi Clear works is it scrapes across the cornea with two parallel plastic blades. One of the blades is a little lower than the other, allowing it to remove epithelial cells in a controlled manner. The cells slide up off the cornea and between the two blades. The blades are designed to be sharp enough to remove epithelium but dull enough to not penetrate Bowman's. It's a single-use blade head."

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Refractive surgeons also make sure to take steps to reduce the risk of haze postop. "The naval centers vary, but most try to rapidly cool the cornea as soon as the refractive ablation is completed," says Dr. Hofmeister. "Some use a chilled Merocel sponge, some use chilled BSS. At our center, since our rooms are so cold, we use room-temperature BSS after the ablation, and this might reduce the risk of haze. We also use mitomycin-C on many of our PRK patients, an off-label use of the drug. We use 0.1 mg/ml for a duration of 15 seconds, followed by copious rinsing with BSS." Drs. Dell and Wiley use MMC for all of their ablation cases. "It's been many years since I've seen a case of haze," avers Dr. Dell. "We saturate a round corneal light shield sponge with 0.02% mitomycin and place it on the cornea, and the surface tension will keep it on the eye for the 12 seconds we need it to be there. Afterward, we irrigate it away with 10 cc of BSS."

Postop Pain Control

Though PRK doesn't stand for Painful Refractive Keratectomy, there are some patients who might disagree for the first couple of days postop. Here are some ways to control PRK's sometimes considerable discomfort.

Dr. Hofmeister takes several measures. "Pain is definitely a big concern for patients following PRK," she says. "We spend a lot of time preop explaining what they should expect so that when they have the pain afterward, they're not shocked or surprised. To try to manage it, we take a multilevel approach: an oral NSAID, and we try to have them keep a steady state of that medication as a baseline; a bandage contact lens postop, which I think is the biggest advance in reducing pain after PRK; ice packs to try to decrease swelling and pain; a breakthrough pain medication such as Norco or Percocet; and a non-preserved topical anesthetic—we use tetracaine—which has been a wonderful source of relief for patients. When the pain gets really bad on the first or second postop night, they can use the non-preserved anesthetic. The benefit of the bandage lens is today's lenses can breathe and move, yet still reduce the friction of the lid against the large epithelial defect that we've created. This really helps with pain management."

In addition to NSAIDs, steroids, antibiotics and an anesthetic rescue drop for two days postop, Dr. Dell has taken a cue from Colman Kraff, MD, of Chicago, and places a drop of Bausch + Lomb's Prolensa under the bandage contact lens, which Dr. Kraff believes helps with healing. Dr. Dell also gives patients an oral pain medication, but, he says, "The vast majority of patients don't need to use it." REVIEW

None of the surgeons has a financial interest in any product mentioned in the article.

JANUARY

8 - 9
NEW YORK CITY

The LuEsther T. Mertz Retinal Research Center at Manhattan Eye, Ear & Throat Hospital will host the Atlantic Coast Retinal Club and MACULA 2016 for a two-day conference on advances in diagnosis and treatment of macular diseases. Participants will discuss alternative concepts for dry and wet age-related macular degeneration, including a discussion on the basic science behind the disease, diabetic retinopathy, idiopathic perifoveal telangectasia, ocular tumors, as well as other vitreo-retinal macular diseases. Information on new and experimental pharmacological therapies, as well as new imaging concepts, vitreoretinal surgical instrumentation and applications will also be presented. CME is available. For more information, visit bit.ly/1hHkQke.

16 - 22
THE BIG ISLAND, HAWAII

In 2016, more than 1,200 comprehensive ophthalmologists, retina specialists, nurses, technicians and administrators will come together for Hawaiian Eye and Retina, held at the Hilton Waikoloa Village on Hawaii's Big Island. Atendees will have a chance to stay up-to-date with today's hot topics as well as receiving a comprehensive update on every aspect of a busy practice, including practice management, cataract/IOL technique and technology, cataract and refractive surgery complications, vitreoretinal issues, glaucoma, medical retina, ocular surface management and refractive surgery. For more information, call (877) 307-5225 or email registration@contactAMS.com.

FEBRUARY

5 - 9
GUADALAJARA, MEXICO

The World Ophthalmology Congress, sponsored by the International Council of Ophthalmology and hosted by the Mexican Society of Ophthalmology, will hold its 2016 meeting at Expo Guadalajara in Guadalajara, Mexico. The Congress brings together approximately 130 member societies of the ICO and ophthalmologists from around the world to share the latest developments in ophthalmology. There will be the opportunity to network with recognized international leaders and professionals in ophthalmology, scientific programs addressing subspecialties and related interests in ophthalmology and an exhibition featuring the latest products and services in the field. For more information, visit woc2016.org.

12 - 14
PARK CITY, UTAH

The Innovative Techniques & Controversies in Ophthalmology symposium will provide the latest information about advanced phacoemulsification technology and techniques, IOLs, and refractive, corneal and glaucoma surgery. Materials will be presented in a highly interactive style utilizing case studies, video and panel discussions. Evening sessions will consist exclusively of video presentations of interesting and challenging complications and cases that encourage audience participation. CME is available. For more information, visit revophth.com/ParkCity2016.

MAY

1- 5
SEATTLE

The theme of the Association for Research in Vision and Ophthalmology 2016 Annual Meeting is "Research: A Vision of Hope." Biomedical research is behind every advance in treatment for blinding conditions, behind every improvement in diagnostic methods and behind all progression in understanding the eye and visual processes. ARVO members are engaged in the research that brings hope to patients and their families that treatments and cures for eye diseases are on the horizon. The ARVO Annual Meeting is the largest gathering of eye and vision researchers in the world; approximately 45 percent of attendees are from outside the United States. The Annual Meeting features five days of innovative and cutting-edge vision science and eight major lectures, including an opening and a closing keynote. CME is available. For more information, visit arvo.org.

6 - 10
NEW ORLEANS

The American Society of Cataract and Refractive Surgery and the American Society of Ophthalmic Administrators' annual Symposium and Congress will take place in New Orleans at the Ernest N. Morial Convention Center. The ASCRS Annual Symposium is the largest U.S. meeting dedicated exclusively to the needs of the anterior segment specialist. Attendees will have the benefits of hands-on skills training, as well as sessions covering legislative and regulatory updates and the latest scientific papers and posters. The meeting will be preceded by a glaucoma subspecialty day covering critical updates, robust debates and interactive case studies. The simultaneous ASOA Annual Congress is the leading practice management program for comprehensive ophthalmology and subspecialties. CME hours will be available. For more information, visit annualmeeting.ascrs.org.

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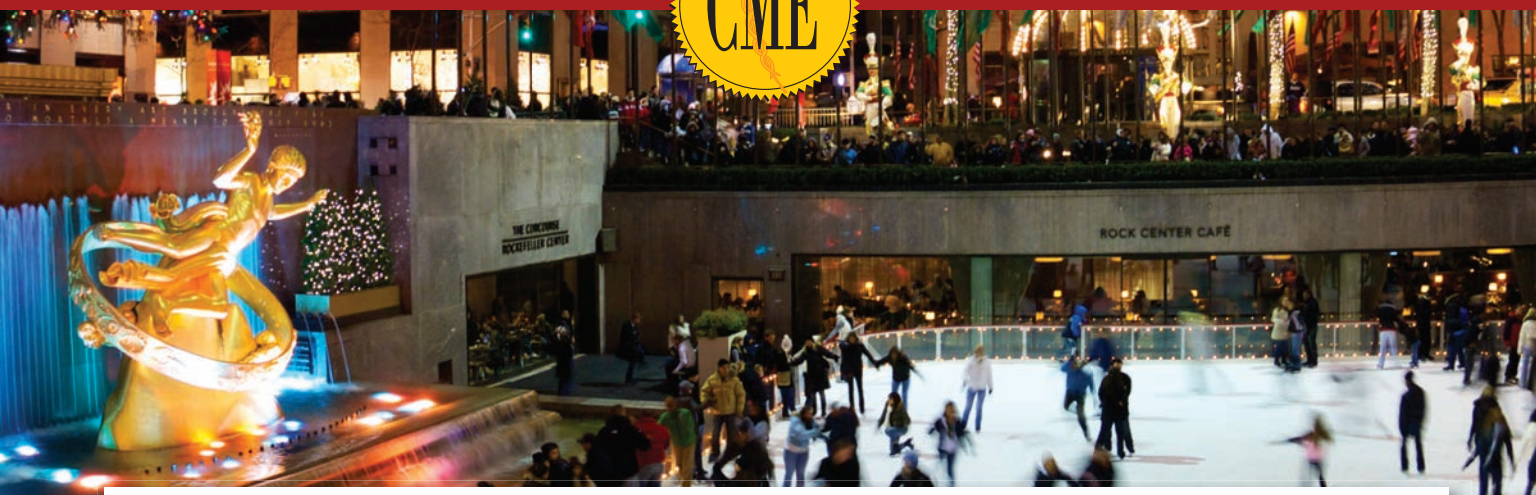

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Putting Injectable Facial Fillers to Their Best Use

Filler indications range from lip and cheek augmentation to treatment of moderate to severe facial rhytids.

Ronald W. Milam Jr., MD, Matthew Zhang, MD, and Behin Barahimi, MD, Nashville, Tenn.

Loss of volume in the face and periocular region leads to rhytid formation (exaggerated skin folds, creases and wrinkles), giving individuals a more aged appearance. Dermal fillers are natural and synthetic materials that are injected into the skin of the rhytids to replace the loss of volume and ultimately diminish the appearance of facial wrinkles and creases. The use of dermal fillers for effacement of facial rhytids has gained popularity since the Food and Drug Administration approved the first collagen filler in 1981.[1] In 2013, injection of soft-tissue fillers was the second most common minimally invasive cosmetic procedure performed in the United States, accounting for 2.2 million procedures.[2] The number of injections increased by 243 percent from 2010 to 2013, which was the second highest rate of increase, behind botulinum toxin injection, for all minimally invasive cosmetic procedures performed in the United States.[2]

While there are numerous filler types available to the clinician, hyaluronic acid is the most commonly utilized today. Hyaluronic acid fillers not only replace the volume loss that is experienced with aging but also stimulate collagen production. A study by Taihao Quan, MD, PhD, and colleagues demonstrated increased fibroblast proliferation, expanded vasculature and increased epidermal thickness when hyaluronic acid was injected into the skin of patients older than 70 years of age. They hypothesized that fillers stiffen the extracellular matrix, induce fibroblast elongation and activation, and upregulate the transforming growth factor-beta pathway, leading to collagen synthesis.[3]

Currently, more than 20 dermal fillers have FDA approval for use in the United States. Filler indications range from lip and cheek augmentation to treatment of moderate to severe facial rhytids *(See Table 1)*.[1] Here, we will discuss the array of materials approved for use as soft-tissue filler in the United States, their ndications and known associated complications.

Types of Filler

Modern dermal/soft-tissue fillers are made from various materials and can be categorized into absorbable fillers and non-absorbable fillers. These are the FDA-approved filler types available in the United States:

Absorbable Fillers

• ***Collagen***. Collagen is a protein that is naturally occurring throughout the human body and is found in the skin, bones, tendons and numerous other tissues. Collagen was the earliest filler material used for the treatment of rhytids and is primarily derived from purified human or bovine collagen products. Collagen fillers have the shortest length of effect of all the filler materials[4-6] and their effects generally last for about three to four months.[7]

• ***Hyaluronic acid***. Hyaluronic acid is a polysaccharide that is naturally occurring throughout the human body and is found in numerous tissues, including the skin, synovial fluid, certain types of cartilage and other connective tissues. Hyaluronic acid fillers are derived from purified bacteria and avian (rooster combs) products. Hyaluronic acid is an excellent filler choice because it is biodegradable, biocompatible and non-immunogenic (i.e., has a very low potential for stimulating allergic reaction). It has excellent viscoelastic and hygroscopic properties,

This article has no commercial sponsorship.

which create good volume expansion for the effacement of facial rhytids.[8]

• ***Poly-l-lactic acid.*** PLLA is a biodegradable and biocompatible synthetic polymer that has widespread medical applications as absorbable sutures, bone screws and soft-tissue fillers.[7] As a filler, PLLA is reconstituted with sterile water into a hydrogel with a methylcellulose carrier. PLLA achieves its effects by causing a foreign-body reaction that stimulates collagen formation and dermal fibrosis.[8] In order to achieve the desired amount of volume replacement, PLLA is injected in multiple treatment sessions over a period of months.

Effects may not be seen for several weeks to months but can last for years, with periodic touch-ups.

• ***Calcium hydroxylapatite.*** CaHA is a biocompatible and nonimmunogenic material that is naturally occurring in human bones and teeth. CaHA fillers are synthetic bone microspheres suspended in a carboxymethylcellulose carrier gel. Its effects last approximately 18 months.[7] It should be noted that this filler type is visible on radiographs and may obscure underlying structures on radiographic images.

Non-absorbable Filler

• ***Polymethylmethacrylate.*** PMMA is a non-biodegradable, biocompatible synthetic material that is used in bone cement, intraocular lens implants and soft tissue fillers. As a dermal filler, PMMA microspheres are suspended in a bovine-based collagen and lidocaine solution and injected over a period of several months. PMMA microspheres are permanent and not absorbed by the body.

Indications & Uses

The main indications for injectable fillers include the filling of rhytids and folds, and the correction of soft-tissue loss due to disease or age. The FDA has approved most fillers for the treatment of moderate to severe wrinkles and localized fat loss (lipoatrophy) in the face. Restylane, Restylane-L and Restylane Silk have also been approve dfor lip augmentation in patients over 21 years of age. As of October 2013, Juvederm Volumna XC received approval for augmentation of the cheeks in patients over 21 years of age *(See Table 1)*. All other uses of fillers are considered off-label and should be disclosed as such to patients.[1,7,9]

Commonly utilized off-label applications include volume replacement and enhancement procedures such as cheek and chin augmentation, lip enhancement, hand rejuvenation, tear trough obliteration, nose reshaping, mid-facial volumization and correction of facial asymmetry.

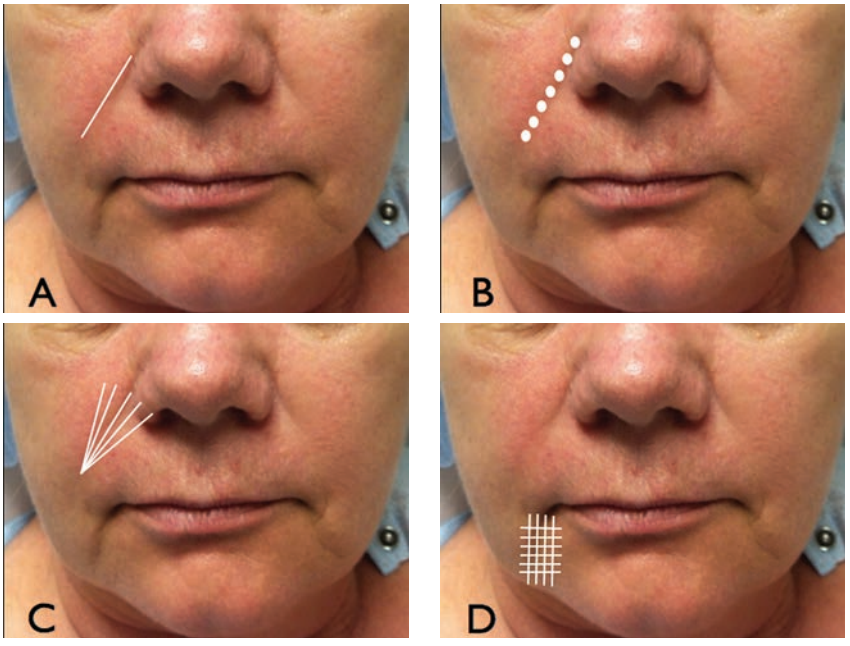


Figure 1. Methods for filler injection. A. Linear threading; B. Serial puncture; C. Radial fanning; D. Cross hatching.

Relative Contraindications

The FDA recommends that patients with the following conditions avoid the use of facial fillers:[9]

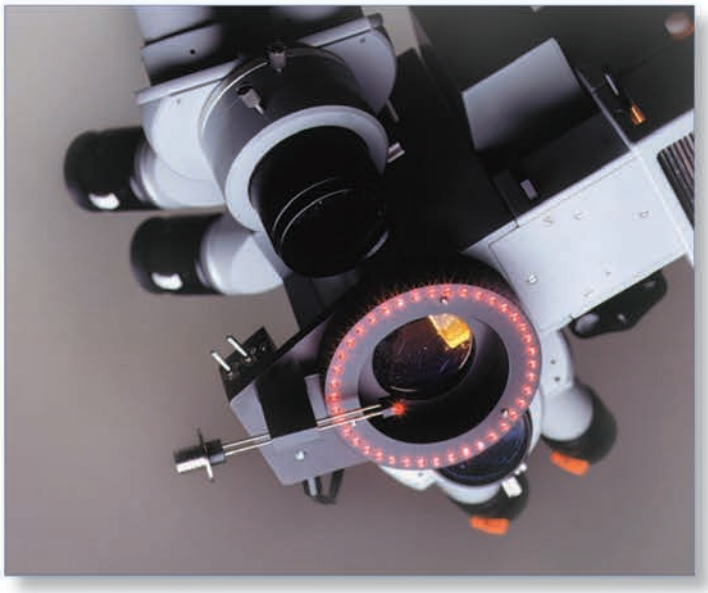
- history of bleeding disorders;
- allergy to eggs or cow collagen;
- any history of allergy causing anaphylactic shock;
- allergy to lidocaine;
- history of or predilection for keloid formation; and
- actively inflamed or infected skin.

Injection Methods

Numerous methods have been discussed in regards to injecting dermal fillers. The depth of the injection depends on the properties of each product and the desired outcome. A few common methods utilized are discussed below.

• ***Linear threading***. In linear threading, as the needle is withdrawn, a tunnel of filler is injected to efface the wrinkle. This technique is commonly used to address isolated creases such as nasolabial folds or marionette lines. In this technique superficial injection of the filler can occur toward the end of the needle withdrawal process, resulting in the Tyndall effect *(See Figure 1A)*.

• ***Serial puncture***. In this tech-



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nique serial injections are made along the length of a wrinkle where small aliquots of filler are deposited. There is potential for more bruising with this technique *(See Figure 1B)*.

• ***Radial fanning.*** The goal of radial fanning is to fill the problem area with minimal skin punctures in hopes of decreasing bruising. A needle is inserted in the desired region and a tunnel of filler is injected as the needle is withdrawn; however, before the needle is completely removed from the skin, it is redirected into a different radial plane and more filler is injected until the desired outcome is achieved *(See Figure 1C)*.

• ***Cross hatching***. Cross hatching builds on linear filling where a series of parallel tunnels of filler is injected. Then perpendicular tunnels are injected to create a cross hatching. This technique is meant for filling in broader areas *(See Figure 1D)*.

Complications

Several complications have been reported with the injection of soft-tissue fillers. Complications from use of non-absorbable fillers (PMMA) are more difficult to manage: As they are not absorbed they may need to be excised. This may result in unwanted scarring and ultimately poor cosmetic results. As a general rule, hyaulonic acid filler complications may be reversed using hyaluronidase, providing a distinct advantage for the clinician in the management of potential complications.[10]

• ***Bruising.*** The most common complication seen with fillers is bruising of the injection site. This can occur regardless of the technique used. However, the following steps can be taken to minimize or prevent bruising:

• Instruct patients to avoid using blood thinners (aspirin, warfarin, clopidogrel, dabigatran, nonsteroidal anti-inflammatory drugs, fish oil, vitamin E, garlic, gingko or ginseng) for one week prior to injection.

Table 1. Facial Fillers Available in the United States and their FDA Approved Indications[1]

Trade Name	Material	DOA	FDA Approved Indications
Belotero Balance	HA	11/14/2011	Smooth facial rhytids
Captique	HA	11/12/2004	Moderate/severe facial rhytids
Elevess	HA + Lido	12/20/2006	Moderate/severe facial rhytids
Hylaform	HA (avian)	4/22/2004	Moderate/severe facial rhytids
Juvaderm 24HV Juvaderm 30 Juvaderm 30HV	HA	6/2/2006	Moderate/severe facial rhytids
Juvederm Volumna XC	HA + Lido	10/22/2013	Cheek augmentation for age-related volume loss (age > 21)
Prevelle Silk	HA + Lido	2/26/2008	Moderate/severe facial rhytids
Restylane	HA	12/12/2003	Moderate/severe facial rhytids
Restylane	HA	3/25/2005	Moderate/severe facial rhytids
Restylane	HA	10/11/2011	Lip augmentation (age > 21)
Restylane-L	HA + Lido	8/30/2012	Moderate/severe facial rhytids and lip augmentation (age > 21)
Restylane Lyft with Lidocaine	HA + Lido	7/1/2015	Moderate/severe facial rhytids; Age-related volume loss (age > 21)
Restylane Silk	HA + Lido	6/13/2014	Lip augmentation & perioral rhytids (age > 21)
Cosmoderm 1 Human-Based C	Collagen	3/11/2033	Correction of soft tissue deficiencies such as wrinkles and acne scars
Evolence	Collagen	6/27/2008	Moderate/Severe facial rhytids
Fibrel	Collagen	2/26/1988	Correction of depressed cutaneous scars
Zyplast	Collagen	6/24/1985	Correction of contour deficiencies
Zyderm	Collagen	9/18/1981	Correction of contour deficiencies
Radiesse	CaHA	6/4/2015	Volume loss in dorsum of hands
Radiesse 1.3CC Radiesse 0.3CC	CaHA	12/22/2006	Moderate/severe facial rhytids; Facial lipoatrophy in HIV
Artefill	PMMA + collagen + lidocaine	10/27/2006	Use in facial tissue around the mouth
Sculptra	PLLA	8/3/2004	Facial lipoatrophy in HIV
Sculptra-Aesthetic	PLLA	7/28/2009	Shallow to deep facial rhytids

HA = hyaluronic acid Lido = lidocaine
CaHA = calcium hydroxylapatite PMMA= polymethymethacrylate
PLLA = poly-l-lactic acid

• Use small-gauge needles and blunt cannulas.

• Minimize the number of puncture sites.

• if bruising is noted or suspected at the time of injection, immediately hold pressure over the area and apply an ice pack.

• Advise patients to avoid activities that can raise their blood pressure or put strain on their head and face for 24 hours after injection (e.g., exercise and activities that cause valsalva).

• Advise patients to keep their head elevated for 24 hours after injection.

• ***Over-filling.*** Overfilling may result from injecting too much filler into

a small area and may create lumps, nodules or asymmetry. Treatment includes: hyaluronic acid—injection of hyaluronidase into area of over-filling; other fillers—incision and drainage of the filler; and large volume nodules—injection of local anesthetic and aspiration of filler with a larger-bore needle.[10] Use caution when planning for correction of multiple nodules within vital anatomical structures.

• ***Under-filling.*** Under-filling may result from injecting too little filler into a rhytid, and is treated by injecting more filler in the area of under-filling.

• ***Granulomatous inflammation.*** Granulomatous inflammation may result from any type of filler. True granulomas from fillers will likely involve multiple sites of injections. Solitary nodules are likely not true granulomatous reactions. Treatment may include graduated injections over period of weeks to months with one of the anti-inflammatory medications, kenalog, triamcinolone or 5-fluorouracil.[10]

• ***Tyndall effect.*** The Tyndall effect results from injecting hyaluronidase fillers too superficially, which places the filler close to the surface of the skin. It causes a bluish discoloration to the overlying skin, which looks like a deep bruise. This complication will not improve until the filler is removed. Treatment entails injection of 15 to 50 IU of hyaluronidase, and gentle massage by rolling a cotton-tipped applicator over the area to disperse the hyaluronidase.[10]

• ***Infection at injection site.*** This is an uncommon complication with fillers. It may be caused by bacterial, viral or Candida species. Herpes simplex is the most common viral infection to spread to an injection site, and is more common in patients with a strong history of cold sores. Consider pretreating with acyclovir, valacyclovir or famciclovir to reduce the risk of complication. Maintain a low threshold for complete ophthalmologic evaluation if there is any concern for ocular involvement of herpes simplex virus.[10]

In cases of abscess formation, treatment involves incision and drainage ±oral antibiotics to cover common skin flora, gram positives if there is concern for cellulitis. Hyaluronidase should always be avoided any time there is suspicion for infection, as it may allow for further spreading of infection through the surrounding soft tissue.

• ***Biofilms.*** Biofilms may result from any implantable device or foreign material placed within the body. They allow bacteria to lie dormant for a long period, then awaken later in time to cause granulomatous inflammation, abscess formation or cellulitis. Treatment includes:

• Permanent fillers (PMMA)—incision and removal of filler. This is why caution must be used when considering permanent fillers for use in vital anatomical structures such as lips and eyelids.

• Hyaluronic acid—injection of hyaluronidase.

• Broad-spectrum oral antibiotics (fluoroquinolones or macrolides).

• Avoid all steroids and NSAIDs.

If infection persists after above treatment, consider laser lysis or incision and drainage.[1,10,11]

• ***Vascular necrosis***.[12] Vascular necrosis is an extremely rare complication from filler use but still must be discussed with patients. The risk for all vascular complications increases with deeper large bolus filler injections. It results from accidental intravascular injection of filler and may lead to local or distant ischemic necrosis of soft tissue. The local injection site necrosis is most commonly seen in the glabella, a potential vascular watershed region.

Clinical signs and symptoms include blanching; mottled discoloration of skin (livedo reticularis); pain; dusky skin discoloration; and sluggish or absent capillary refill. Immediate treatment is critical for recovery of vascular supply and includes:

• injection of hyaluronidase directly into the ischemic tissue (works if injected filler is HA);

• oral aspirin;

• topical nitropaste over ischemic tissue;

• warm compress and massage of the affected tissue; and

• hyperbaric oxygen therapy, which may be considered in persistent cases failing initial treatment with above.

• ***Central retinal artery occlusion.*** CRAO is an extremely rare complication from filler use but still must be discussed with patients.[12] It presents with sudden visual field defect or vision loss. Funduscopy is warranted and may show signs of CRAO. Treatment includes ocular massage; hyperventilation; oral aspirin; and hyperbaric oxygen therapy. Treatment is widely ineffective for CRAO related to filler embolus. REVIEW

Drs. Milam, Zhang and Barahini are at the Vanderbilt Eye Institute, Vanderbilt University Medical Center. Contact Dr. Milam at 4505 Georgia Ave. Nashville, Tenn. 37209. Phone: (704) 929-8811; fax: (615) 936-4979; Email: ronald.milam@vanderbilt.edu.

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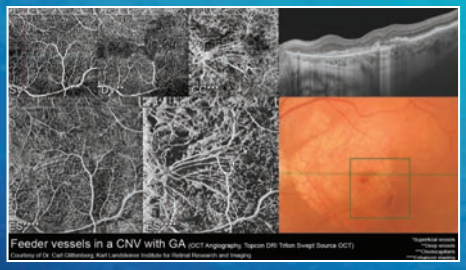

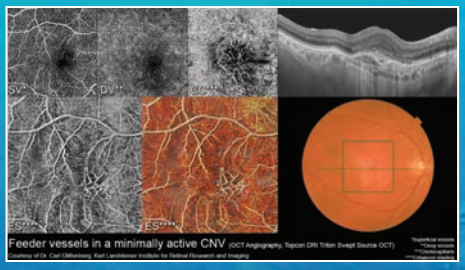

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Richard Spaide, MD	Vitreous-Retina-Macula Consultants of New York	*"Swept-Source OCT and OCT Angiography for Evaluation of the Retina"*
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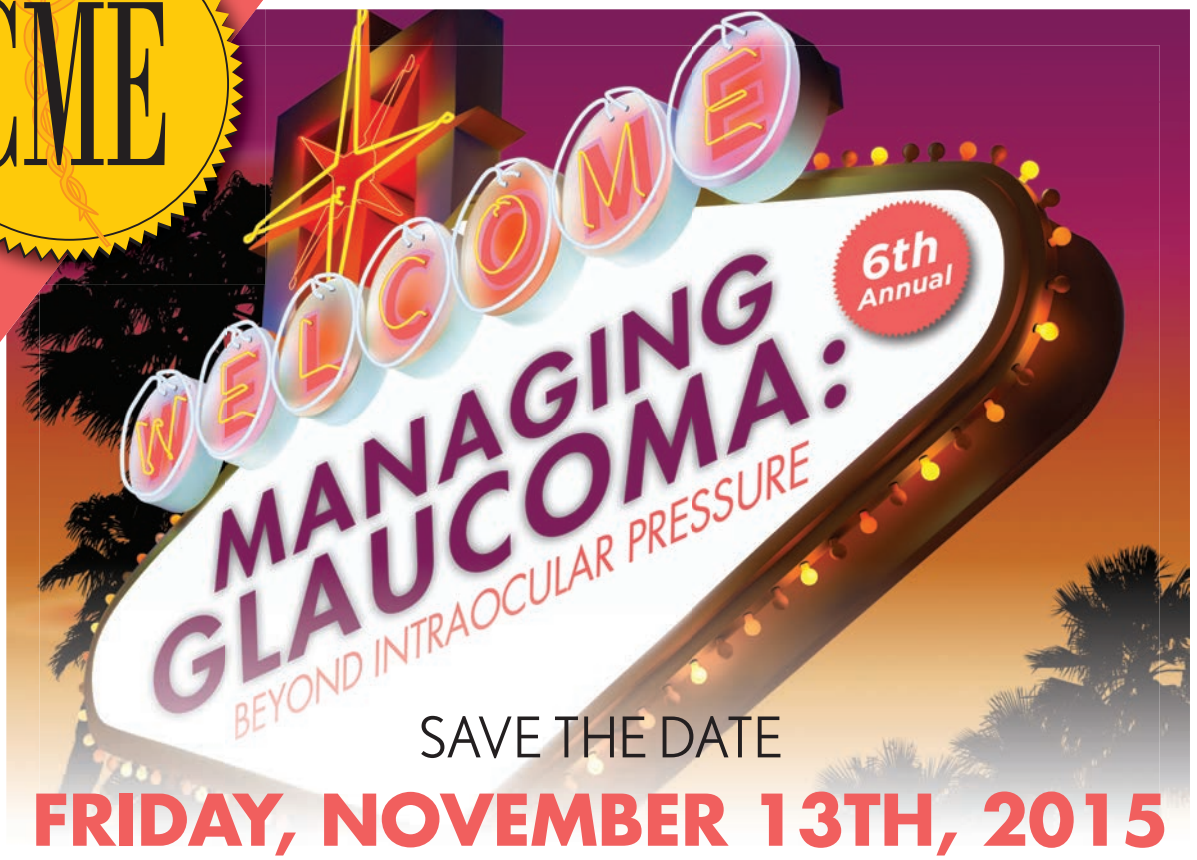

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TFO or MMP-9 Tests To Detect Dry Eye

Researchers from Germany evaluated the performance of matrix metalloproteinase 9 and tear-film osmolarity in diagnosing early-stage dry-eye disease and determined that, similar to corneal staining, MMP-9 is likely a late-stage sign of dry eye that is rarely overexpressed in mild subjects. However, tear osmolarity tends to be a more frequent early indicator of ocular disequilibrium with mild cases of dry-eye disease.

A group of 20 patients aged 60 years and above, previously undiagnosed with dry-eye disease, were selected for this study. The following dry-eye disease tests were performed: tear osmolarity; MMP-9 (InflammaDry); Schirmer test; tear-film breakup time; Ocular Surface Disease Index questionnaire; corneal fluorescein staining; and conjunctival lissamine green staining. MMP-9 concentrations in tears collected through Schirmer strips were analyzed by an MMP-9 enzyme-linked immunosorbent assay. The 20 subjects were classified by symptoms (classification A: OSDI ≥10, n=nine); based on suspected mild dry eye (classification B, n=14); TFO difference >8 mOsm/L between both eyes (classification C, n=13); and TFO cutoff at 308 mOsm/L (classification D: >308 mOsm/L, n=11).

Eleven percent of the symptomatic and 14 percent of the suspected mild dry-eye patients were positive for MMP-9. InflammaDry MMP-9 tests were confirmed to be accurate through an ELISA. Sixty-seven percent of the symptomatic and 64 percent of the suspected mild dry eye patients were positive for tear osmolarity. None of the evaluated tear-film parameters showed a significant correlation, although tear osmolarity and symptoms trended towards significance (r^2=0.443, p=0.06) whereas MMP-9 and corneal staining showed a positive association (r^2=0.376, p=0.10).

Cornea 2015;43:739-744.
Chargus M, Ivanova S, Kakkassery V, Dick HB, Joachim S.

Time Burden in Treating and Managing Neovascular AMD

A 17-month multicenter study concluded that management of neovascular age-related macular degeneration imposes a substantial time burden on physicians, staff, patients and caregivers. Based on this, there may be a need for additional support and/or reimbursement for services required by patients and caregivers and provided by physicians.

The study was conducted at multiple sites from March 2011 through August 2012. Retina specialists administering ≥50 vascular endothelial growth factor-inhibitor injections monthly were surveyed and completed records for ≥five patients scheduled for office visits within three weeks for anti-VEGF injection or monitoring. A survey was administered to 75 neovascular AMD patients aged ≥50 years who received one or more anti-VEGF injections in the past six months. Telephone interviews were conducted with 13 neovascular AMD patient caregivers.

Fifty-six physicians provided data for 221 patients with neovascular AMD. Patients accounted for 20 percent of the health-care staff's time per week, with an average of 23 staff members. An average patient visit for neovascular AMD was 90 minutes (range: 13 minutes to >4 hours). Patients reported an average time per visit of almost 12 hours, including pre-appointment preparation (16 minutes); waiting time (37 minutes); treatment time (43 minutes); and post-appointment recovery (nine hours). Patients stated that caregivers took time away from work (22 percent) and personal activities (28 percent) to provide transportation to appointments.

Am J Ophthalmol 2015;160:4:725-731.
Prenner J, Halperin L, Rycroft C, Hogue S, et al.

Trabeculectomy vs. Ex-PRESS Shunt: Efficacy and Safety

A study from Israel comparing standard trabeculectomy with the Ex-PRESS miniature glaucoma shunt found the two have similar efficacy

and safety profiles.

A retrospective review of the records of 100 eyes of 100 patients who underwent trabeculectomy or Ex-PRESS shunt implantation between July 2010 and June 2012 was conducted. Of these, 61 eyes (61 percent) underwent trabeculectomy and 39 eyes (39 percent) underwent Ex-PRESS shunt implantation. Demographic information, glaucoma type, surgical details, preoperative and postoperative data including intraocular pressure, number of medications, reoperation and occurrence of any complications were recorded.

No differences in IOP reduction or number of postop IOP-lowering medications were demonstrated between the two procedures. Success rates were 86.9 percent for trabeculectomy and 84.6 percent for Ex-PRESS shunt. Rates of failure and hypotony were not significantly different between the groups. No parameter was correlated with success or failure of any procedure. As the Ex-PRESS shunt is considerably more expensive, its use may be unjustified, especially as a primary procedure, the authors suggest.

J Glaucoma 2015;24:410-416.

Moisseiev E, Zunz E, Tzur R, Kurtz S, Shemesh G.

IOP in Neovascular AMD After IVI Aflibercept or Ranibizumab

Analyses from two randomized, active-controlled, Phase III trials of intraocular pressure in patients with neovascular age-related macular degeneration indicates that eyes receiving intravitreal injections of aflibercept had lower IOP than eyes receiving intravitreal injections of ranibizumab.

A total of 2,457 patients with neovascular AMD were enrolled in the two trials. Patients received intravitreal aflibercept injection 2 mg every four weeks (2q4), 0.5 mg every four weeks (0.5q4), 2 mg every eight weeks (after three monthly doses; 2q8) or ranizibumab 0.5 mg every four weeks (Rq4) for 52 weeks. At week 52, patients were switched to a variable regimen requiring at least quarterly dosing and allowing interim injections based on anatomic and visual assessment. Pre-injection IOP was analyzed in study and uninjected fellow eyes from baseline to week 96. Prespecified end points included mean change in IOP from baseline and a prevalence of a >21 mmHg and >10 mmHg increase in IOP from baseline. Cumulative incidence of sustained (at two consecutive visits) IOP >21 mmHg, a single event of IOP >25 mmHg and sustained IOP increase from baseline (≥5 mmHg) were also evaluated.

Mean IOP change from baseline over 96 weeks in all IAI groups (2q4, 2q8, 0.5q4) was consistently lower than in the Rq4 group, and this finding was replicated in both trials. In an analysis integrating both studies, the proportion of study eyes with IOP >21 mmHg at week 96 was 20.2 percent for the Rq4 group, 14.2 percent for the 2q4 group, 12.1 percent for the 2q8 group and 12.5 percent for the 0.5q4 group. Reduction in risk, relative to Rq4, of having sustained IOP >21 mmHg over 96 weeks was 62 percent (95 percent confidence interval, 37 to 78 percent), 50 percent (95 percent CI, 19 to 70 percent) and 69 percent (95 percent CI, 45 to 84 percent) for 2q4, 2q8 and 0.5q4, respectively. Risk reduction in the IAI groups for a sustained IOP increase >5 mmHg was 31 percent in the 2q4 group (95 percent CI, 8 to 48 percent), 38 percent in the 2q8 group (95 percent CI, 17 to 54 percent) and 47 percent (95 percent CI, 27 to 61 percent). In uninjected fellow eyes only sustained IOP >21 mmHg events were higher in the Rq4 groups compared with all IAI groups.

Ophthalmology 2015;122:1802-1810.

Freund KB, Hoang QV, Saroj N, Thompson D.

Cardiovascular Risk Factors in Central Retinal Artery Occlusion

A well-defined, homogenous group of patients (n=77) with nonarteritic central retinal artery occlusion who were enrolled in the European Assessment Group for Lysis in the Eye were analyzed for cardiovascular risk factors. Previously undiagnosed vascular risk factors were found in 78 percent of the patient group. The most meaningful risk factor was ipsilateral carotid artery stenosis. This suggests that a comprehensive and prompt diagnostic workup is mandatory for all CRAO patients.

Both vascular risk factor and underlying diseases were detected by questionnaire along with a standardized physical examination within one month after retinal artery occlusion. The standardized physical exam included carotid Doppler; ultrasonography; echocardiography; electrocardiography; blood pressure monitoring; pulse rate; urine analysis; body mass index analysis; and laboratory tests.

Fifty-two patients (67 percent) had cardiovascular risk factors in their medical history, and comprehensive phenotyping identified at least one new risk factor in 60 patients (78 percent; 95 percent confidence interval, 67 to 87 percent). In total, 71 patients (92 percent) had cardiovascular risk factors or events. Thirty-one patients (40 percent) had carotid artery stenosis of at least 70 percent. Eleven patients experienced a stroke, five of those within four weeks after CRAO occurred. Arterial hypertension was found in 56 patients (73 percent) and was newly diagnosed in 12 study participants (16 percent). Cardiac diseases were also highly prevalent (22 percent coronary artery disease; 20 percent atrial fibrillation; 17 percent valvular heart disease).

Ophthalmology 2015;122:1881-1888.

Callizo J, Feltgen N, Patenburg S, Wolf A, et al.

(continued from page 98)

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Managing Hypotony After Trabeculectomy

Very low intraocular pressure following surgery can have serious visual consequences. These strategies can help prevent trouble.

Valerie Trubnik, MD, FACS, Mineola, N.Y.

Trabeculectomy remains a mainstay in the management of glaucoma, despite problems frequently associated with it, such as hypotony. Leaving postoperative hypotony untreated can result in permanent visual damage, so it's crucial to be on the lookout for it and address it when it becomes apparent.

Here, I'll summarize some of the key issues relating to hypotony and offer suggestions for how best to manage it when it occurs.

Defining Hypotony

Hypotony can be defined either statistically or clinically. The statistical definition of hypotony is an intraocular pressure less than 6.5 mmHg (although the specific number depends on which source you consult). What really matters is the clinical definition: an IOP that's low enough to cause clinically significant complications such as vision loss. The primary cause of these complications is hypotony maculopathy—low intraocular pressure associated with fundus abnormalities such as chorioretinal folds, optic nerve edema and vascular tortuosity.

The reported incidence of hypotony ranges from less than 1 percent of cases to 32 percent. The reason the range is so broad is that the amount of hypotony triggered by the surgery is greatly affected by factors such as surgical technique and the way mitomycin-C is used. For example, the Tube Versus Trabeculectomy Study reported a 13-percent rate of hypotony. That was undoubtedly partly a result of using an MMC concentration of 0.4 mg/ml—which is on the higher end of MMC concentrations—and applying it for four minutes using pledgets. In the Collaborative Initial Glaucoma Treatment Study, the reported percentage of hypotony was 9 percent; the antifibrotic agent used in that study was 5-fluorouracil. I inject 0.1 cc of 0.2 mg/ml of MMC into the sub-Tenon's layer at the start of the trabeculectomy procedure, rather than applying it with sponges. I find this method to be efficient, with similar or better outcomes, and it's not associated with an increased rate of hypotony. (My current rate of hypotony ranges between 3 and 5 percent.) Hence, the amount of hypotony you encounter will depend at least partly on your technique, the amount of MMC you use and how long you apply it. Of course, other factors such as the nature of your patient population can also influence your hypotony rate.

Hypotony generally falls into two categories: early and late. These tend to have different causes and prognoses and require different treatment. Early hypotony occurs in the first two weeks after surgery, most of the time secondary to bleb leaks resulting from poor wound closure or from overfiltration; this type of hypotony is usually mild and transient and resolves on its own. Most of the time, observation and conservative medical management are sufficient to address it.

Hypotony that occurs more than two weeks after surgery, or late hypotony, may be secondary to an ischemic, avascular, thin bleb or overfiltration by the bleb. Late hypotony is usually more serious than early hypotony, and the prognosis for visual recovery depends on its duration. It becomes a cause for concern if it exceeds more

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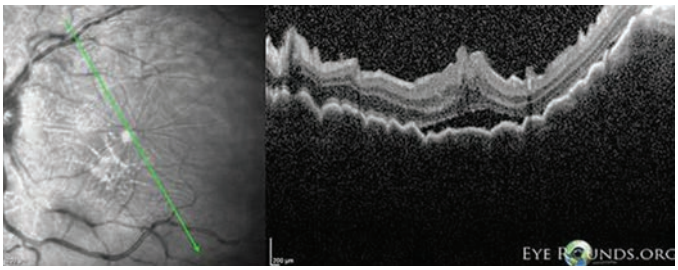
than six months, since progression beyond that time frame may result in irreversible chorioretinal fibrosis.

Hypotony can be caused by either increased outflow of aqueous or by decreased aqueous production. Increased outflow could indicate overfiltration of the bleb secondary to loose scleral flap closure, or a leaking bleb. Other possibilities include cyclodialysis cleft, ciliochoroidal detachment, rhegmatogenous retinal detachment and trauma, although these are uncommon.



Hypotony following trabeculectomy that is not addressed can lead to hypotony maculopathy (above)—low intraocular pressure associated with fundus abnormalities such as chorioretinal folds, optic nerve edema and vascular tortuosity.

Decreased aqueous production can be secondary to a number of issues: iritis or iridocyclitis; ocular ischemia, where you have hypoperfusion of the ciliary body; pharmacologic aqueous suppression caused by the patient continuing to take a glaucoma medication such as timolol or Cosopt in the surgical eye unbeknownst to you, or a possible crossover effect from medication being used in the contralateral eye; tractional ciliary body detachment; rhegmatogenous retinal detachment; cyclodialysis cleft; or chemical toxicity to the ciliary body from antimetabolites like 5-FU or MMC. Some of these can be unintentional consequences of the trabeculectomy surgery.

Managing a Bleb Leak

One issue when a patient appears to be developing hypotony is deciding when to intervene. Certainly you need to intervene if the patient is having visually significant symptoms—if vision is deteriorating as a result of the low pressure. Other considerations include the possibility of endophthalmitis or imminent risk of bleb failure if the patient has a persistent bleb leak. Choroidal effusion can lead to visual impairment or persistent ocular pain, as well. The specific response to hypotony depends on the cause and the extent of the problem. An extremely low pressure, for example, may call for a different response than a moderately low pressure.

If the cause of early hypotony is a bleb leak, I begin by trying a few conservative measures, in particular a bandage contact lens and an aqueous suppressant, assuming the pressure is not already extremely low. Although using an aqueous suppressant to manage a situation relating to hypotony may sound counterintuitive, it can help address the cause of the low pressure by relieving the pressure inside the bleb and reducing flow through the leak, giving it a chance to heal. So, if I put on a bandage lens to tamponade the leak, I usually also have the patient use timolol or brimonidine. (I don't always combine the contact lens with a suppressant; I may try one or the other, depending on how the patient responds.)

Needless to say, if the pressure is very low—say, 2 mmHg—I wouldn't use an aqueous suppressant. In that situation I'd try a contact lens first and cover the area with a non-epithelial-toxic antibiotic, preferably a fourth-generation fluoroquinolone, to prevent an infection. Some surgeons believe that using an antibiotic such as gentamicin may serve as a mild irritant, stimulating epithelial cells to proliferate and seal the leak.

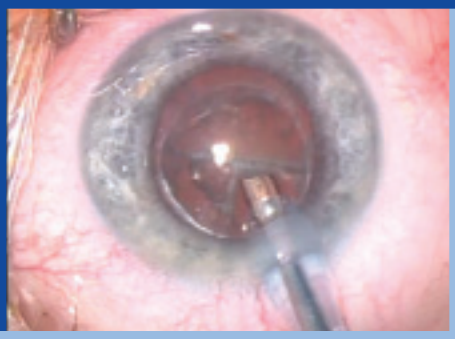
Other options to address the leak would include fibrin tissue glue, argon laser and direct suturing of the conjunctiva. (I rarely have to resort to these alternatives.) If none of these approaches work to resolve an early leak, I move on to surgical treatment.

Late-onset Leakage

The main surgical management for late-onset bleb leaks, which I use very often, is excision of the avascular, ischemic bleb followed by advancement of surrounding healthy conjunctiva or an autologous conjunctival graft. If the affected area of the bleb and the amount of excised tissue is large, there may not be enough tissue for conjunctival advancement, and an autologous conjunctival graft (usually harvested from the inferior bulbar conjunctiva) may be performed. Generally, the bleb is leaking because the tissue on top of it is not healthy. Ideally, during the repair you want to avoid disturbing the filtration that's happening underneath.

Of course, the risk here is that the new bleb will scar down. I tell these patients: Your pressure is 4 mmHg now, because you're leaking. Once I fix this, there's a very good possibility that your pressure will go up again and you may need another glaucoma surgery or medication. But we do need to fix the leak; in addition to hypotony maculopathy, leaving a leak unrepaired leaves you vulnerable to infection.

In some cases, you may want to resuture the scleral flap, either by taking down the conjunctiva, suturing the flap again, and then bringing the conjunctiva forward, or by doing a



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Agenda session times have changed this year

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4:00 - 7:00PM Evening Sessions & Working Dinner	6:30 - 12:00PM Morning Session	6:30 - 12:00PM Morning Session
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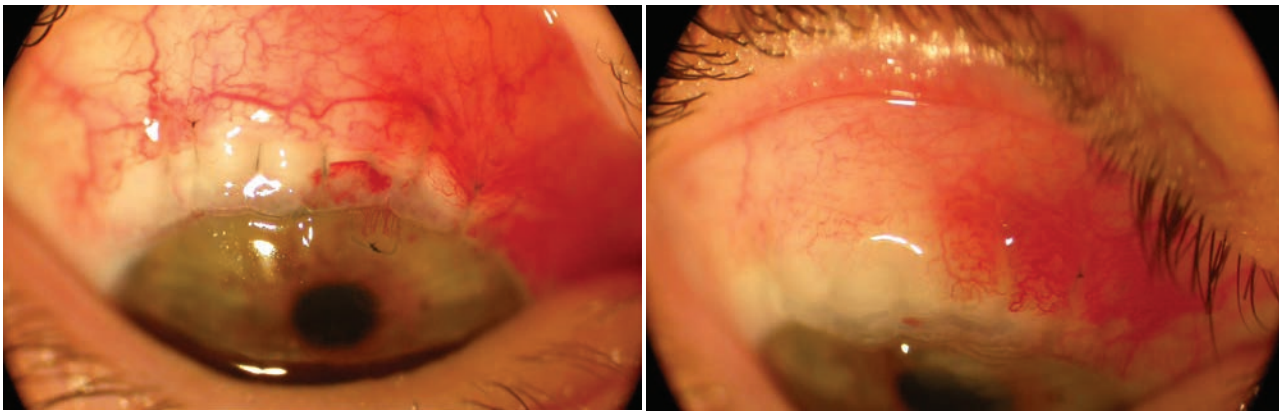

Compression sutures used to manage overfiltration hypotony four months after a trabeculectomy. Left: One day after the placement of compression sutures. The sutures were removed one and three weeks after placement. Right: three months after suture placement. At this point the patient's pressure had improved from 3 mmHg to 15 mmHg.

transconjunctival revision—placing sutures into the flap through the conjunctiva. You would employ this technique if there is overfiltration secondary to loose scleral flap sutures or if the sutures were cut too early in the postoperative period.

Some clinicians try to address a late-onset leaking bleb using an autologous blood injection. Basically, this means taking blood from the patient and injecting it into the bleb. The theory is that the fibroblasts in the blood can cause a transformation in the Tenon's capsule that leads to scarring. Some patients are attracted to this option because they may avoid the need for surgical revision in the operating room if they end up on the winning side of the "coin toss" (the 50/50 success rate). I usually proceed directly to a more definitive surgical repair of the problem. I think if you're going to address a bleb leak you might as well do something that will give you a higher success rate.

It's possible to encounter a melted flap in a patient with an autoimmune disease such as rheumatoid arthritis, or even prior MMC exposure. In that situation, you need to put a scleral patch graft where the flap was, reinforce it with sutures, and then put conjunctiva over it.

Another good option for addressing a bleb leak is compression sutures, which I discuss below.

Managing an Overfiltering Bleb

In some cases, when the cause of hypotony is an overfiltering bleb, nonsurgical management approaches such as cycloplegia using atropine or Cyclogyl may be worth trying. If there is a shallow anterior chamber secondary to the overfiltration, the cycloplegic agent will move the lens iris diaphragm back and help the ciliary body restart the production of aqueous.

Some clinicians believe that if overfiltering happens in the early postoperative period it may be effective to taper the anti-inflammatory medications, like NSAIDs and steroids; this may facilitate faster episcleral scarring so you don't get as high a bleb. Some will also try an autologous blood injection, as described above. Unfortunately, my experience has been that these methods are probably not going to work. Sooner or later you'll have to resort to surgical management.

One of the most effective surgical ways to manage an overfiltering bleb is to use compression sutures. In fact, compression sutures are an excellent option whether your bleb is overfiltering or has a leak. Compression sutures tamponade the tissue in order to prevent fluid from moving past the suture. If a leak is in the periphery of the bleb, for example, Paul Palmberg, MD, has demonstrated that a compression suture can be used to wall off that section of the bleb. Meanwhile, the rest of the bleb is functioning normally, giving it a chance to heal.

Marlene Moster, MD, uses a slightly different technique, mostly for overfiltering blebs, that was initially published by Judith Eha, MD.[1] In this variation you take several radial interrupted sutures (10-0 nylon 7707 Ethicon suture) and put them all the way through the full-thickness scleral flap. The suture pass starts at the limbus and goes through the conjunctiva, through the full-thickness sclera, and then out again through the conjunctiva. By suturing these layers very tightly together, you bring down the profile of the bleb; at the same time, you're tamponading the bleb because you're suturing through the flap.

One of the nice things about this technique is that if you use multiple compression sutures, the sutures can be selectively removed. For instance, suppose you put 10 sutures through and the pressure rises from 3 mmHg to 40 mmHg. You can remove two sutures and reassess the pressure. This elegant approach is

less involved than a full bleb revision, and also provides you with some room to maneuver, thus providing a more gradual tapering of pressure.

I recently published a prospective case study of 15 patients with my colleagues Drs. Jesse Richman, Marlene Moster and Thandeka Myeni.[2] Hypotony was reversed in 100 percent of cases and all but two patients (87 percent) achieved success, as defined in the study. They started out with a mean pressure of 3.3 mmHg and visual acuity of 20/150; after one year their mean IOP was 10.4 and vision improved to 20/30. (Additional surgery was necessary in two patients for elevated IOP post-procedure.)

A video showing this technique can be seen at https://youtu.be/v4i2ROPh7MA on the Web.

Management Tips

These strategies will help ensure that hypotony doesn't become a serious problem for you or your patient:

• ***Err on the side of tighter sutures, not looser.*** You can always open your sutures with laser suture lysis or remove them, if you're doing releasable sutures. On the other hand, if you make the sutures too loose at the outset you may end up with hypotony, which is much more difficult to fix.

• ***Try using the modified Wise technique for conjunctival flap closure.*** Gary Condon has popularized this technique, originally described by Dr. James Wise.[3] This technique involves making an incision at the limbus to create a fornix-based flap. The incision may be at the limbus or about 1 mm posterior to the limbus, while leaving an anterior lip of the conjunctiva to act as a bolster for watertight closure. After the filtration portion of the procedure is done, you use a minimally spatulated needle, either with a 9-0 monofilament vicryl Ethicon suture (D8760), a 8-0 braided vicryl TG140-6 suture (the more affordable version), or a 9-0 vicryl suture on a BV needle—probably the most commonly used—to close with a running mattress suture. You make multiple passes in the conjunctiva and the sclera using suture bites that are longer than the space between the bites, anchoring the suture at both ends in the conjunctiva and sclera outside the confines of the incision. This ensures that you don't have any breaks at the limbus, especially when doing a fornix-based flap.

The learning curve associated with this technique is steep; however, once you've learned to do it, it's quick and efficient and always reproducible. I've had no bleb leaks since adopting this technique. I've also found that this technique minimizes astigmatic distortion. (You can watch a video illustrating this technique at https://youtu.be/nsKMjvbVuAo.)

• ***If there's a potential problem, have the patient return frequently.*** In general, if a patient has hypotony, seeing the patient every couple of days is reasonable. If there's no initial indication of a problem, I usually see patients on the first postoperative day, and at the first and second weeks. Then, depending on how they do, I'll see them two weeks later and then a month after that. As long as there's no sign of trouble, I keep lengthening the time between visits.

• ***Be patient with the pressure in the early postoperative period.*** You want to aim for a pressure between 15 and 20 mmHg, but I always tell my patients not to get too excited about the initial number. The initial postoperative period is a roller coaster, so the number matters less, as long as it doesn't get too far out of the 15 to 20 mmHg range. But if the patient comes in on the first postoperative day and the pressure is 5 mmHg and her vision is blurry and she has choroidals—which is rare on the first day—then I would say, "Let me see you tomorrow or the day after. Let's try this conservative treatment with steroids and atropine and see how you do."

• ***If the patient has both an overfiltering bleb and a cataract, cataract surgery may resolve the bleb problem.*** In this situation, doing the cataract surgery may help address the overfiltration by inducing episcleral inflammation. It's the same principle as tapering the patient's anti-inflammatory medications. So if the patient has a cataract that is out of the immediate postoperative window, cataract surgery may induce some scarring, which will treat the hypotony and improve visual acuity.

• ***Remember that not all hypotonous eyes require intervention.*** The condition of the patient's vision should always guide treatment, and the timing of any intervention should depend on the severity of the symptoms, patient preference and the status of the fellow eye. For instance, if you have a 90-year-old Caucasian female with a pressure of 3 mmHg, a diffuse filtering bleb and 20/25 vision, the most you should offer in terms of intervention would be the use of a plastic shield at night and having the patient sleep on the opposite side. On the other hand, if you're dealing with a 20-year-old myopic Asian male with low scleral rigidity, a pressure of 6 mmHg and 20/400 vision, immediate intervention will proably be needed. REVIEW

Dr. Trubnik is an attending surgeon at Ophthalmic Consultants of Long Island in New York.

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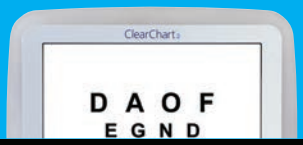

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(continued from page 106)

alternatives are available outside the United States. A New Drug Application was submitted to the FDA for 0.18% HA ophthalmic solution (Rejena, NDA 22-358); however, it wasn't approved despite positive results in clinical trials.[8,11] Ophthalmic solutions of 0.1 to 0.3% HA have been marketed in Japan, Europe, Australia, Russia and parts of Asia under the trade names Hyalein, Vismed, Vislube, Opticalm, Hylabak and Hylovis *(See the table on p. 106)*. In the United States, HA is listed as an inactive ingredient in the over-the-counter artificial tear product Blink Tears.

Bionic Hyaluronic?

There is an unmet medical need in the United States for next-generation HA products that can outperform the available artificial tear options in terms of increasing ocular residence time, decreasing dosing frequency, lubricating and improving the tear film, and alleviating symptoms associated with acute and chronic dry eye. While clinical trials have provided evidence that HA is superior to other polymers as a lubricant, there's still a requirement for q.i.d. (or more frequent) dosing and much room for improvement. There is extensive literature on chemical modification of HA that may point the way for such improvements.

Pharmaceutical companies have aimed to chemically modify HA to improve its properties, thus offering superior formulations for multiple indications. The primary chemical strategy used to modify HA is the cross-link, either by direct reaction of side chains or through the addition of spacer arms, which can then form stabilizing links between HA molecules.[5]

One such cross-linked HA, carboxymethyl hyaluronic acid, is the active ingredient globally marketed for veterinary applications as ReMend (BayerDVM), is sold in more than 400 clinics. While piggybacking on the extensive amount of HA data already generated by others, Jade Therapeutics is in the process of bringing a formulation with this active, modified HA to human clinical trials. This lightly cross-linked eye-drop formulation is designed to modulate the gelation of the solution, thereby improving residence time and tear-film stability as compared to currently marketed products.

Another HA product is SI-614, under development by Seikagaku, a pioneer in glycoscience research since 1950. This compound has shown promise in several clinical studies, and is currently in Phase III clinical trials.

Chemically modified HA tear substitutes *(shown in the table, p. 106)* may represent more than an incremental improvement over the previously used artificial tear formulations, and can be viewed as a long-acting or sustained-release therapy. Rather than supplementing the existing tear film as current artificial tear formulations do, modified HA solutions are designed to be genuine treatments with significant therapeutic value.

Assessment of HA Products

With the aid of stains and other tests, we can fairly accurately assess how well a tear substitute is doing its job. The Schirmer's test has been used for decades as a rapid and telling, albeit variable, assessment of aqueous tear production. This test would not be expected to be altered with tear substitute therapy. However, with long-term, disease-modifying treatments, it could demonstrate improved wetting. Tear-film breakup time measures instead the evaporation of the tear film, and is an assessment of evaporative dry eye due to mucin or lipid tear deficiencies. TFBUT should improve with tear substitute use, particularly if the product has an ingredient such as modified HA to increase wetting. The clinician routinely uses rose bengal, lissamine green and fluorescein dyes to stain ocular surfaces prior to examination, though lissamine green has largely supplanted rose bengal due to the potential for intolerance of the latter. While rose bengal and lissamine green preferentially stain damaged conjunctival tissues, fluorescein concentrates in areas of cell-cell junction disruption on the cornea.[14]

There are other more experimental tests that we frequently use to test the performance of an artificial tear product. Various measures based on the blink, including rate; inter-blink interval; patterns of blink; and partial, complete and extended blinks, can be used as surrogates for ocular discomfort and in some tests of visual function.

The ocular protection index and the interval visual acuity decay test assess very different aspects of ocular surface health with the aid of blink measures. We know that optimal blink rates enable the maintenance of a stable tear film, thus ensuring good ocular surface tissue health, while low blink rates and incomplete blinking lead to excess tear evaporation and dry eye. Ocular surface protection depends on the patient's TFBUT matching or exceeding his or her IBI, or inter-blink interval.

The ocular protection index, which is the ratio of TFBUT over IBI, gives us a rapid snapshot of ocular surface vulnerability. If the OPI score is less than one, then a patient's cornea is at risk of exposure; if the OPI equals or is greater than one, it is not.[15] Another newer metric, OPI 2.0, measures blink rate and TFBUT simultaneously in real time.[16,17] The IVAD test uses a standardized task for all patients before and after treatment, to evaluate the decay of visual acuity in the time between blinks.[18] These more sophisticated measures enable investigators to establish an accurate comparative assessment of the effects of dry-eye

(continued on page 137)

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A middle-aged woman with a history of rheumatoid arthritis awakens and discovers visual field loss in one eye.

Tim Arlow, MD, PhD, and Robert Sergott, MD

Presentation

A 56-year-old woman presented with nonspecific infero-nasal visual field loss in the right eye. The vision loss was noticed upon waking two weeks prior. She denied any pain, trauma, headache, diplopia, photophobia or infection.

Systemic review was significant for chronic hand numbness and pain secondary to rheumatoid arthritis, but was otherwise negative—she denied presence of any rashes, headache, jaw claudication, scalp tenderness, abnormal bowel movements or urinary symptoms.

Medical History

Medical history was significant for rheumatoid arthritis, for which she was on prednisone 5 mg and had stopped rituximab infusions nine months before. She also had a history of having had a positive purified protein derivative test for tuberculosis (PPD), which was treated with "months of antibiotics" two years prior to presentation. She also had hypertension and hypothyroidism. She denied tobacco use or drinking, denied illicit drug use and did not have any allergies.

Medications included: daily prednisone 5 mg; carvedilol 6.25 mg; ramipril 10 mg; armour thyroid 45 mg; and venlafaxine 75 mg. She had completed five courses of rituximab infusions occurring every six months over the past several years before stopping nine months prior to presentation due to insurance issues.

Examination

Examination demonstrated a best corrected visual acuity of 20/30 in the right eye without pinhole improvement and 20/20-2 in the left eye. External examination was within normal limits; no mass, proptosis or ptosis was noted. Pupillary exam was normal with no afferent pupillary defect. She was orthophoric in all positions of gaze and extraocular motility was full bilaterally. Confrontation visual fields disclosed an infero-nasal defect OD but were otherwise full to confrontation OU. Ishihara color plates were 15/15 OU.

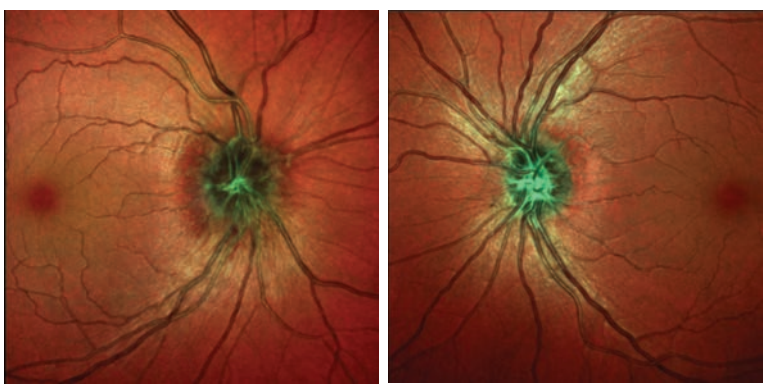

Figure 1. Multicolor fundus optical coherence tomography demonstrating nerve head edema OD and crowded nerve OS.

Anterior slit-lamp examination of the right and left eyes were within normal limits—conjunctiva was quiet, cornea clear, anterior chamber quiet and lens clear. Intraocular pressure by Goldmann applanation tonometry was 16 mmHg OU.

Funduscopic examination of the right eye disclosed optic nerve head edema with trace vitreous white cells *(See Figure 1)*. Funduscopic examination of the left eye showed a small crowded nerve without edema.

What is your differential diagnosis? What further workup would you pursue? Please turn to p. 136

Diagnosis, Workup and Treatment

Given our patient's clinical history and exam, a differential diagnosis was constructed and included conditions that were associated with optic neuritis. Notably, we were concerned about vascular (giant cell arteritis, nonarteritic anterior ischemic optic neuropathy); demyelinating (multiple sclerosis); autoimmune (systemic lupus erythematous, Sjögren's syndrome); infectious (tuberculosis, herpes zoster, Lyme disease, syphilis, toxoplasmosis, Bartonella); and inflammatory (sarcoidosis) etiologies. Given the clinical presentation, suspicion for giant cell arteritis was not high. The presence of a crowded optic disc in the left eye along with hypertension and older age was highly concerning for nonarteritic anterior ischemic optic neuropathy (NAION).

Humphrey visual field testing was reliable and confirmed the inferior nasal defect in her right eye and was otherwise normal in the left eye. Optical coherence tomography demonstrated retinal nerve fiber layer thickness of 123 µm in the right eye with significant swelling and 85 µm in the left with atrophy.

Magnetic resonance imaging of the brain demonstrated several nonspecific scattered punctate foci of FLAIR hyperintense signals within the cerebral white matter, predominantly in a subcortical distribution. These signs were suspicious for small vessel ischemic changes. Additionally, there were several larger oval lesions suspicious for demyelinating disease, but not specific for MS *(See Figure 2)*. There was no evidence of acute ischemia, intracranial hemorrhage or masses. MRI examination of the orbits was unremarkable and did not disclose optic nerve enhancement. Magnetic resonance angiography identified an incidental medially directed 6-mm left paraclinoid ICA aneurysm and 2-mm aneurysm from right ACA. CT of the chest was within normal limits and did not demonstrate evidence of tuberculosis.

Laboratory evaluation was within normal limits except for Neuromyelitis Optica (NMO) antibody against aquaporin-4 (AQP4) at a positive value of 6.3 (>5), which is consistent with diagnosis of or predisposition to NMO.

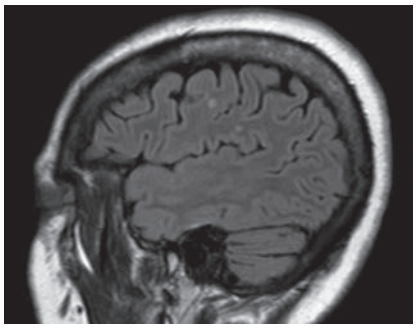

Figure 2. Sagittal magnetic resonance imaging demonstrating FLAIR hyperintense signals in cerebral white matter.

Following the diagnosis of NMO or Devic's disease, the patient was started on 50 mg of prednisone and instructed to taper down by 10 mg every five days until she returned to her original dosage of 5 mg, as per her rheumatologist for her RA. In conjunction with her rheumatologist, she was restarted on rituximab infusions.

Discussion

NMO or Devic's disease is an autoimmune disorder that results from inflammation and demyelination of the optic nerves and spinal cord. Originally identified in 1894 by Dr. Eugène Devic, NMO can result in blindness, weakness/paraplegia, loss of sensation, bowel and bladder dysfunction as well as other symptoms.[1] In this regard, NMO shares some similarities with MS and was initially proposed to be on the MS spectrum. However, recent immunological, clinical, radiographical and pathological studies delineate NMO as a unique disease. The prevalence of NMO is believed to be between 0.5 and 4.4 per 100,000 individuals and does not appear to have racial predilection.[2,3] The average age of onset for NMO is 34 to 43 years with a range of 4 to 88 years old.[2,4] Numerous studies have documented that women are three- to tenfold more likely to be diagnosed with NMO as compared to men.[2,5]

Modern evidence supports that NMO is caused by an autoantibody against aquaporin-4 (AQP4), a channel protein residing on astrocytes.[6] Specifically, the deposition of IgG and complement in central nervous system lesions, as well as loss of AQP4 from these lesions, suggests antibody and complement-mediated cellular toxicity are the primary mechanism of pathologic changes.[1,7] The cell-based assay for detecting AQP4 autoantibodies has sensitivity of 76 percent and specificity of 99 percent[9] and has been proven effective in delineating NMO from MS.

MS is roughly 40 times more prevalent than NMO.[4] Distinguishing NMO from MS is important clinically due to the fact that MS treatments of IFN-β, natalizumab and oral fingolimod may exacerbate NMO in certain patients.[4,10] The recently updated diagnostic criteria for NMO with positive AQP4 antibody requires at least one core clinical characteristic (optic neuritis or transverse myelitis) and exclusion of alternative diagnoses (notably brain MRI not meeting usual diagnostic criteria for MS).[8]

Treatment options for NMO are currently based on small, mostly ret-

rospective studies—to date there have been no prospective randomized clinical trials to establish efficacy of current treatments. With acute presentation, methylprednisolone 1g IV is delivered daily for three to five days. If symptoms do not improve, plasma exchange is administered daily or every other day for up to five treatments.[4] Afterwards, systemic immunosuppression with a variety of agents (including azathioprine, mycophenolate, cyclophosphamide and rituximab) have been employed to prevent attack recurrences.[4,10] Several studies have demonstrated rituximab treatment performs superiorly at decreasing annual relapse rates and disability indices.[11,12]

As compared to MS, the myelopathy in NMO is typically more severe and has less of a chance of recovery.[10] Additionally, the transverse myelitis in the spine can cause respiratory failure and death.[13] Within the first year, 55 percent of patients will have a relapse, and 90 percent of patients will do so in the first five years—these neurological deficits usually do not resolve between episodes.[2]

In summary, NMO is an autoimmune disease resulting in demyelination and inflammation of the optic nerves and spinal cord from autoantibodies directed against aquaporin-4. NMO may manifest with loss of vision or spinal-cord dysfunction and may be clinically similar to MS. Diagnosis is based primarily on MRI, evidence of optic neuritis and transverse myelitis, presence of IgG against AQP4, and exclusion of alternative diagnoses. Acutely, patients are treated with steroid or plasmapheresis before using systemic immunosuppression to prevent recurrent attacks. Without treatment, prognosis for NMO is guarded. REVIEW

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(continued from page 131)

treatments on the ocular surface and visual function. Furthermore, using these tests in conjunction with the Controlled Adverse Environment heightens the magnitude of change from baseline and gives us a greater chance of seeing differences between vehicle and active test compounds, or between two tear substitutes.[19]

An adequate assessment of artificial tear products enables patients to be paired with formulations most suited to them. The future looks bright and artificial tear products with modified HA appear to have demonstrable clinical effectiveness. The use of these new products will mark the beginning of a new era for tear substitutes, an era in which we begin prescribing the best of these long-acting formulations for patients when "nature's lotion" fails them. REVIEW

Dr. Abelson is a clinical professor of ophthalmology at Harvard Medical School, and emeritus surgeon at the Massachusetts Eye and Ear Infirmary. Mr. Ousler is vice president of dry eye at Ora Inc. Ms. Smith and Dr. Santanam are medical writers at Ora Inc.

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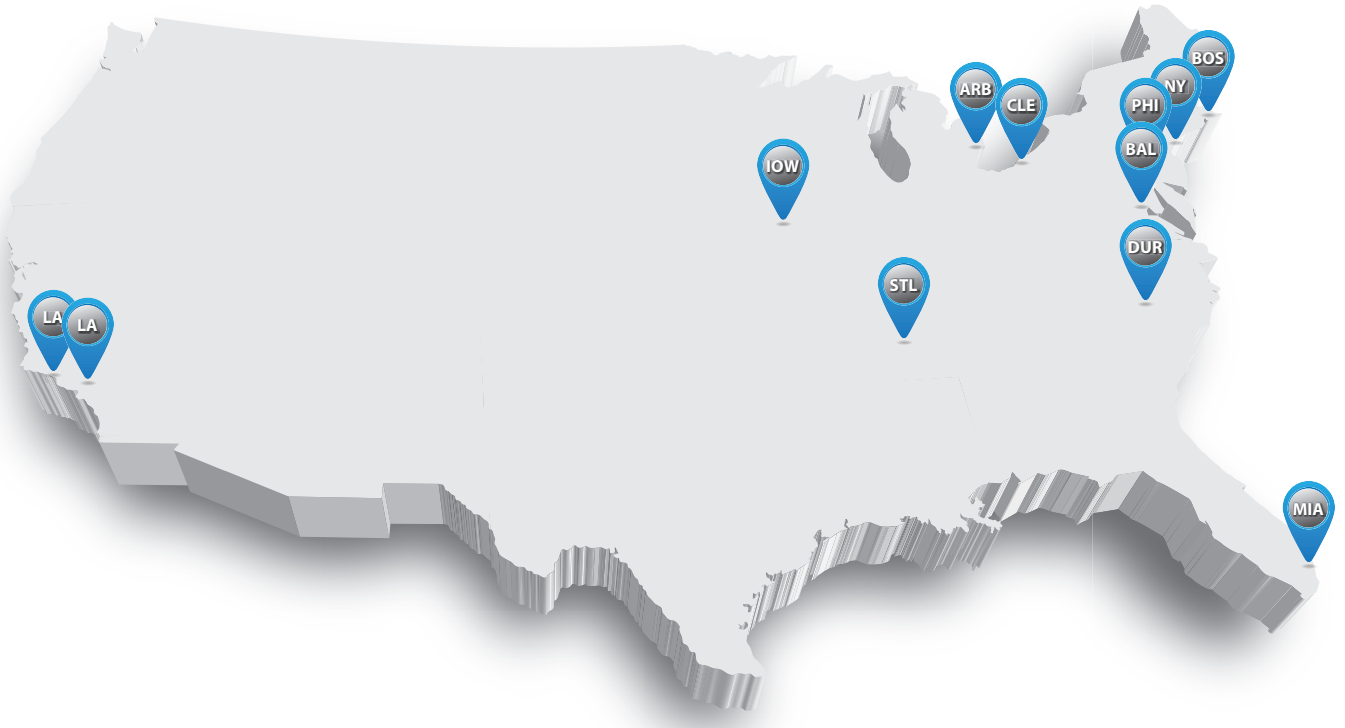

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Restasis®
(Cyclosporine Ophthalmic Emulsion) 0.05%

For patients with decreased tear production presumed to be due to ocular inflammation associated with Chronic Dry Eye

THE DRY EYE TREATMENT SHE NEEDS TODAY. BECAUSE TOMORROW MATTERS.

RESTASIS® twice a day, every day, helps patients experience increased tear production

Increased tear production was seen at 6 months.[1]

Indication and Usage

RESTASIS® (cyclosporine ophthalmic emulsion) 0.05% is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

Important Safety Information

Contraindications

RESTASIS® is contraindicated in patients with known or suspected hypersensitivity to any of the ingredients in the formulation.

Warnings and Precautions

Potential for Eye Injury and Contamination: To avoid the potential for eye injury and contamination, individuals prescribed RESTASIS® should not touch the vial tip to their eye or other surfaces.

Use With Contact Lenses: RESTASIS® should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of RESTASIS® ophthalmic emulsion.

Adverse Reactions

In clinical trials, the most common adverse reaction following the use of RESTASIS® was ocular burning (upon instillation)—17%. Other reactions reported in 1% to 5% of patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).

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

Reference: 1. RESTASIS® Prescribing Information.

ALLERGAN