REVIEW® of Ophthalmology

July 2015

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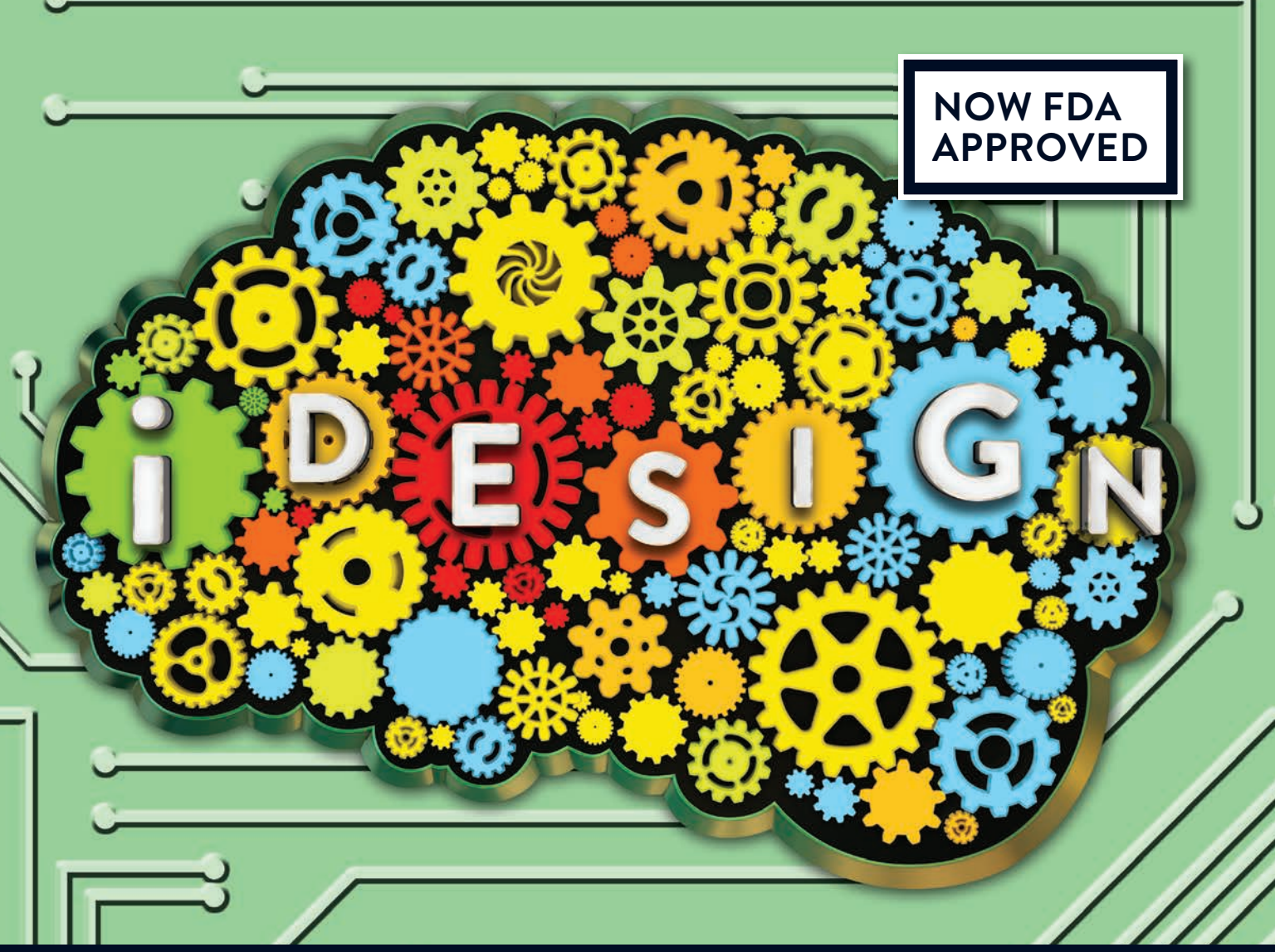

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REVIEW NEWS Volume XXII • No. 7 • July 2015

Protein Identified That Joins VEGF to Produce DR Damage

Researchers at Johns Hopkins University and the University of Maryland say that blocking a second blood vessel growth protein, along with one that is already well-known, could offer a new way to treat and prevent diabetic retinopathy. Forty to 45 percent of Americans with diabetes have diabetic retinopathy, according to the National Eye Institute.

Laser-sealing eye blood vessels can save central vision, but this often sacrifices peripheral and night vision, according to Akrit Sodhi, MD, PhD, an assistant professor of ophthalmology at the Johns Hopkins University School of Medicine. Bevacizumab, ranibizumab and aflibercept can help treat these blood vessels by blocking the action of VEGF, the growth factor released as part of a chain of signals in response to low oxygen levels, which stimulates the growth of new, often abnormal, blood vessels. But studies have shown that although these drugs slow progression to proliferative diabetic retinopathy, they do not reliably prevent it.

Looking for an explanation, postdoctoral fellow Savalan Babapoor-Farrokhran, MD, and Kathleen Jee, a student at the school of medicine who will begin her residency in ophthalmology at the Wilmer Eye Institute at Johns Hopkins next year, tested levels of VEGF in samples of fluid from the eye taken from healthy people, people with diabetes who did not have diabetic retinopathy and people with diabetic retinopathy of varying severity.

While levels of VEGF tended to be higher in those with proliferative diabetic retinopathy, some of their fluid had less VEGF than did the healthy participants. But even the low-VEGF fluid from patients with proliferative diabetic retinopathy stimulated blood vessel growth in lab-grown cells.

"The results suggested to us that although VEGF clearly plays an important role in blood vessel growth, it's not the only factor," Dr. Sodhi says.

A series of experiments in lab-grown human cells and mice revealed a second culprit, a protein called angiopoietin-like 4. When the researchers blocked the action of both VEGF and angiopoietin-like 4 in fluid from the eyes of people with proliferative diabetic retinopathy, it markedly reduced blood vessel growth in lab-grown cells.

If a drug can be found that safely blocks the second protein's action in patients' eyes, it might be combined with the anti-VEGF drugs to prevent many cases of proliferative diabetic retinopathy, Dr. Sodhi suggests.

The team is now investigating whether angiopoietin-like 4 might also play a role in other eye diseases, such as macular degeneration.

A summary of the study appeared online May 25 in *Proceedings of the National Academy of Sciences*.

FDA Allows Aerie Endpoint Change

Aerie Pharmaceuticals reported that the Food and Drug Administration has agreed that Aerie may change the primary endpoint range of its second Phase III registration trial of Rhopressa, named Rocket 2. With this agreement, Aerie is changing the primary endpoint range to include patients with baseline intraocular pressures ranging from above 20 mmHg to below 25 mmHg. The former range for the primary endpoint of above 20 mmHg to below 27 mmHg will now represent a secondary endpoint range for Rocket 2.

The Rocket 2 primary endpoint range is now changed to the same range where the Phase III registration trial results of Rocket 1 demonstrated success. In the Rocket 1 trial, in this range, Rhopressa demonstrated non-inferiority to timolol, and numerical superiority over timolol at the majority of time points. According to the Baltimore Eye Survey, nearly 80 percent of newly diagnosed glaucoma patients have unmedicated baseline IOPs below 26 mmHg.

The FDA also agreed that Aerie may use a hierarchically based statistical approach in determining whether this three-arm trial is adequately powered at the revised primary endpoint range. Using this methodology, Aerie believes that the new primary endpoint range is adequately powered, and there is no need to recruit additional patients into Rocket 2. Three-month efficacy results for Rocket 2 are expected by the end of the third quarter of 2015. An additional Rhopressa Phase III registration trial, named Rocket 4, is expected to commence in the third

quarter of 2015.

"We are extremely pleased with the outcome of our communications with the FDA," said Vicente Anido Jr., PhD, Aerie's chairman and CEO. "If Rocket 2 results resemble those of Rocket 1, we believe we may have a much greater opportunity for success in meeting the clinical endpoint of non-inferiority to timolol. We are also very appreciative of the thoughtful guidance provided by the FDA, and believe their feedback will prove very useful as our programs progress." Rocket 4 is expected to be established with a primary endpoint range of above 20 mmHg to below 25 mmHg.

Rhopressa is a novel triple-action eye drop that, if approved, would become the only once-daily product available that specifically targets the trabecular meshwork. Preclinical results have demonstrated that Rhopressa also lowers episcleral venous pressure, which contributes approximately half of IOP in healthy subjects. Further, Rhopressa provides an additional mechanism that reduces fluid production in the eye and therefore lowers IOP. Biochemically, Rhopressa is known to inhibit both Rho Kinase (ROCK) and norepinephrine transporter.

There were originally three Phase III registration trials for Rhopressa. Rocket 1 was a 90-day efficacy trial, with results reported in April 2015; Rocket 2 is a 12-month safety trial with a 90-day interim efficacy readout; and Rocket 3 is a safety-only study being conducted in Canada. In Rocket 1, for the primary endpoint range of above 20 mmHg to below 27 mmHg, Rhopressa did not demonstrate non-inferiority to timolol. However, Rhopressa did demonstrate non-inferiority to timolol at all ranges below 26 mmHg. As a result, Aerie plans to commence in the third quarter of 2015 an additional Phase III registration trial, named Rocket 4. Based on the current clinical trial status, Aerie may submit a New Drug Application filing in the second half of 2016.

Contact Lens Wear May Alter Microbiome

Using high-precision genetic tests to differentiate the thousands of bacteria that make up the human microbiome, researchers at NYU Langone Medical Center suggest that they have found a possible—and potentially surprising—root cause of the increased frequency of certain eye infections among contact lens wearers.

In a study report on their work presented at the annual meeting of the American Society for Microbiology on May 31 in New Orleans, NYU Langone researchers say they have identified a diverse set of microorganisms

in the eyes of daily contact lens wearers that more closely resembles the group of microorganisms of their eyelid skin than the bacterial grouping typically found in the eyes of non-wearers.

Specifically, the NYU Langone team found that the conjunctiva has surprisingly higher bacterial diversity than the skin directly beneath the eye and three times the usual proportion of *Methylobacterium*, *Lactobacillus*, *Acinetobacter* and *Pseudomonas* bacteria in the eyes of the study's nine contact lens wearers than is typically found on the surface of the eyeballs of 11 other men and women in the study who did not wear contact lenses. When measured and plotted on a graph, statistical germ diversity scores showed that the eye microbiome of contact lens wearers had a composition more similar to that of the wearer's skin than the eye microbiome of non-lens wearers.

"Our research clearly shows that putting a foreign object, such as a contact lens, on the eye is not a neutral act," says senior study investigator and NYU Langone microbiologist Maria Gloria Dominguez-Bello, PhD.

"What we hope our future experiments will show is whether these changes in the eye microbiome of lens wearers are due to fingers touching the eye, or from the lens's direct pressure affecting and altering the immune system in the eye, and what bacteria are suppressed or are allowed to thrive," says Dominguez-Bello, an associate professor at NYU Langone.

"These findings should help scientists better understand the long-standing problem of why contact-lens wearers are more prone to eye infections than non-lens wearers," says Dr. Dominguez-Bello, whose research focuses on the different microbiomes of the gut and other body parts, how they interact and how

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REVIEW News

contemporary lifestyle practices may affect the microbiome and increase disease risk. Such understanding, she says, should point to better means of preventing infections.

"There has been an increase in the prevalence of corneal ulcers following the introduction of soft contact lenses in the 1970s," says study co-investigator Jack Dodick, MD, professor and chair of ophthalmology at NYU Langone. "A common pathogen implicated has been *Pseudomonas*. This study suggests that because the offending organisms seem to emanate from the skin, greater attention should be directed to eyelid and hand hygiene to decrease the incidence of this serious occurrence," he says.

As part of the study, researchers took hundreds of swabs of various parts of the eye, including the conjunctiva, as well as along the skin directly beneath the eye. Both swabs and used contact lenses were then subjected to genetic analysis in the lab to determine which bacteria were present.

While the bacterial composition in the eye of contact lens wearers more closely resembled that of the skin, some 5,245 distinct bacterial strains and subtypes were identified in the eye conjunctiva of lens wearers, and 5,592 strains were identified in the eyes of non-lens wearers. A similar but different composition of 2,133 strains and subtypes was identified in the skin directly beneath the eye of those with contact lenses, while 3,849 distinct bacteria were identified in non-lens wearers.

Surprisingly, researchers say, more *Staphylococcus* bacteria, which are linked to eye infections and more prominent on the skin, were found in the eyes of non-lens wearers, and researchers do not yet have an explanation for the disparity. Estimates vary, but many cases of potentially scarring bacterial keratitis, as well as conjunctival infections, occur in contact lens wearers. REVIEW

BP Researchers Discover Protein that Leads to Glaucoma

A team of Bascom Palmer Eye Institute researchers has discovered the protein cochlin, most recognized in concentrated levels within the inner ear, is present in the eye and has an effect on glaucoma. The interdisciplinary team at the University of Miami Miller School of Medicine found that levels of cochlin, a protein product of the COCH gene, rise just prior to the elevation of intraocular pressure.

The team measured cochlin in experimental models and found peak levels of the protein precede clinical glaucoma symptoms. "The ability to detect and quantify cochlin in the local tissues of the eye prior to clinical detection of the disease offers potential diagnostic and prognostic value," says Sanjoy K. Bhattacharya, PhD, M Tech, professor of ophthalmology. "This discovery paves the way for physicians and researchers to record levels of protein and lipid biomarkers in the eyes for progressive blinding eye diseases such as glaucoma." The findings were shared in the June 5, 2015 online edition of *Scientific Report*, a Nature Group publication.

Dr. Bhattacharya's research concentrates on the cell biology of the trabecular meshwork. An imbalance in the fluid can result in elevation of intraocular pressure, which damages the optic nerve and results in gradual vision loss associated with glaucoma. Vision loss from glaucoma is irreversible.

Co-author Jianhua Wang, MD, PhD, MS, an associate professor of ophthalmology, develops state-of-the art imaging equipment that provides clearer images and detailed information about the eye. For these studies supported by National Institutes of Health grants, Dr. Wang specifically designed and built a sophisticated optical coherence tomography instrument combining two different approaches, (spectroscopic and magnetomotive). This specialized instrument, available only at Bascom Palmer, was used to detect the levels of cochlin.

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at 12, 14, and 20 hours post-dose in a 3-month study[1,2]*

TRAVATAN Z® Solution has no FDA-approved therapeutic equivalent[3]

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INDICATIONS AND USAGE

TRAVATAN Z® (travoprost ophthalmic solution) 0.004% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

Dosage and Administration

The recommended dosage is 1 drop in the affected eye(s) once daily in the evening. TRAVATAN Z® Solution should not be administered more than once daily since it has been shown that more frequent administration of prostaglandin analogs may decrease the IOP-lowering effect.

TRAVATAN Z® Solution may be used concomitantly with other topical ophthalmic drug products to lower IOP. If more than 1 topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Pigmentation—Travoprost ophthalmic solution has been reported to increase the pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as travoprost is administered. After discontinuation of travoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. The long-term effects of increased pigmentation are not known. While treatment with TRAVATAN Z® Solution can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Eyelash Changes—TRAVATAN Z® Solution may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Use With Contact Lenses—Contact lenses should be removed prior to instillation of TRAVATAN Z® Solution and may be reinserted 15 minutes following its administration.

Adverse Reactions

The most common adverse reaction observed in controlled clinical studies with TRAVATAN Z® Solution was ocular hyperemia, which was reported in 30 to 50% of patients. Up to 3% of patients discontinued therapy due to conjunctival hyperemia. Ocular adverse reactions reported at an incidence of 5 to 10% in these clinical studies included decreased visual acuity, eye discomfort, foreign body sensation, pain, and pruritus. In postmarketing use with prostaglandin analogs, periorbital and lid changes including deepening of the eyelid sulcus have been observed.

Use in Specific Populations

Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

For additional information about TRAVATAN Z® Solution, please see the brief summary of Prescribing Information on the adjacent page.

***Study Design:** Double-masked, randomized, parallel-group, multicenter non-inferiority comparison of the efficacy and safety of travoprost 0.004% preserved with benzalkonium chloride (BAK) to TRAVATAN Z® Solution after 3 months of treatment in patients with open-angle glaucoma or ocular hypertension. Baseline IOPs were 27.0 mm Hg (n=322), 25.5 mm Hg (n=322), and 24.8 mm Hg (n=322) at 8 AM, 10 AM, and 4 PM for TRAVATAN Z® Solution. At the end of Month 3, the TRAVATAN Z® Solution group had mean IOPs (95% CI) of 18.7 mm Hg (-0.4, 0.5), 17.7 mm Hg (-0.4, 0.6), and 17.4 mm Hg (-0.2, 0.8) at 8 AM, 10 AM, and 4 PM, respectively. Statistical equivalent reductions in IOP (95% confidence interval about the treatment differences were entirely within ±1.5 mm Hg) were demonstrated between the treatments at all study visits during the 3 months of treatment.

References: 1. Data on file, 2013. **2.** Lewis RA, Katz GJ, Weiss MJ, et al. Travoprost 0.004% with and without benzalkonium chloride: a comparison of safety and efficacy. *J Glaucoma*. 2007;16(1): 98-103. **3.** Drugs@FDA. FDA Approved Drug Products: TRAVATAN Z. www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails. Accessed July 31, 2014.

TRAVATAN Z®

(travoprost ophthalmic solution) 0.004%

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TRAVATAN Z®

(travoprost ophthalmic solution) 0.004%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE
TRAVATAN Z® (travoprost ophthalmic solution) 0.004% is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

DOSAGE AND ADMINISTRATION
The recommended dosage is one drop in the affected eye(s) once daily in the evening.
TRAVATAN Z® (travoprost ophthalmic solution) should not be administered more than once daily since it has been shown that more frequent administration of prostaglandin analogs may decrease the intraocular pressure lowering effect.

Reduction of the intraocular pressure starts approximately 2 hours after the first administration with maximum effect reached after 12 hours.

TRAVATAN Z® Solution 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.

CONTRAINDICATIONS
None

WARNINGS AND PRECAUTIONS
Pigmentation
Travoprost ophthalmic solution has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes. Pigmentation is expected to increase as long as travoprost is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of travoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with TRAVATAN Z® (travoprost ophthalmic solution) 0.004% can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Eyelash Changes
TRAVATAN Z® Solution may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation
TRAVATAN Z® Solution should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

Macular Edema
Macular edema, including cystoid macular edema, has been reported during treatment with travoprost ophthalmic solution. TRAVATAN Z® Solution should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Angle-closure, Inflammatory or Neovascular Glaucoma
TRAVATAN Z® Solution has not been evaluated for the treatment of angle-closure, inflammatory or neovascular glaucoma.

Bacterial Keratitis
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.

Use with Contact Lenses
Contact lenses should be removed prior to instillation of TRAVATAN Z® Solution and may be reinserted 15 minutes following its administration.

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 rates in the clinical studies of another drug and may not reflect the rates observed in practice. The most common adverse reaction observed in controlled clinical studies with TRAVATAN® (travoprost ophthalmic solution) 0.004% and TRAVATAN Z® (travoprost ophthalmic solution) 0.004% was ocular hyperemia which was reported in 30 to 50% of patients. Up to 3% of patients discontinued therapy due to conjunctival hyperemia. Ocular adverse reactions reported at an incidence of 5 to 10% in these clinical studies included decreased visual acuity, eye discomfort, foreign body sensation, pain and pruritus. Ocular adverse reactions reported at an incidence of 1 to 4% in clinical studies with TRAVATAN® or TRAVATAN Z® Solutions included abnormal vision, blepharitis, blurred vision, cataract, conjunctivitis, corneal staining, dry eye, iris discoloration, keratitis, lid margin crusting, ocular inflammation, photophobia, subconjunctival hemorrhage and tearing.

Nonocular adverse reactions reported at an incidence of 1 to 5% in these clinical studies were allergy, angina pectoris, anxiety, arthritis, back pain, bradycardia, bronchitis, chest pain, cold/flu syndrome, depression, dyspepsia, gastrointestinal disorder, headache, hypercholesterolemia, hypertension, hypotension, infection, pain, prostate disorder, sinusitis, urinary incontinence and urinary tract infections.

In postmarketing use with prostaglandin analogs, periorbital and lid changes including deepening of the eyelid sulcus have been observed.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category C
Teratogenic effects: Travoprost was teratogenic in rats, at an intravenous (IV) dose up to 10 mcg/kg/day (250 times the maximal recommended human ocular dose (MRHOD), evidenced by an increase in the incidence of skeletal malformations as well as external and visceral malformations, such as fused sternebrae, domed head and hydrocephaly. Travoprost was not teratogenic in rats at IV doses up to 3 mcg/kg/day (75 times the MRHOD), or in mice at subcutaneous doses up to 1 mcg/kg/day (25 times the MRHOD). Travoprost produced an increase in post-implantation losses and a decrease in fetal viability in rats at IV doses > 3 mcg/kg/day (75 times the MRHOD) and in mice at subcutaneous doses > 0.3 mcg/kg/day (7.5 times the MRHOD).

In the offspring of female rats that received travoprost subcutaneously from Day 7 of pregnancy to lactation Day 21 at doses of ≥ 0.12 mcg/kg/day (3 times the MRHOD), the incidence of postnatal mortality was increased, and neonatal body weight gain was decreased. Neonatal development was also affected, evidenced by delayed eye opening, pinna detachment and preputial separation, and by decreased motor activity.

There are no adequate and well-controlled studies of TRAVATAN Z® (travoprost ophthalmic solution) 0.004% administration in pregnant women. Because animal reproductive studies are not always predictive of human response, TRAVATAN Z® Solution should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
A study in lactating rats demonstrated that radiolabeled travoprost and/or its metabolites were excreted in milk. It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRAVATAN Z® Solution is administered to a nursing woman.

Pediatric Use
Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

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

Hepatic and Renal Impairment
Travoprost ophthalmic solution 0.004% has been studied in patients with hepatic impairment and also in patients with renal impairment. No clinically relevant changes in hematology, blood chemistry, or urinalysis laboratory data were observed in these patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Two-year carcinogenicity studies in mice and rats at subcutaneous doses of 10, 30, or 100 mcg/kg/day did not show any evidence of carcinogenic potential. However, at 100 mcg/kg/day, male rats were only treated for 82 weeks, and the maximum tolerated dose (MTD) was not reached in the mouse study. The high dose (100 mcg/kg) corresponds to exposure levels over 400 times the human exposure at the maximum recommended human ocular dose (MRHOD) of 0.04 mcg/kg, based on plasma active drug levels. Travoprost was not mutagenic in the Ames test, mouse micronucleus test or rat chromosome aberration assay. A slight increase in the mutant frequency was observed in one of two mouse lymphoma assays in the presence of rat S-9 activation enzymes.

Travoprost did not affect mating or fertility indices in male or female rats at subcutaneous doses up to 10 mcg/kg/day [250 times the maximum recommended human ocular dose of 0.04 mcg/kg/day on a mcg/kg basis (MRHOD)]. At 10 mcg/kg/day, the mean number of corpora lutea was reduced, and the post-implantation losses were increased. These effects were not observed at 3 mcg/kg/day (75 times the MRHOD).

PATIENT COUNSELING INFORMATION
Potential for Pigmentation
Patients should be advised about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of TRAVATAN Z® (travoprost ophthalmic solution) 0.004%.

Potential for Eyelash Changes
Patients should also be informed of the possibility of eyelash and vellus hair changes in the treated eye during treatment with TRAVATAN Z® Solution. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

Handling the Container
Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

When to Seek Physician Advice
Patients should also be advised that if they develop an intercurrent ocular condition (e.g., trauma or infection), have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of TRAVATAN Z® Solution.

Use with Contact Lenses
Contact lenses should be removed prior to instillation of TRAVATAN Z® Solution and may be reinserted 15 minutes following its administration.

Use with Other Ophthalmic Drugs
If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes between applications.

Rx Only
U.S. Patent Nos. 5,631,287; 5,889,052, 6,011,062; 6,235,781; 6,503,497; and 6,849,253

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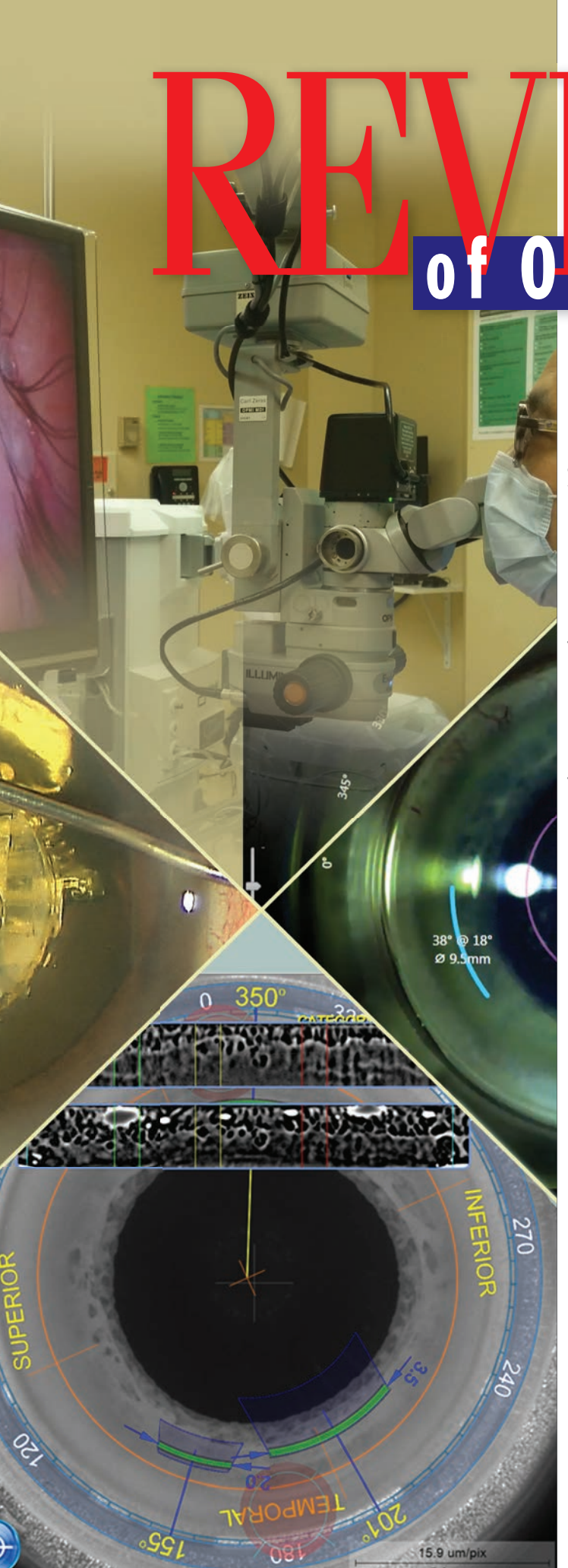

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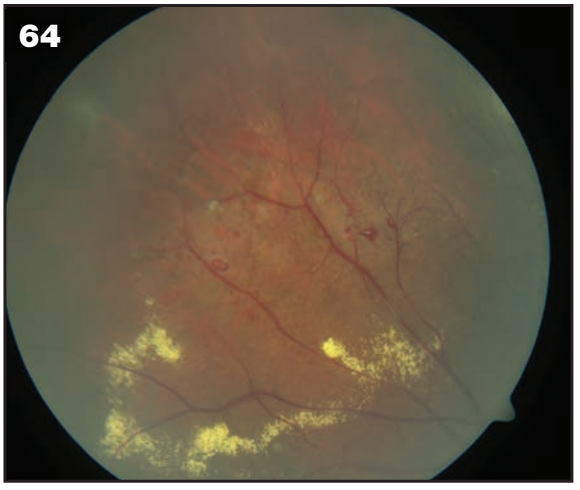

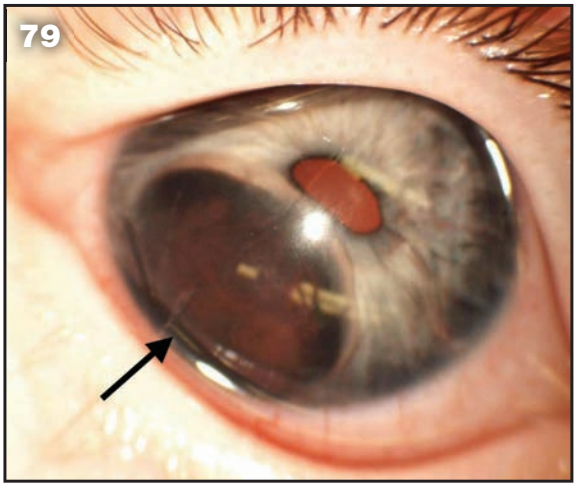

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Virtual Reality: A New Frontier in Eye Care?

Simulated reality is creating new possibilities for testing vision, capturing surgery and helping those with limited vision.

Christopher Kent, Senior Editor

Every so often, a new technology comes along that has the potential to be game-changing. Virtual reality—in which a subject is immersed in a manufactured visual and audio environment in which he can look around and even move around—is one of those technologies. Up until recently, virtual reality has been minimally used outside of the field of video gaming, for two reasons: technical problems and cost. The usefulness of early attempts to immerse people in a virtual setting were severely limited by lag-time; if you turned your head, the shift in your visual perspective took an instant to follow. This delay tended to make the subject feel sick. In addition, the cost of the equipment was prohibitive for most purposes.

Today, new technologies may surmount both of those limitations. The latest virtual reality headsets, such as the Oculus Rift (Oculus, Menlo Park, Calif.), allow the visual to follow our changing gaze so quickly that the brain can't detect a delay. Hence, no more feeling ill. And thanks to the ever-dropping cost of technology, the Oculus Rift will soon be available to the public for a cost of about $300. (Software developers can currently buy a kit to create one for $350.)

This technology could have a drastic impact on many fields, from entertainment (virtual movies in which you can look around during the action) to extremely realistic training simulators (without most of the physical equipment) to mini-vacations (spend a few hours on a tropical island without leaving your home) to 3-D remote interactions with other people.

Here, five individuals using this technology in ways relating to medicine talk about how it's likely to impact the field of ophthalmology.

Real-world Visual Testing

One of the most promising uses of virtual reality in medicine is creating performance tests that simulate real-life conditions. (Traditional tests may bear little relation to the visual challenges faced by patients every day.) Felipe A. Medeiros, MD, PhD, a professor of clinical ophthalmology at the University of California, San Diego, and director of the Visual Performance Laboratory at the Shiley Eye Institute at UCSD, and colleagues have become the first to publish a study using virtual reality in this way. Their study used the Oculus Rift device to test subjects' balance response to vection—the sense of motion we feel when the environment around us moves (or appears to move).[1]

"In real life we use vision in a dynamic way, involving complex scenes and motion," Dr. Medeiros explains. "The tests we commonly perform to evaluate visual loss in glaucoma are static tests, like standard perimetry fields. We hypothesized that using dynamic stimuli would be a more effective way of evaluating how impaired a glaucoma patient has become.

"We used an immersive 3-D virtual-reality environment to help us evaluate balance in patients who have glaucoma, in comparison to controls," he continues. "The subjects wore an Oculus Rift while standing on a force platform. We projected a series of different visual stimuli, such as moving through a tunnel (translational stimulus) and standing in a rotating environment (rotational stimulus). Subjects reacted to the perceived movement by shifting their bodies to compensate. The platform measured

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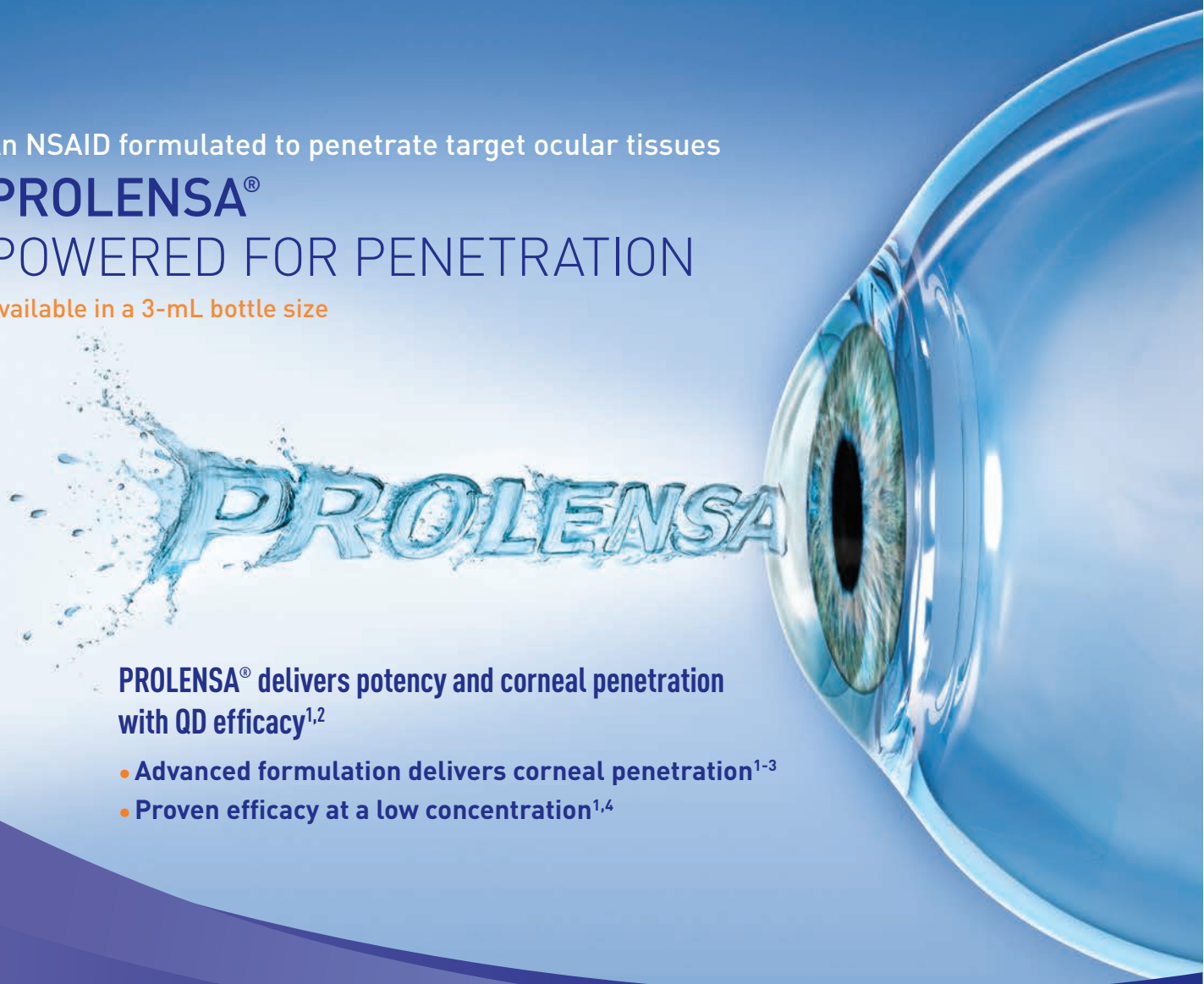

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PROLENSA® (bromfenac ophthalmic solution) 0.07% is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.

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.

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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.

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the force their bodies applied when they attempted to regain or prevent their perceived loss of balance.

"In patients with glaucoma, the responses were not appropriate," he says. "Their responses were more erratic than those of healthy subjects, and they lost their balance much more easily. More importantly, we found that the metrics produced by this test were predictive of the risk of falling. A history of falls in these subjects revealed that those who had more falls performed worse in the test." (Potentially being able to predict falling is a big deal; falling is the leading cause of injury-related death in older adults, especially those with glaucoma.)

Dr. Medeiros points out that virtual reality offers ophthalmology a chance to break free of the traditional constraints of in-office testing. "Studies have shown that tests like the standard visual field are not very predictive of how patients actually perform in the real world," he says. "I see virtual reality as a way of testing things in a more realistic way that will allow us to assess how visual impairment affects our patients' ability to do things. For example, we have a very elaborate driving simulator in my lab; it's a full car, so the test is very realistic. With virtual reality we might be able to recreate a portable version of that test."

Dr. Medeiros notes that the technology involved in the balance test is rapidly becoming less expensive. "An Oculus Rift can be purchased for a few hundred dollars," he says. "And although we used an expensive force platform in our experiment to maximize our accuracy and the value of our data, the same test might be accomplished using the kind of floor mat people stand on when they play some Wii video games. We're now working to develop a simplified version of the test that could be routinely used in clinical practice to predict which patients are at higher risk of falling. If you know your patient is at higher risk, you can provide some counseling and perhaps have the patient go into a program designed to reinforce balance through exercise or other means."

Felipe A. Medeiros, MD, PhD

Using virtual reality to cause a subject to correct for perceived motion has revealed that glaucoma patients' reactions are more erratic than those of healthy individuals.

Dr. Medeiros notes that his group's intention was not to create a diagnostic screening tool. "However, we did find that this test is able to predict the risk of falling even in those with only mild or moderate glaucoma, who may not realize they are at risk," he says. "It would be interesting to evaluate the potential of this kind of test as a screening tool."

Another Virtual Vection Test

Researchers at the Vision Science Research Program of the Toronto Western Research Institute are also investigating the use of virtual reality to create vection—the sensation that you are moving—as a way to evaluate the status of glaucoma in a patient. Their results indicate that even individuals with early glaucoma experience vection differently than healthy controls, raising the possibility of a simple screening test for the disease. (They conducted their initial tests seating subjects in front of large screens to create images that fill the entire visual field, but they plan to replace those screens with a virtual reality headset.)

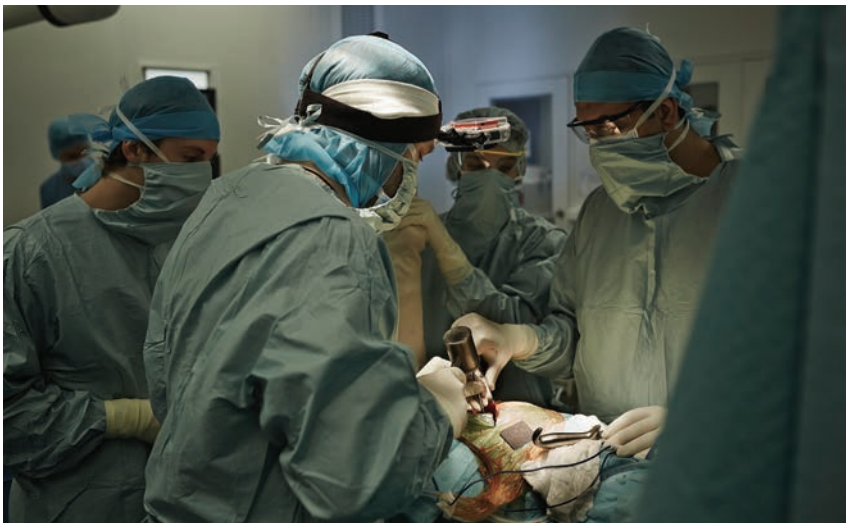
"Our test presents the study participants with a random dot pattern that fills their entire visual field," explains Taylor Brin, a graduate student in the Ocular Motor Laboratory, which is part of the VSRP. "The dot pattern rotates in a circle. This causes the participant to feel as if he or she is moving; in other words, it induces vection. The subjects simply press and hold a button as soon as they feel like they're moving. We compared the vection response in individuals with healthy vision to the response from those with mild-stage glaucoma; we found that individuals with glaucoma had vection that was either impaired or completely absent compared to those with healthy vision."

Ms. Brin says the idea for this test originated when other members of the lab noted studies showing that vection was altered in individuals with age-related macular degeneration. "Initially we did our vection test in macular degeneration patients; we found they have a stronger sensation of vection because they have damaged central vision. That led us to think, why not try this in glaucoma where the damage is sort of the opposite of macular degeneration? Instead of having damaged central vision, people with glaucoma typically have damaged peripheral vision at first."

Ms. Brin says the early results have been highly statistically significant. "As we hypothesized, individuals with glaucoma have a weaker sensation of vection," she says. "They either don't experience vection at all—in contrast to healthy controls who universally experience vection—or it takes them a lot longer to experience it than controls. Notably, we only tested patients

with early glaucoma, which makes this very promising as a screening tool. Even patients with 20/20 vision and very few visual deficits showed this effect."

Ms. Brin says the team is very interested in trying the same test using a tool such as the Oculus Rift. "Reality-based tests involving things like vection are very promising, but performing the test with a large screen is inconvenient," she notes. "Virtual reality is compact and convenient; it's easy to have in the doctor's office, and it's relatively inexpensive compared to some of the tests we have now. Using virtual reality to perform this sort of test could help to make diagnosis much easier."



Julie Mercier/Moveo Foundation

France's Moveo Foundation has funded 3-D, open-field recording of surgeries (note cameras attached to surgeon's head), which are then translated into virtual reality format. The viewer can turn and look in any direction during the virtual playback.

Making Standard Tests Portable

One of the advantages of current virtual reality technology is its portability. Thus, existing tests such as perimetry can be recreated in virtual reality, eliminating the need for bulky, non-portable equipment. Along those lines, CREWT Medical Systems in Tokyo has developed a head-mounted device that can conduct a standard perimetry test without the usual equipment. The virtual test should be available for purchase in Japan later this year.

Shinji Kimura, director and general manager at CREWT Medical Systems in Tokyo, notes that it's not practical for most surgeons to increase the number of measurements taken in the office. "We chose to develop the head-mounted perimeter partly because its high portability helps to solve this problem," he says. "In addition, the problem of finding a suitably dark place to give the test is settled because the head mount provides its own darkroom, and finding space for the equipment is no longer an issue.

"This device is equipped with an optical system that provides a field of vision of 35 degrees from the center to the right and left," he continues. "It uses a liquid crystal display and can create the broad dynamic range of brightness and various sizes of stimulus necessary for a perimeter. It makes it possible to measure perimetry binocularly, and there's no need to close one eye for a monocular test. In fact, when performing binocular random perimetry, it is impossible for the subject to know which eye is being tested. The device can also monitor the pupil with high precision and use that information to control the stimulus point, making it easy for the subject to maintain fixation." Mr. Kimura notes that the device is balanced to avoid feeling too heavy on the head, although he admits some elderly individuals might be bothered by the weight.

Mr. Kimura says they have conducted a study comparing the device to a standard perimeter. "The correlation is very good, but the study has not yet been published, so I can't share the numbers," he says. He adds that the company is currently conducting a study including a questionnaire to help determine how subjects feel about taking the test in this way. They hope to eventually bring the product to the United States.

Dr. Medeiros, along with members of the neuroscience department at the University of Southern California, San Diego, is also working on a virtual reality-based perimeter that takes things one step further: It removes the subjective part of the test by measuring visual responses using electroencephalograph technology embedded in the headset worn by the patient. "This not only eliminates the need for the standard perimeter, it will be an objective test of visual impairment that does not rely on subjective patient responses," he says. "We'll analyze the patient's brain waves to determine whether he saw the stimulus or not. We've already created a prototype of the device."

Capturing Virtual Live Surgery

The MOVEO Foundation, based in France, focuses on research projects aiming to modernize orthopedic surgery. Recently, the Moveo Foundation supported a project that pioneered the capturing of surgical procedures in 3-D; the procedures are then translated into a virtual reality experience that can be shared via the Oculus Rift, for multiple purposes

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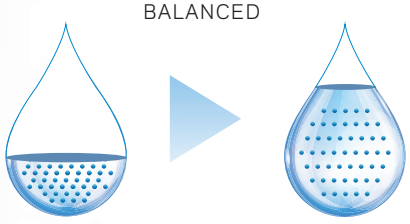

HYPEROSMOLARITY

Increased concentration of the tears leads to irritation and potential damage to the ocular surface.

HEALTHY TEAR

TheraTears® Dry Eye Therapy replicates the electrolyte balance of natural tears to restore comfort.

RESTORE + CLEANSE + NOURISH

thera tears®
THERAPY FOR YOUR EYES™

DRY EYE THERAPY

Restores Eyes Natural Balance™

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AKORN Consumer Health

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.

including training.

"Virtual reality enables the trainee to become an avatar of the surgeon, to be virtually in the operating theater," says Thomas Gregory, MD, an associate professor at the European Teaching Hospital Georges Pompidou at Paris Descartes University in France, who is a founding member of the MOVEO Foundation. "This research project uses two advanced technologies: an open-field camera and a virtual reality headset. Two synchronized open-field cameras are placed on the surgeon's head while he performs a surgery. *(See picture, p. 20.)* The visual and audio data are then adapted to virtual reality format.

"When you watch the procedure through the virtual reality headset, you can move your head in this virtual world," he continues. "If you are more interested in what the assistant is doing, or the scrub nurse, just turn your head toward them to see what they are doing; the stereoscopic 3-D and wide field of view create a striking immersive effect. A student can replay the surgery in detail and watch it through the eyes of the surgeon. Surgeons can also use this to observe and learn from their own work."

Taking the element of reality one step further, an English product-development firm, Plextek Consultancy, has been working with its government's Defense Science and Technology Laboratory to create an immersive virtual reality simulation training system for medical members of the military, using the Oculus Rift. The system creates battlefield environments that can be experienced by multiple individuals at once, allowing them to learn to treat casualties in three-dimensional, high-stress, under-fire situations. Notably, the system also records the participants' actions while responding to the virtual situation for later evaluation.

"We've enabled the system to record everything that happens, monitoring the actions of the participants, visually and verbally," explains Collette Johnson, medical business development manager at Plextek. "Everything is time-stamped and searchable. This should be very useful for surgeons in training; you can see whether the person was following the steps correctly. It could also be useful for a surgeon who simply wants to review his own surgery. What makes this different from simply filming a procedure is that it's an intelligent system and a data pool; you can search for key moments and go straight to them; you can search for specific words in the audio track. And of course, because it's virtual reality, you can look around, 360 degrees, at any moment during the recorded procedure. And it can automatically become part of the electronic record, if desired."

What Lies Ahead?

"Like other highly demanding surgical disciplines, ophthalmology will benefit from affordable immersive systems such as virtual reality," says Dr. Gregory. "This will be a powerful way to train young surgeons, especially as the demand for remote training systems increases with the development of health-care systems in emerging countries. The potential of virtual reality is also huge for patient care, as it can be used advantageously in the framework of minimally invasive surgical techniques."

Ms. Johnson sees multiple potential uses for virtual reality. "Virtual reality can allow patients and family members to experience procedures and their benefits ahead of time," she notes. "For example, many patients are nervous about getting an injection in the eye. With virtual reality they and any concerned family members can see what's involved. Virtual reality could also be used to conduct tests that would normally have to be done in the office, tests that can detect musculature problems or neuro-ophthalmological problems, and conduct them outside the office in the community. That might make it easier to discover problems earlier when they're more amenable to treatment."

Ms. Johnson also sees virtual reality helping individuals with low vision experience things that would be challenging or impossible to experience firsthand. "An individual with low vision might want to visit the Metropolitan Museum of Art, but find it very frustrating—if he could even get there," she notes. "Virtual reality would allow that person to spend as much time as desired interacting with the art, as closely as desired, either in the museum or at home. Possibilities like this might help to prevent some of the side effects we see in people with low vision, such as depression and feeling isolated. This technology is already helping people who can't go outside for other reasons, such as anxiety about being in public, or individuals with late-stage cancer who simply can't travel."

Dr. Medeiros also sees great potential in using virtual reality to overlay 3-D data on live images—which he refers to as augmented reality—such as the images seen through a microscope during surgery. "Having a reticle overlaid on the microscope view is a simple version of this," he says. "I think this will go far beyond that. You could overlay topographic data, or a 3-dimensional rendition of the best incision architecture for a given case. Companies are already developing augmented reality glasses that will allow you to see a patient's records and data while talking to the patient. You might even be able to turn the page or move the visuals around by waving your hand, as the characters did in the movie 'Minority Report.' " REVIEW

1. Diniz-Filho A, Boer ER, Gracitelli CP, Abe RY, van Driel N, Yang Z, Medeiros FA. Evaluation of Postural Control in Patients with Glaucoma Using a Virtual Reality Environment. Ophthalmology 2015;122:6:1131-8. doi: 10.1016/j.ophtha.2015.02.010. Epub 2015 Apr 16.

WHEN IT COMES TO EARLY GLAUCOMA DETECTION, EVERY SECOND COUNTS.

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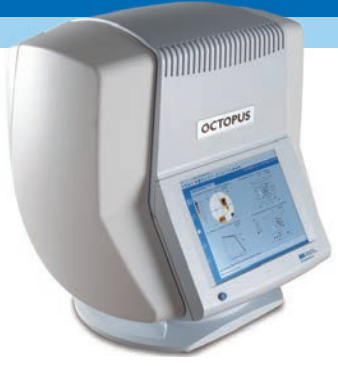

Thanks to our new Pulsar Technology, we're once again leading the race for early glaucoma detection. The **Octopus 600 with Pulsar Technology** is specifically designed to target the disease for faster, easier, more accurate results. Even better, your patients will find the exam itself is now quicker and more comfortable than before. So in the end, everybody wins.

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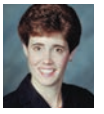
Donna McCune, CCS-P, COE, CPMA



The Medicare 2012 Physician Data Release

The CMS *Provider Utilization and Payment Data* Public Utilization File is now open to the public; here's what you should know.

Q What is the Medicare Physician Data Release, and where can it be found?

A The Centers for Medicare & Medicaid Services released data on more than 880,000 health-care professionals on April 9, 2014. The data was previously inaccessible to the public. The data includes the number, type of services and associated Medicare payments for services delivered to Medicare Part B beneficiaries in 2012 for each of these providers. The cumulative total of payments in this data release is $77 billion. It is expected that the 2013 data will be released in 2015.

The data resides on the CMS website, and can be found by searching on "Medicare Physician Data Release."

Q Did ophthalmology realize significant payments in the data release?

A Yes. Of the top 25 highest-paid providers in the release, 12 are ophthalmologists, and the number one physician on the list is an ophthalmologist.

Q Is this the first time this data was released?

A No. In March 1977, the Department of Health and Human Services made public the names of physicians or physician groups whose billing reached $100,000 or more of Medicare payments in 1975. In November 1977, the Secretary of HHS directed its carriers to publish another more detailed list, identifying all physicians and providers who received Medicare reimbursements in 1977. Prior to the anticipated release date of April 30, 1978, the Florida Medical Association and six individual physicians filed suit alleging that further release of such information would violate the Freedom of Information Act, the Privacy Act, the Trade Secrets Act and the United States Constitution. After the filing of various other legal motions, on October 22, 1979, the court issued a "*Final Declaratory Judgment and Permanent Injunction*" precluding the release of information.

Q If an injunction existed to preclude the release of information, how did the 2014 release occur?

A On January 25, 2011, Dow Jones Inc., publisher of *The Wall Street Journal*, filed a Motion to Intervene in this case. Its goal was to remove the 1979 FMA Injunction. On May 31, 2013, the injunction was lifted, opening the door for the April 9, 2014 release.

Q What is the purpose of releasing this data?

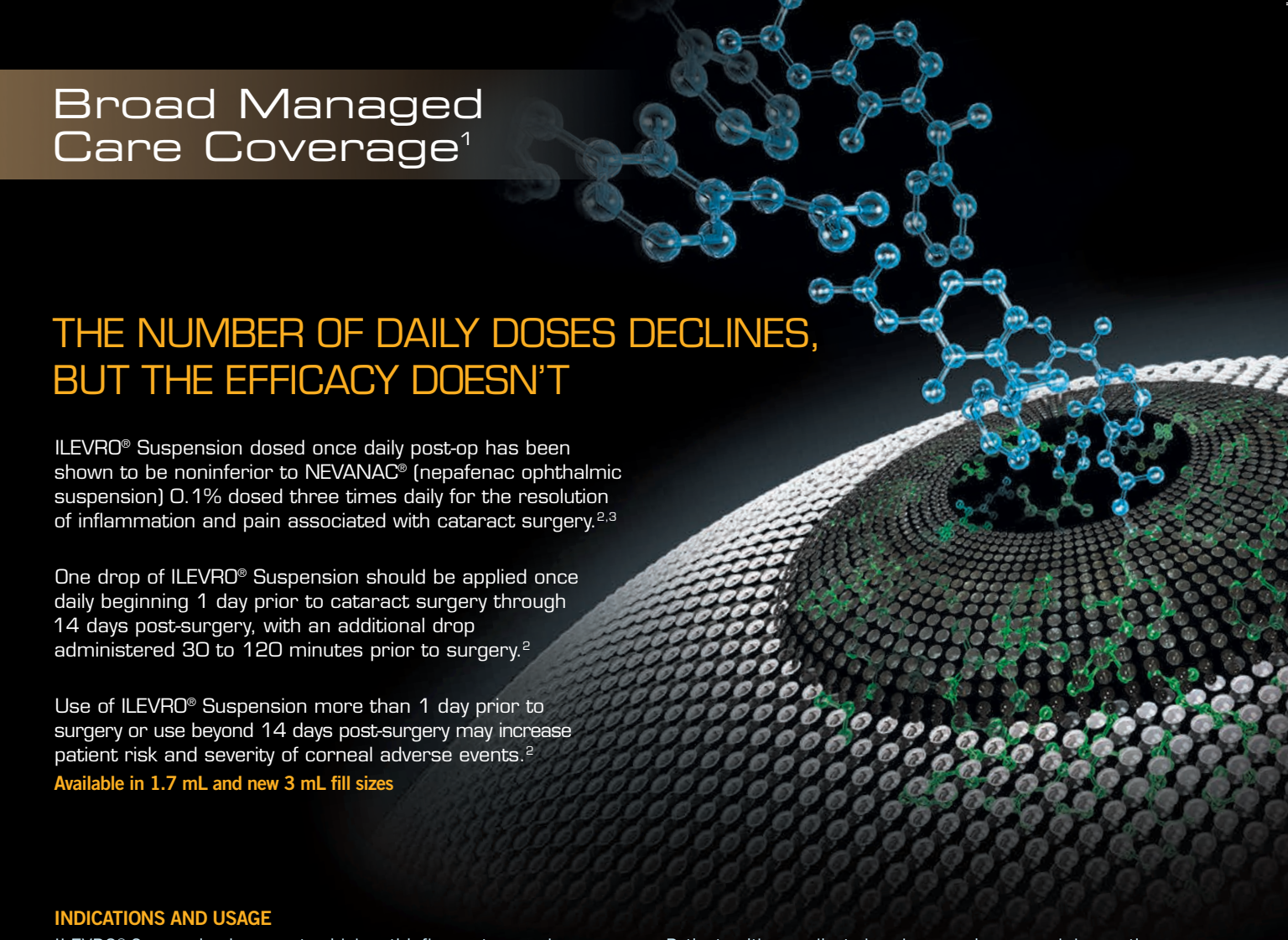
A President Obama stated early on in his presidency that he wanted a more open, involved and cooperative government. He set in motion an open-data policy in all federal departments. The catchword associated with this initiative has been "transparency." CMS believes that this term captures the purpose of the data release. The attitude of CMS is that by making this payment information available, beneficiaries and consumers can better understand the delivery of care through the Medicare program and ultimately improve the system.

Q Are there limitations to how the data is presented?

A Yes. The data, although very dense and detailed, has limitations, particularly for those uninitiated to the Medicare program and how physicians are paid. Some of the limitations are:

1. The data is specific to Medicare

Broad Managed Care Coverage[1]



THE NUMBER OF DAILY DOSES DECLINES, BUT THE EFFICACY DOESN'T

ILEVRO® Suspension dosed once daily post-op has been shown to be noninferior to NEVANAC® (nepafenac ophthalmic suspension) 0.1% dosed three times daily for the resolution of inflammation and pain associated with cataract surgery.[2,3]

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]

Available in 1.7 mL and new 3 mL fill sizes

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.

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

ILEVRO®
(nepafenac ophthalmic suspension) 0.3%

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 7/14 ILV14057JAD

ILEVRO®

(nepafenac ophthalmic suspension) 0.3%

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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Fort Worth, Texas 76134 USA

Part B beneficiaries only. No data for patients with Medicare Advantage (Part C) plans is included. This currently comprises about 30 percent of Medicare beneficiaries. As a result, the information does not represent the full complement of patients a physician serves and is thus not a full disclosure of aggregate physician reimbursement.

2. CMS reported paid claims, which always contain some errors. In response to physician criticism of the accuracy of the data, CMS suggested physicians report their concerns, including the possibility that payments were made to the wrong provider.

3. Physician payment rates differ depending on geography. For example, in 2012, cataract surgery (CPT 66984) was allowed at $805.59 in metropolitan Boston, but in Alabama it was allowed at only $688.93.

4. No distinction regarding the quality of care or the medical necessity of the services delivered exists in the data set. ICD-9 codes are omitted from the report.

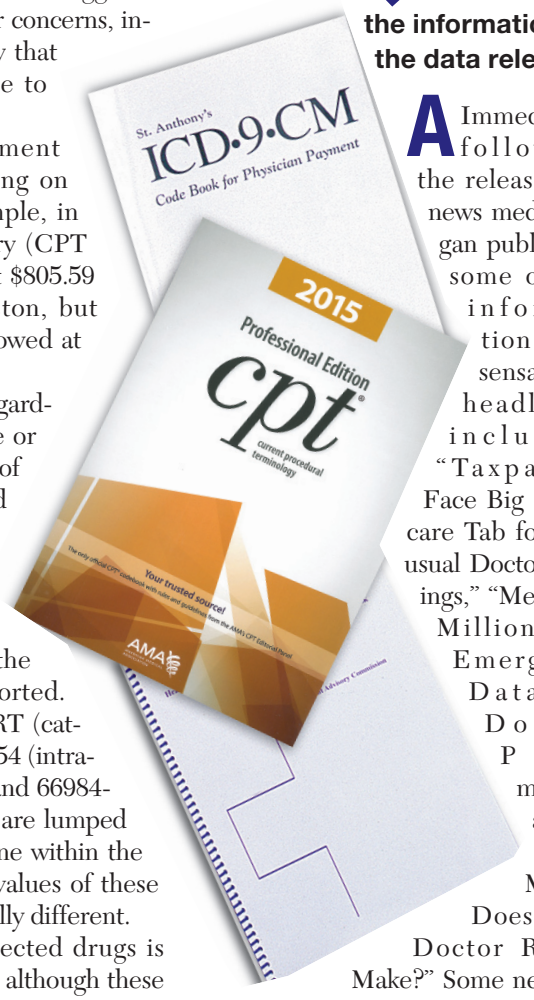
5. Modifiers skew the data but are not reported. For example, 66984-RT (cataract surgery), 66984-54 (intraoperative care only), and 66984-55 (postop care only) are lumped together in a single line within the report, although the values of these services are substantially different.

6. Payment for injected drugs is included in the report although these drugs are a supply and also represent a sizeable cost to the physician. For ophthalmologists, high-cost anti-VEGF medications, such as Lucentis, tend to dramatically increase total reimbursement.

Q Is there a use of this data for the individual provider(s)?

A If handled and presented appropriately, it can be useful in marketing and advertising efforts. It can assist in identifying referral sources and similar providers.

Q How did the media react to the information in the data release?



A Immediately following the release, the news media began publishing some of the information with sensational headlines, including "Taxpayers Face Big Medicare Tab for Unusual Doctor Billings," "Medicare Millionaires Emerge in Data on Doctor Payments" and "How Much Does Your Doctor Really Make?" Some newspapers published the names of local physicians and their 2012 Medicare payments on the front page. Most articles cited ophthalmologists as receiving some of the largest amounts.

Q How should ophthalmologists respond if approached by the media about this data and future data releases?

A Various medical societies, including the American Academy of Ophthalmology and the American Society of Cataract and Refractive Surgery, published their analysis of the data and suggested how physicians should respond if approached by the media or their patients:

- Act positive and put a positive spin on the data release;
- Demonstrate expertise and provide up-to-date information about these procedures;
- Describe how patient's lives are improved, sometimes dramatically;
- Describe how society benefits from patients with better vision (that you made possible);
- Make a point that practice makes perfect, so busier surgeons tend to be better surgeons;
- Don't act defensively or play the blame game; and
- Don't deny the data, but do point out some of the limitations.

Q Who else might be interested in this data?

A One concern about the use of the data is that fraud investigators and potential whistleblowers will be interested and interpret the data inaccurately, creating unnecessary lawsuits. In addition, other payers, accountable care organizations, independent physician associations, investors and competitors may be interested. REVIEW

Ms. McCune is vice president of the Corcoran Consulting Group. Contact her at DMcCune@corcoranccg.com.

OR Aberrometry: Coming into Its Own?

Christopher Kent, Senior Editor

Surgeons familiar with this technology say it's making a difference in outcomes.

As refractive cataract surgery becomes more common and patient expectations continue to rise, surgeons have searched for tools that can increase the precision of surgical outcomes. One technology that has been a contender for several years is intraoperative aberrometry, which allows the surgeon to check the eye's refraction while the patient is on the operating table. In theory, this should improve a surgeon's results, and the latest data suggests that it does. However, as is always the case with new technologies, there are caveats and limitations. Here, three surgeons who have extensive experience with this technology share their experiences, their data and their thoughts about what lies ahead.

An Evolving Technology

Vance Thompson, MD, who practices at Vance Thompson Vision/Sanford Health in Sioux Falls, S.D., and is assistant professor of ophthalmology at the University of South Dakota School of Medicine, has been using WaveTec's intraoperative aberrometer since its early days when he worked with the company to refine the algorithms and hardware. "For the first few years we just did data acquisition, comparing intraoperative power recommendations to postoperative outcomes for validation of accuracy and algorithm development," he explains.

"The turning point for me came about two years into this process," he says. "I had a patient who had undergone 3-D myopic LASIK at my practice, so I had all of the historical data. I plugged that data and the current measurements into the formulas and chose an appropriate lens power. During the surgery, however, the ORA device told me that if I put in the implant I had chosen the patient would end up with 3 D of myopia. We were going for a plano outcome, so I had a decision to make. I hadn't been listening to the technology for two years; I was just acquiring data. Given that I had accurate historical data, I decided to put in the implant that I had chosen based on my calculations. The patient ended up with 3 D of myopia.

"Because her cornea was not thick enough for a conservative enhancement, she and I agreed that a lens exchange made the most sense," he continues. "During the second surgery I took another ORA measurement; it told me to use the same power lens it recommended the first time. I did, and she ended up plano. So that was the beginning of my actually listening to the technology."

Samuel Masket, MD, in private

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BIMATOPROST 0.03% OPHTHALMIC SOLUTION

Potentially save your patients money on their open angle glaucoma or ocular hypertension treatment

Write generic Bimatoprost 0.03%

First generic bimatoprost on the market!

- ✓ If writing a script, please note the importance of writing the molecule name and strength to ensure proper dispensing at the pharmacy
- ✓ If using an EMR system, please make sure to search by molecule name

Currently the Only Generic Available*

Important Safety Information

Bimatoprost ophthalmic solution 0.03% has been reported to cause darkening (pigmentation) of eye color, eyelid skin, and eyelashes as well as increased growth of eyelashes. Pigmentation changes can increase as long as bimatoprost ophthalmic solution 0.03% is used. After stopping bimatoprost ophthalmic solution 0.03%, darkening of eye color is likely to be permanent, while darkening of the eyelid skin and eyelash changes may be reversible. The effects of increased darkening beyond 5 years are not known. When only one eye is treated, there is a possibility of eyelash changes in the eye treated with bimatoprost ophthalmic solution 0.03%. These changes may result in differences between the eyes in eyelash length, thickness, darkness, number of eyelashes, and/or direction of eyelash growth. These changes are usually reversible upon stopping bimatoprost ophthalmic solution 0.03% therapy. Patients should avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions. In the event patients develop an intercurrent ocular condition (e.g., trauma or infection), have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of bimatoprost ophthalmic solution, 0.03%. Contact lenses should be removed prior to instillation of bimatoprost ophthalmic solution, 0.03% and may be reinserted 15 minutes following its administration. The most common side effects are conjunctival hyperemia, growth of eyelashes, and ocular pruritus.

Please see Brief Summary of Prescribing Information on the adjacent page.
For additional information, please visit www.lupinpharmaceuticals.com

LUPIN
PHARMACEUTICALS, INC.

***As of the date of advertising material submission, 5/19/2015**

BIMA060415TRG

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

BIMATOPROST Ophthalmic Solution, 0.03%

INDICATIONS AND USAGE

Bimatoprost ophthalmic solution, 0.03% is indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

In clinical studies of patients with open angle glaucoma or ocular hypertension with a mean baseline IOP of 26 mmHg, the IOP-lowering effect of bimatoprost ophthalmic solution, 0.03% once daily (in the evening) was 7 to 8 mmHg.

WARNINGS AND PRECAUTIONS

Pigmentation

Bimatoprost ophthalmic solution has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes. Pigmentation is expected to increase as long as bimatoprost is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of bimatoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with bimatoprost ophthalmic solution, 0.03% can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Eyelash Changes

Bimatoprost ophthalmic solution, 0.03% may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation

Prostaglandin analogs, including bimatoprost, have been reported to cause intraocular inflammation. In addition, because these products may exacerbate inflammation, caution should be used in patients with active intraocular inflammation (e.g., uveitis).

Macular Edema

Macular edema, including cystoid macular edema, has been reported during treatment with bimatoprost ophthalmic solution. Bimatoprost ophthalmic solution 0.03% should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Bacterial Keratitis

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.

Use with Contact Lenses

Contact lenses should be removed prior to instillation of bimatoprost ophthalmic solution, 0.03% and may be reinserted 15 minutes following its administration.

ADVERSE REACTIONS

In clinical trials, the most frequent events associated with the use of bimatoprost ophthalmic solution, 0.03% occurring in approximately 15% to 45% of patients, in descending order of incidence, included conjunctival hyperemia, growth of eyelashes, and ocular pruritus. Approximately 3% of patients discontinued therapy due to conjunctival hyperemia.

Ocular adverse events occurring in approximately 3 to 10% of patients, in descending order of incidence, included ocular dryness, visual disturbance, ocular burning, foreign body sensation, eye pain, pigmentation of the periocular skin, blepharitis, cataract, superficial punctate keratitis, periorbital erythema, ocular irritation, and eyelash darkening. The following ocular adverse events reported in approximately 1 to 3% of patients, in descending order of incidence, included: eye discharge, tearing, photophobia, allergic conjunctivitis, asthenopia, increases in iris pigmentation, and conjunctival edema. In less than 1% of patients, intraocular inflammation was reported as iritis.

Systemic adverse events reported in approximately 10% of patients were infections (primarily colds and upper respiratory tract infections). The following systemic adverse events reported in approximately 1 to 5% of patients, in descending order of incidence, included headaches, abnormal liver function tests, asthenia and hirsutism.

USE IN SPECIFIC POPULATIONS

Pregnancy Category C

Nursing Mothers

It is not known whether bimatoprost is excreted in human milk, although in animal studies, bimatoprost has been shown to be excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when bimatoprost is administered to a nursing woman.

Pediatric Use

Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

Please see full Prescribing Information.

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May 2015

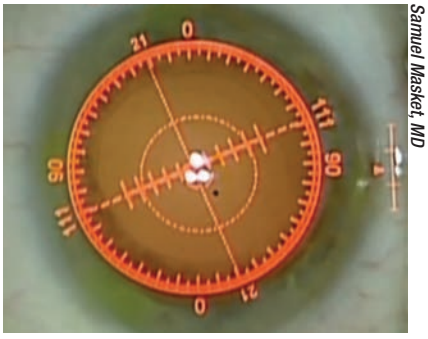
practice at Advanced Vision Care in Los Angeles and clinical professor of ophthalmology at the Jules Stein Eye Institute, Geffen School of Medicine, UCLA has been using intraoperative aberrometry for about four years. "I started with [WaveTec Vision's] ORange," he says. "Improved software in the ORA made it faster and easier to obtain readings. Next, ORA with VerifEye+ was introduced; it provides streaming information. Recently, as an alpha test site, I evaluated another new version with a dynamic reticle. I've used four generations of the device, each with changes making the unit faster, easier and more accurate."

Dr. Masket notes that adding the dynamic reticle to the ORA instrument makes a big difference. "Having streaming information with the addition of VerifEye+ has been a big help in terms of accuracy when aligning a toric lens," he says. "However, the surgeon still has to look away from the microscope to see it. With the dynamic reticle in the ocular of the microscope, the surgeon can see that information without looking away. I think that's a really wonderful improvement."

When IA Is Most Useful

Although some surgeons use intraoperative aberrometry on every cataract patient, most agree that it makes the most significant difference in three situations: when evaluating post-laser refractive surgery patients; when implanting a premium lens; and when correcting astigmatism.

"Today this technology has become a cornerstone in my practice, something that I use on all post-refractive candidates, the ones where calculations can be most challenging," says Dr. Thompson. "For example, if we have a virgin cornea in a myope, our traditional methods of measuring corneal curvature extrapolate the relationship between the anterior and posterior cornea. That's a relatively accurate extrapolation in virgin corneas, but not in post-refractive corneas. And it's becoming increasingly common to see patients who have had refractive corneal surgery and have no preoperative data. That's where intraoperative aberrometry shines. In fact, using intraoperative aberrometry on post-refractive cataract cases is our most common ophthalmologist cataract surgery referral."



Samuel Masket, MD

The latest version of the ORA with VerifEye+ will add a dynamic reticle to the view through the microscope.

Dr. Thompson says this technology is also a cornerstone in his premium implant program. "With premium implants we're trying to hit a specific refractive target meant for that particular implant because the patient's goal is to go without glasses," he says. "I'm trying to minimize the likelihood that I'll need to enhance the patient—or at least get the patient close enough that if a laser enhancement is needed, the patient won't need temporary glasses during the three months I wait between cataract surgery and the enhancement. So intraoperative aberrometry has become a very important part of my premium implant program.

"The third situation in which this technology is most useful is when implanting toric lenses," he says. "In toric cases we do all of our preoperative calculations and place the implant lined up with the steep axis of corneal astigmatism, per the surgical plan. But then we take an intraoperative measurement and rotate the lens to the axis suggested by the VerifEye+ device. This has greatly improved my astigmatism outcomes with these implants."

"Intraoperative aberrometry is particularly helpful in people receiving toric IOLs, because most of us don't go to surgery with knowledge of posterior corneal astigmatism," Dr. Masket points out. "We go to surgery with knowledge of the eye's anterior corneal astigmatism, but the aphakic refraction is altered by posterior corneal astigmatism. Unless we have a good device to measure that—and most of us don't—we don't know for sure what the posterior cornea is contributing to the eye's optics. Doug Koch has shown that there is, on average, a half-diopter of against-the-rule shift caused by the back surface of the cornea. For that reason I have found this technology very helpful to not only determine the axis of astigmatism, but also the magnitude of astigmatism."

Another surgeon who has used this technology on many patients is David F. Chang, MD, clinical professor of ophthalmology at the University of California, San Francisco, and in private practice in Los Altos, Calif. Dr. Chang has used the ORA system with VerifEye+ regularly for more than 18 months, and has also used Clarity Medical Systems' HOLOS IntraOp prototype during its development. (The HOLOS system is not approved in the United States.)

Dr. Chang says that in addition to post-refractive surgery eyes, he uses the ORA when implanting refractive IOLs and for eyes receiving limbal relaxing incisions. "I don't have a femtosecond laser; therefore I perform all LRIs manually," he explains. "One advantage of this is having the ability to monitor and titrate the LRIs intraoperatively with the ORA system. This is particularly helpful with a diffractive multifocal IOL. There have been cases where I did not plan to do an LRI because preoperative measurements showed only 0.5 D of cylinder; how-

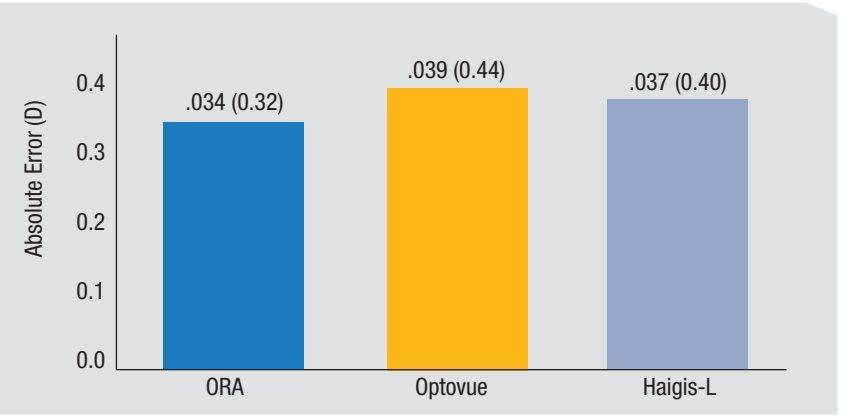
ever, the pseudophakic ORA reading indicated closer to 1 D of against-the-rule cylinder. As a result, I went ahead and added one or two LRIs. Using the ORA with a pseudophakic eye, you can decide in real time whether to add a second incision or lengthen existing incisions. You cannot do this with a femtosecond laser."

Dr. Thompson points out that he doesn't use intraoperative aberrometry with every patient. "For instance, if someone is having traditional cataract surgery and he's happy wearing spectacles and hasn't had previous corneal surgery, I'm very comfortable doing the surgery based on my traditional calculations," he says. "The formulas are quite good, and they've gotten better over time. But for all those other cases, I do use this technology. That includes individuals who have an A-scan that's challenging to interpret, or who couldn't sit up for a good-quality reading, or who have a big difference in readings between eyes. Whenever I have any concerns, it's a nice tool to have at my disposal for reassurance. And it has made a difference; it has reduced our enhancement rate by about 20 percent in those patients who have the goal of being able to do a lot without glasses. It's had a significant impact."

What the Data Shows

When he first tried using the technology, Dr. Masket conducted a study to test its value. "I did 200 consecutive cases," he says. "I wanted to see how intraoperative aberrometry would compare to the methods I had used in the past. At that point, we were measuring the eye with two instruments, the IOLMaster and the LenStar; then we'd run the data through five different formulas and I would choose an IOL power based on the results. For this study, my protocol was that if ORA said to change my previously decided IOP power, I would.

Mean Absolute Error by Method (Without Historical Data)



In this group of 39 eyes with previous laser vision correction but no historical data, using the ORA produced better results, on average, than basing treatment on the Optovue or the Haigis-L formula. The difference between the groups, however, was not statistically significant. (Based on Fram, Masket, et al, 2015.[1])

"To evaluate the effectiveness of the new technology, I looked for cases among the first 200 consecutive eyes that had all been implanted with the same lens design—a single-piece acrylic lens—and in which the patients had no prior corneal surgery, corneal pathology or other comorbidity that would reduce vision to less than 20/25," he continues. "Out of the 200 cases, 131 eyes fit those parameters. Among those cases, I had changed IOL power in response to the ORA in 42.7 percent of the eyes. Then I compared the two groups: those eyes in which we changed the IOL power at the suggestion of the ORA device, and the 57 percent of patients where ORA and my methods agreed. I only looked at the resulting spherical error, not spherical equivalent, because toricity was not always addressed.

"When I looked at the spherical portion of the refraction I found that in both groups 94 percent were within ±0.5 D of the intended outcome," he says. "What that told me was that when ORA agreed with my calculations, the results were right on; and when ORA disagreed and I went with ORA, the results were also accurate. I concluded that ORA is legitimate and useful technology. Today I use it in nearly every case."

Dr. Masket and co-authors Nicole Fram and Li Wang recently conducted a study comparing intraoperative aberrometry to his traditional methods for determining post-laser-vision-correction IOL power. "Traditionally in our office, when we know what excimer laser ablation was done, we've used the Masket formula to calculate the IOL power," Dr. Masket explains. "That has worked well over the years. If we don't have the information about the laser ablation, we have relied primarily on the Haigis-L formula.

"We wanted to see how new technology compared to this approach," he continues. "The new technology we used in the study included ORA intraoperative aberrometry and RT-Vue OCT with total corneal power, or TCP. Our study, which was prepublished in *Ophthalmology*, included 39 eyes.[1]

"In terms of accuracy, the data found no statistically significant difference among any of the methods," he says. "However, when we knew the previous laser treatment, the trend was toward better results with the Masket formula. If we didn't have the laser treatment information, the

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trend with the remaining tools was toward intraoperative aberrometry being a little stronger, although statistically similar. As an example, we found that when using intraoperative aberrometry, 50 percent of patients were within ±0.25 D of the intended target and close to 75 percent were within 0.5 D. We think these outcomes are pretty remarkable, given that these were post-refractive-surgery eyes. Even though there was no statistically significant difference in the results, ORA stood up very well against the other methods."

Dr. Chang co-authored a recent paper that compared ORA's wavefront aberrometry refractive methodology to other formulae for IOL power accuracy in post-myopic LASIK and PRK eyes.[2] "Using the ORA algorithm and intraoperative aphakic measurements, 67 percent of eyes were within 0.5 D of the target refraction, compared to 48 percent with Haigis-L, 50 percent with Shammas and 46 percent with the surgeon's preoperative selection based on the ASCRS online calculator," he says. "I tell patients that this doesn't negate the challenges posed by having had prior LASIK, but it improves our batting average compared to other methods."

Other Issues

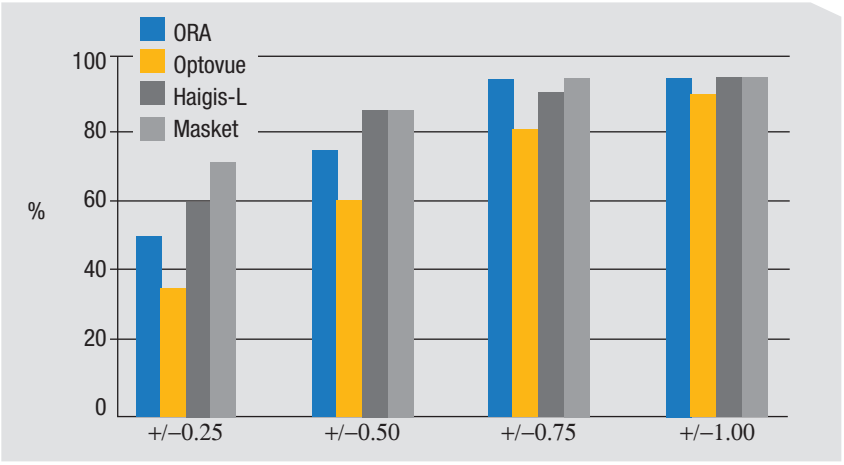
Surgeons considering adopting this technology may have other concerns besides its effectiveness, including the possibility of lengthening the time required for cataract surgery and the possibility of false readings.

"Using this technology doesn't take much time," says Dr. Thompson. "When we first started using it it was slower, but it's become very quick and intuitive. That's mainly because of improvements in the acquisition speed, which is very fast in the latest generation. My part as the surgeon has never taken very long."

"There is some learning curve for the surgeon and the OR staff, which adds more operative time initially," agrees Dr. Chang. "The ORA VerifEye+ system is much faster at data acquisition than earlier generations. However, I do spend some time reviewing the ORA recommendation alongside my preop diagnostics before deciding on the final IOL power."

"When you're starting out, you might want to schedule a couple fewer cases for your first day of using it," says Dr. Thompson. "But within a week or two you'll be back to your regular volume and comfortable with the technology. You do have to get used to the fact that your working distance is slightly reduced, because the instrument fits under the microscope; if you aren't careful, you can touch it with an instrument or your hand, and then you have to hand off the instrument and change gloves. But it doesn't take long at all to get used to the smaller working distance."

IOL Refractive Prediction Error (D) in Eyes With Historical Data



In this group of 20 eyes with previous laser vision correction and historical data available, there was a trend toward more accurate results using the Masket method, although no method was statistically significantly superior. (Based on Fram, Masket, et al, 2015.[1])

"There are many potential artifacts that can undermine the quality of the data," notes Dr. Chang. "This is universally acknowledged. Corneal surface drying, ocular hypotony or overinflation, poor fixation, and pressure from the lid speculum and drapes can cause misleading results. However, having a continuous display of refractive data allows you to assess the effect of patient fixation, intraocular pressure and lid speculum pressure in real time. This teaches the surgeon when erroneous artifacts are introduced, and how to better avoid them."

Making the Most of IA

Surgeons offer these strategies to help make sure that intraoperative aberrometry provides you with the best possible results:

• ***Don't expect to get out of doing preoperative calculations.*** "It's not a good idea to go into the OR without a solid idea of the correct power and cylinder for the lens," says Dr. Thompson. "Your calculations are critical. An electrical or software glitch is rare, but they can happen, and if they do you're going to find yourself in a very uncomfortable situation. Also, in highly aberrated corneas it's possible that the aberrometer won't be able to acquire a measurement."

Dr. Masket agrees. "I know there are surgeons who don't use the formulas to calculate a likely IOL power, relying only on intraoperative aberrometry," he says. "I would go to surgery with a plan and then use intraoperative aberrometry to refine it."

• ***Remember that this technology is less helpful in patients who have had radial keratotomy.*** "Sometimes it's hard to achieve good quality readings in these eyes," notes Dr. Masket. "Among other things, we induce intraoperative change in the corneal shape in these eyes."

• ***Make sure the patient is properly oriented with the instrument.*** "The patient should be oriented with the device in a vertical fashion in order for it to work its best," says Dr. Thompson. "You need to decide whether you're doing a superior or temporal incision. If you're doing a superior incision, you want the instrument lined up with 90 degrees and 270 degrees, or 6 o'clock and 12 o'clock. If you're doing temporal surgery, it should be lined up with 0 degrees and 180 degrees, or 3 o'clock and 9 o'clock. If you aren't lined up perfectly, the instrument doesn't know that, and it will affect the reading. Fortunately, the dynamic reticle helps us avoid that."

• ***Monitor the intraocular pressure.*** "You don't want too low or too high of a pressure during the reading," says Dr. Thompson. "For that reason we use a Barraquer tonometer in surgery to make sure the pressure is around 20 mmHg. This becomes even more important in radial keratotomy cases because the corneal curvature can change rather dramatically with lower or higher pressure."

• ***Be aware of intraoperative factors that can produce inaccurate readings.*** Dr. Masket notes that a number of things can cause inaccurate readings. "One may run into trouble with an irregular incision; if you overhydrate the incision; if the corneal surface is irregular; if there's been too much drying because of insufficient hydration; if the patient isn't cooperative and is not looking at the target; or if the speculum or other instruments are pushing on the eye," he says.

Dr. Thompson concurs. "Overhydrating the incision will induce changes in the astigmatism reading," he notes. "For that reason, thinking about your incision architecture ahead of time is very important. You want to have a self-sealing incision that requires minimal or no hydration. Corneal power readings can also be altered by a fluid meniscus. So, right before taking the reading I moisten the cornea and dry the fornices with a Weck-Cel sponge to make sure there's not an excess amount of fluid. Once you have dry fornices and a pristine, moist corneal surface, you take your measurement."

• ***Use an ophthalmic viscosurgical device with a low index of refraction.*** "We recently completed a study to determine the effect of leaving the OVD in the eye when readings are obtained," says Dr. Masket. "What we found was that when using

an OVD that has a low index of refraction close to that of BSS, the refractive readings will be the same. But with an OVD with a higher index of refraction, the intraoperative aberrometry readings will be in error. That may lead one to undercorrect the optical error."

• ***Adjust your use of viscoelastic during the reading based on the purpose of the reading.*** "I typically remove the viscoelastic for my toric measurements," explains Dr. Thompson. "You want to make the measurement with a consistent medium—just BSS, not a mix of some BSS and viscoelastic. On the other hand, in the aphakic state I leave the eye filled with viscoelastic when we take the measurement because it's usually a post-refractive or premium cataract case. Also, when you're measuring with viscoelastic in the eye, make sure there are no bubbles in the pupil area. Those can distort the reading."

• ***Don't blindly follow an ORA recommendation if it contradicts your preoperative decision.*** Dr. Chang notes that even with this technology there is still a lot of "art" to determining the optimal spherical and toric power and axis. "Many of us employ multiple IOL formulae and different preoperative diagnostic measures of cylinder," he says. "One should never blindly follow the ORA recommendation if it contradicts the preoperative diagnostics. Instead, it should be used as an adjunct or tie-breaker. Now that we've been using the ORA, I am impressed with how often I'm undecided between a choice of two spherical or toric powers, or two different astigmatic axes. In these situations I have found ORA to be correct about four out of five times when used as a tie-breaker."

What the Future May Hold

As with any technology, there's room for improvement. For example, Dr. Thompson notes that the technology reaches its limits with severely aberrated corneas. "The more aberrated a cornea is, the less you can rely on the measurements," he says. "If you encounter a highly aberrated eye, you have to use your own clinical judgment. Of course, if the eye is extremely aberrated, the instrument flashes a red light and won't give a reading. I look forward to reaching the point at which there are no red lights and you get an accurate measurement even in highly aberrated corneas."

Other systems, such as Clarity Medical Systems' HOLOS IntraOp wavefront aberrometer, are in the pipeline. "The HOLOS system will also display astigmatic data in real time in order

to titrate LRIs or toric IOL positioning," notes Dr. Chang, who used the HOLOS prototype during its development. "However, it will not be able to calculate the recommended spherical IOL power, at least initially."

Dr. Thompson foresees a day when this technology will be used in concert with Calhoun Vision's light-adjustable lens, which he has also worked with during its development. "That technology will allow us to adjust the power of the implant after it's inside the eye," he notes. "Let's say a patient has a final refractive error of +0.25, -0.3, axis 180, and sees 20/20 uncorrected—but with this best-corrected refraction the patient sees better. We typically would not treat that amount of refractive error on the cornea because the limits of biological healing. But with the light-adjustable lens you're changing a polymer inside the eye, so we make corrections this small all the time. You'd be amazed how crisp someone's vision becomes when you take her to a 0 correction without touching her cornea.

"Ultimately, I see these technologies working together," he says. "I can imagine a day when we'll use intraoperative aberrometry to determine our very best refractive endpoint. Then, whatever final changes occur because of biologic variables such as incisional healing, corneal healing, capsular bag contraction and so on, we'll do the final adjustment with the Calhoun lens."

Is It Worth the Investment?

No matter how good a given technology may be, surgeons still have to decide whether the technology is worth the cost of purchasing and implementing it.

"In my opinion, this technology is definitely worth the cost," says Dr. Thompson. "In fact, I would pay more for it because of all the value it brings me. We used to have this technology in one room of our two-room surgical suite. Now we have it on both microscopes because we use it so frequently. I don't ever want to operate in an OR that doesn't have one."

Dr. Thompson sees intraoperative aberrometry as one of the three most impactful technologies in current cataract surgery. "In terms of the most significant advancements in our technology," he says, "I'd list the amazing advanced implants we now have available to us, the excimer laser that allows us to enhance the final refractive state if necessary, and third, intraoperative aberrometry. I like to use the femtosecond cataract laser, and I prefer it to manual cataract surgery. However, I

can do quite accurate cataract surgery without it. I can't document refractive power intraoperatively without an aberrometer. It's an important tool for taking refractive cataract surgery to the next level. If I had to choose between the femtosecond laser and the aberrometer, the aberrometer would be my choice. Of course, I'm glad I don't have to make that choice."

Dr. Chang agrees. "For improving our refractive results, I think intraoperative aberrometry adds significant value—certainly more than a femtosecond laser would," he says. "Because it offers an IOL recommendation based on intraoperative aphakic and pseudophakic refractions, it provides extra data that we previously didn't have. At a minimum, it provides confirmation of the preoperative plan. When used as a tie-breaker in the proper context, it usually steers us toward the better result. Finally, for our demanding post-LASIK patients, it appears to be the single best methodology that we currently have—particularly when the historical data is unavailable, as is so often the case. However, you should not expect it to replace or circumvent your experience and judgment, or extensive preoperative testing."

Dr. Masket admits that using intraoperative aberrometry does add time to the surgery, and the surgeon must follow specific protocols to get accurate results. However, he feels it's worth the time and effort. "Using this technology makes me more confident of my IOL power selection," he says. "When I sit and look at the patient's chart prior to surgery to decide what power to use, if I'm on the fence about which way to go, I don't worry. I know the ORA will help me make that decision. I have no doubt that surgeons who are compulsive about accuracy, who are reproducible in their incision construction and are discerning about correcting astigmatism, would benefit from this technology." REVIEW

Dr. Thompson is a researcher and consultant for Calhoun, WaveTec and Alcon. Dr. Chang is a consultant for Clarity Medical Systems; he has no financial interest in WaveTec or Alcon. Dr. Masket has been a consultant to WaveTec, which also provided support for some of his research. He is currently a consultant to Alcon.

1. Fram NR, Masket S, Wang L. Comparison of Intraoperative Aberrometry, OCT-Based IOL Formula, Haigis-L, and Masket Formulae for IOL Power Calculation after Laser Vision Correction. Ophthalmology 2015;122:6:1096-101. doi: 10.1016/j.ophtha.2015.01.027. Epub 2015 Mar 10.
2. Ianchulev T, Hoffer KJ, Yoo SH, Chang DF, Breen M, Padrick T, Tran DB. Intraoperative refractive biometry for predicting intraocular lens power calculation after prior myopic refractive surgery. Ophthalmology 2014;121:56-60.

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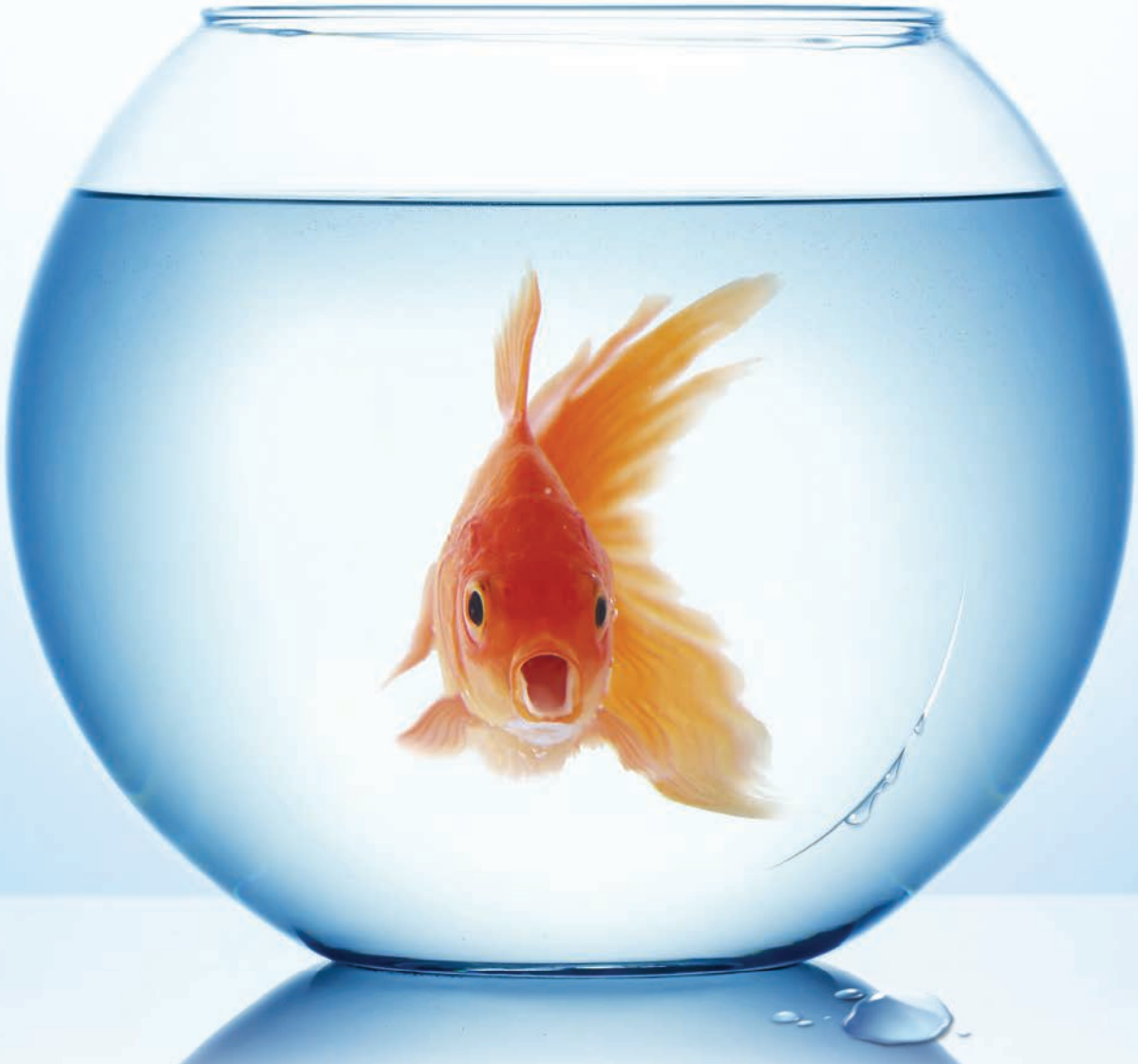

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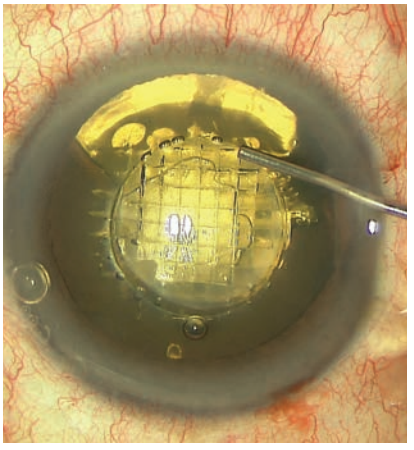
Get to Know Your Femtosecond Options

Walter Bethke, Managing Editor

Here are the features and benefits these units offer if you're in the market.

When femtosecond lasers for cataract surgery first began to appear on the scene, only one was approved in the United States, and even as more became available they weren't approved for all the steps of the cataract procedure. Now, however, surgeons have four lasers to choose from, each able to perform all the femtosecond steps of cataract surgery, from incisions to nucleus fragmentation. Though more choices are good to have, they also bring the confusion of having to sift through different features and recent software updates. To help make this process a little easier, here's a rundown of the central features of the four lasers approved for sale in the United States.



Catalys surgeons can alter the femto fragmentation cube sizes, using smaller cubes to achieve greater softening.

Catalys

The first aspect of the AMO Catalys laser that surgeons will put into action is called the Liquid Optics patient interface. This is the part of the system that fits on the patient's eye and allows the laser to dock and deliver its energy accurately.

The Liquid Optics interface is a small reservoir that's placed onto the patient's eye and filled with balanced salt solution. The laser is then brought down onto this liquid/cornea interface. The company says the liquid helps smooth out corneal imperfections that could affect the beam. "It's an elegant way to dock with a femtosecond laser," says Doug Koch, MD, chair of the ophthalmology department at the Baylor College of Medicine in Houston. "It's easy to place on the eye and it's not threatening to the patient; it's just a small suction ring being placed rather than a large gantry coming down. Also, it raises the intraocular pressure minimally, raising it by 5 mmHg, 10 mmHg at the most."

Once the machine is docked, the system helps the surgeon visualize

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- LOTEMAX® GEL is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.
- Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. If this product is used for 10 days or longer, IOP should be monitored.
- Use of corticosteroids may result in posterior subcapsular cataract formation.
- Use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation and occurrence of perforations in those with diseases causing corneal and scleral thinning. 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, and where appropriate, fluorescein staining.
- Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infection. In acute purulent conditions, steroids may mask infection or enhance existing infection.
- Use of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and 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.
- Patients should not wear contact lenses when using LOTEMAX® GEL.
- The most common ocular adverse drug reactions reported were anterior chamber inflammation (5%), eye pain (2%) and foreign body sensation (2%).

Please see brief summary of Prescribing Information on adjacent page.

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WARNINGS AND PRECAUTIONS

Intraocular Pressure (IOP) Increase

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

Cataracts

Use of corticosteroids may result in posterior subcapsular cataract formation.

Delayed Healing

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

Bacterial Infections

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

Viral Infections

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

Fungal Infections

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

Contact Lens Wear

Patients should not wear contact lenses during their course of therapy with LOTEMAX.

ADVERSE REACTIONS

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

The most common adverse drug reactions reported were anterior chamber inflammation (5%), eye pain (2%), and foreign body sensation (2%).

USE IN SPECIFIC POPULATIONS

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 flexures) 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 with 0.5 mg/kg/day (6 times the maximum 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.

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

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 appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when LOTEMAX is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment Of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma tk assay, or in a chromosome aberration test in human lymphocytes, or *in vivo* in the single dose mouse micronucleus assay. Treatment of male and female rats with up to 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (600 and 300 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender.

PATIENT COUNSELING INFORMATION

Administration

Invert closed bottle and shake once to fill tip before instilling drops.

Risk of Contamination

Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the gel.

Contact Lens Wear

Patients should be advised not to wear contact lenses when using LOTEMAX.

Risk of Secondary Infection

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

FOR MORE DETAILED INFORMATION, PLEASE READ THE PRESCRIBING INFORMATION.

Bausch & Lomb Incorporated
Tampa, Florida 33637 USA
US Patent No. 5,800,807

and plan the treatment using a 3-D optical coherence tomographer and an Integral Guidance system. The OCT images such structures as the anterior and posterior cornea, the iris and the pupil. "It does a great job figuring out the tilt and position of the lens," Dr. Koch avers. It will adjust the photodisruption pattern based on any tilt, helping to avoid complications from disrupting the wrong structures. "The advantage is that you can feel confident going to a deeper level with the laser," Dr. Koch adds. "You can get a consistent, deep softening of the lens. It consistently goes to a good depth and leaves very little residual lens material. In particular, you're very rarely left with any residual epinucleus, because a portion of the epinucleus is softened. This eliminates the sometimes frustrating step of having to remove the epinucleus after you've removed the lens itself."

Surendra Basti, MD, associate professor of ophthalmology at Northwestern's Feinberg School of Medicine, says the instantaneous nature of the OCT is a boon, as well. "The most recent version of the software has yielded a clear improvement in managing cataracts," he says. "It shows a real-time OCT image. Let's say, for instance, that the OCT was taken and you then make some adjustments. When you're about to make the incision, you can quickly check a real-time image. So, if the patient's eye has moved in the interim between your initial imaging and now, it will show you and allow you to make an adjustment."

As with other femtosecond cataract technology, Catalys surgeons have been discovering which patterns work best for fragmenting the nucleus. The device has different options to choose from to help them select the pattern that's right for them. "You can segment it into four, six or eight pieces," explains Dr. Koch. "You also have a lot of flexibility with regard to softening: You can do no softening, you can do large cubes, medium cubes or small cubes. If you create quadrants, you can determine the amount of lens that you want to soften, leaving some unsoftened area right in the center along the vertical and horizontal splitting line. The advantage to such a pattern is that leaving a little lens material can make it easier to aspirate and pull that quadrant to the center; it's harder to pull it to the center if you're pulling directly on the cubes."

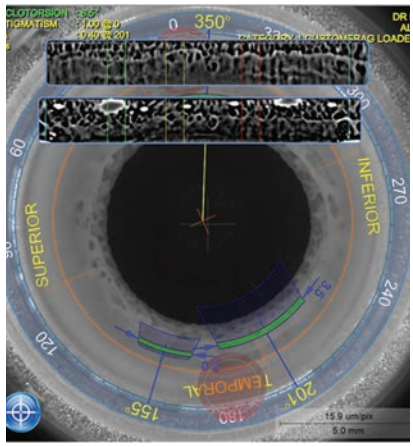
Dr. Basti says not many lens-softening cubes are necessary in less-dense lenses. "In a lens such as a 1+ nuclear sclerotic cataract, what you really need is some weakening of the lens so you can break it into pieces," he says. "If the cataract is a 3+, though, you need weakening of the lens as well as softening, so you'd do well to break it into cubes so the total amount of phaco energy is lower. For a dense nucleus, I use 350-µm cubes."

Overall, Dr. Koch says the strides the Catalys has taken since its inception are noticeable. "The flow of the Catalys is very quick now," he says. "My typical suction times are now around two minutes. This includes placing the ring with the bed outside the laser, moving it in, docking and performing the treatment."

LensAR

The past year saw a sizeable upgrade to the LensAR system in terms of a new software bundle, called Streamline, that increases the system's functionality.

"Streamline is enough of a change that it required Food and Drug Administration studies to achieve clearance," says Largo, Fla., surgeon Robert Weinstock, who performed some of the studies for the FDA clearance trial. Streamline involves five new



LensAR's Streamline iris registration can compensate for cyclorotation during the incision-planning phase of the procedure.

features, two of which are built into the LensAR, and three that require the i-Optics Cassini Corneal Shape Analyzer device.

The Streamline features of the laser itself are automatic cataract density grading and customized fragmentation pattern creation. "One of the unique aspects of LensAR is that it uses Scheimpflug imaging of the anterior segment, which the company refers to as augmented reality," explains Dr. Weinstock. "This allows the surgeon to see details of the cataract to the degree that you can see how dense the cataract is, which resulted in some surgeons having the idea to have the laser grade the cataract for you. This led to the upgrade. Now, the laser software can analyze the image from the Scheimpflug camera and grade the cataract on a scale of one through four based on its size and density. The laser will then select a fragmentation pattern that the surgeon pre-programmed for that particular density. For instance, for a very dense cataract, graded as a 3+ or 4+, the surgeon can have a very robust fragmentation pattern programmed in, so he doesn't have to select that pattern himself during the time of surgery, or make changes to patterns on the fly based on what

he's seeing. The laser is doing all that thinking, so to speak. This actually decreases laser time, because instead of us overtreating soft cataracts with a preprogrammed pattern, this is being a little bit more proactive."

The other Streamline features center on the fact that the laser can now interface with the Cassini Analyzer. "The interface involves taking preop corneal measurements, pupillometry and slit-lamp photos with the Cassini, then feeding them wirelessly to the laser," explains Dr. Weinstock. "This accomplishes several things: One, it can automate limbal relaxing incisions and corneal wound placement with automated nomograms that the surgeon can customize. For instance, if the patient has 1 D of cylinder at 90 degrees on the Cassini, and the system is programmed to understand that the surgeon has a surgically induced astigmatism of 0.3 D at 180, there will be an automatic nomogram adjustment that will be waiting there for the surgeon when he gets behind the laser and enters the patient's name.

"On top of that," adds Dr. Weinstock, "since the Cassini takes an infrared image, iris registration software was created. Using the Cassini's undilated image of the iris and the image provided by the laser once it's docked, the laser registers the eye based on the iris architecture. Software compensates for head tilt, cyclotorsion and movement that might occur during docking. This allows you to find the 'true North' and the true primary meridians, which can then be reference points for your LRIs and corneal wounds. This feature can potentially improve the accuracy, predictability and outcomes of astigmatic correction." Also, if the surgeon owns a TrueVision 3D system, the LensAR/Streamline can interface with that, too.

Dr. Weinstock says his femtosecond laser has become key to managing certain patients. "It's become so integral to managing eyes with pseudoexfoliation and/or Fuchs' dystrophy and dense cataracts that, if such a patient came in and couldn't afford the astigmatism correction part of laser cataract surgery, I'd go ahead and do the laser and eat the cost," he says. "I know it will lead to a better outcome because that sick eye is going to heal much better and have less risk for complications both intraop and postop."

LenSx

The LenSx laser (Alcon) has replaced the solid applanation plate it originally used with a patient interface known as SoftFit. It also uses a high-res OCT for imaging of the anterior chamber and to help program the locations of corneal incisions.

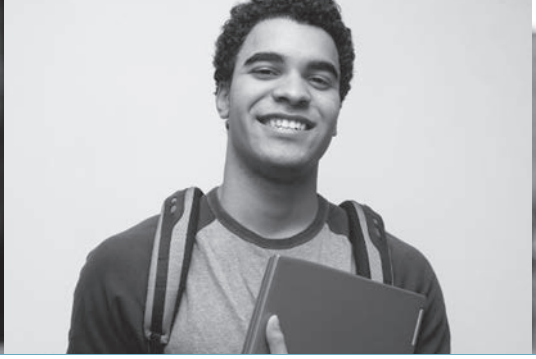
"The older, original interface resulted in a certain percentage of corneas having striae due to compressional corneal folds," explains LenSx user Ming Wang, MD. "These striae inhibited the laser energy that passed through them, resulting in capsulorhexes with certain parts not being cut or having a tissue tag. This was an issue because, even if you tried completing the capsulotomy with Utrata forceps, some of these tags would have a small radial component that could increase the risk of a radial tear-out. The compressional striae can also impede the OCT too, creating a shadow on the image.

"The SoftFit interface that Alcon eventually introduced uses a soft contact lens that acts as a buffer to neutralize the compression on docking," Dr. Wang adds. "So, for example, on corneas that are very steep and are pressing on the contact lens, the peripheral part of the lens isn't pressed, resulting in an interface on the underside that fits the patient's cornea better. The second advantage is patient comfort, because you don't need to press the cone down very hard like you used to with a solid applanation." Alcon says the SoftFit interface raises IOP an average of 16 mmHg above baseline.

The OCT's resolution has improved since the LenSx was first introduced, as well. "In terms of resolution, it's tremendously improved," says Dr. Wang. "You want a good signal-to-noise ratio when you're reaching the backside of the lens and trying to gauge how deep your laser should go with respect to the distance to the posterior capsule. A high-resolution OCT improves this visualization, especially through a dense lens.

"There are other software improvements also," Dr. Wang adds. "This includes auto-recognition/auto-centration. Once the suction ring's on, you want to reduce the time it takes to set the laser parameters and the actual photodisruption. There's a big dif-

Ming Wang, MD, uses a "phaco-less" removal of lens fragments after having pre-chopped them with the LenSx femtosecond laser.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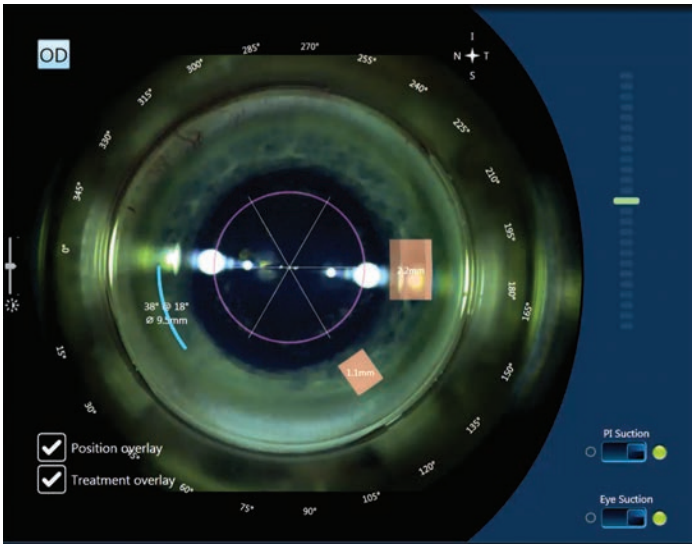
ference between doing all the steps in 20 to 30 seconds versus 40 or 50, and with an increased time come significant increases in the risk of suction loss. With auto-recognition software, you hit the button and the system immediately centers the capsulorhexis on the pupillary center. It also helps center the nuclear fragmentation and the laser AK. The auto-recognition of the anterior capsule has improved, too. You can input 300 µm anterior to the anterior capsule and 250 µm posterior to it and it will automatically recognize the capsule and set that zone of laser treatment automatically."



Originally created for corneal applications, surgeons say the Bausch + Lomb Victus laser is proficient at making corneal incisions, such as entry wounds, paracenteses and limbal relaxing incisions (above).

For astigmatism management, the LenSx can receive registration data from the Verion system. "Rather than eyeballing it under the microscope or using a Mendez ring/protractor device to determine the degrees," Dr. Wang says, "the surgeon can perform the Verion digital imaging preop. That data is sent to the LenSx laser and the system can place the LAK incision exactly where the preop image dictates. The beauty of it is, once the eye is registered, the LenSx can do the LAK right away. With manual marking, you can have an error, but this automatically places the LAK incisions based on the digital markings. It helps avoid error."

Victus

Bausch + Lomb's Victus femtosecond laser features a live-action, swept-source OCT and docking technology that helps reduce the risk of eye tilt and distortion. The Victus is the only femtosecond cataract laser that can also make a LASIK flap (the LenSx is approved for them but doesn't currently do them).

Dallas surgeon Jeffrey Whitman has worked with the new SS-OCT and says it offers some unique views. "It gives you extremely high-res images," he says. "It's so accurate, you can pick up a tumor on the iris. When you perform your femto capsulotomy, you can see the bubbles from the capsulotomy and the Bernoulli effect of them swirling around the anterior chamber as they rise to the top of the cornea, all on the OCT image. One of the advantages of this is you get a real-time view as you do each part of the procedure, rather than it just taking a static picture that you have to look at and decide what's what. You can change things on the fly."

For the docking portion of the procedure, the Victus actually has a "wet-to-dry" approach. It uses a curved interface with a thin layer of fluid for internal eye operations (such as the capsulotomy) and a dry, direct-contact interface for corneal applications (such as corneal incisions). It also has pressure sensors to help the surgeon know when a good dock is achieved. "Having a fluid interface allows the system to more accurately detect, measure and treat structures for the anterior capsulotomy and the femto fragmentation," Dr. Whitman says. "The pressure sensors are helpful; as you bring the eye up into the patient interface using your hand control, the sensors begin at the bottom of the screen in red, meaning the docking is not yet satisfactory, to yellow and then green. It's colormetric and easy to see.

"When the internal treatments are done," Dr. Whitman continues, "we raise the bed, push out the fluid, and then it's dry again. We can then use the dry interface for the entry and arcuate incisions. It's important to recall that the system was originally created for use on the cornea, so it's proficient at treating it."

The new Victus software also provides a variety of patterns for femtofragmentation. "For myself, I prefer to do six radials for softer nuclei, say 2+ or less, and when there are 3+ and harder lenses, I like to create three to four circles within a 4-mm radius, and then six radials mixed with that so I have an interesting chop pattern," says Dr. Whitman. "Whenever I hear arguments about whether this technology is worthwhile, I just say, 'Do a dense cataract with this and you'll be sold,' because it's made my dense cataracts much easier to handle." REVIEW

Drs. Koch and Basti are consultants to AMO. Dr. Weinstock is a consultant to LensAR and Dr. Whitman is a consultant to Bausch + Lomb. Dr. Wang has no financial interest in any of the products discussed.

Residual Astigmatism After IOL Implantation

Jeremy Z. Kieval, MD, Lexington, Mass.

The treatment depends on the cause.

Today's cataract patients expect optimal vision after intraocular lens implantation, and those who choose toric IOLs do not expect to have to wear glasses or contact lenses full-time after cataract surgery. So, many patients who are left with residual astigmatism after cataract surgery desire corrective treatment, and the first step is determining the cause.

Causes

Many of the organic and iatrogenic etiologies need to be ruled out as the cause, and the following are several considerations: ocular surface disease; anterior basement membrane dystrophy; other irregular astigmatism; surgically induced astigmatism; posterior astigmatism; extremes of axial length/IOL prediction errors; and IOL tilt.

If a patient presents with residual astigmatism after the implantation of any IOL, surgeons should first examine his preoperative and postoperative keratometry values to determine whether the astigmatism is naturally occurring or surgically induced.

If the amount of astigmatism present after surgery is different from the preoperative amount, it may be surgically induced astigmatism. In these cases, we would look at the preoperative and postoperative keratometry readings and evaluate for any astigmatism induced by the incision. This can be determined just by looking at the keratometry readings.

Another likely cause of residual astigmatism is posterior astigmatism, which has been shown to significantly influence corneal astigmatism in certain cases.[1] Even if posterior astigmatism was not identified or measured preoperatively, surgeons may be able to find evidence of it in after-the-fact analysis of a patient's corneal imaging. A groundbreaking study found that ignoring posterior corneal astigmatism may yield incorrect estimation of total corneal astigmatism.[1] The study included 715 corneas of 435 consecutive patients, and the mean amount of posterior corneal astigmatism was -0.30 D. The steep corneal meridian was aligned vertically in 86.6 percent of eyes for the posterior surface and in 51.9 percent of eyes for the anterior surface. As patients aged, the steep anterior corneal meridian tended to change from vertical to horizontal, while the steep posterior corneal meridian stayed the same. When the steeper anterior meridian was aligned vertically, the magnitudes of anterior and posterior corneal astigmatism were correlated; however, this was not the case when the steeper anterior meridian was aligned horizontally. Ac-

This article has no commercial sponsorship.

cording to the study results, " … anterior corneal measurements underestimated total corneal astigmatism by 0.22 @ 180 and exceeded 0.5 D in 5 percent of eyes."

If the cause of the astigmatism is not evident after looking at the keratometry readings and imaging, the next step would be to evaluate for ocular surface disease. Irregular topography can indicate corneal disease, such as severe dry-eye disease, ocular surface disease, basement membrane dystrophy or some other subtle corneal pathology that may have been missed. One of these conditions could be inducing the astigmatism that you're now measuring in the refraction. Topography tends to be the best diagnostic tool to evaluate for the location of irregularities on the ocular surface. Diffuse irregularity on topography is often consistent with dry-eye disease, and this can be confirmed using vital dye staining and examining tear breakup time at the slit lamp. Evaluation of dry-eye markers such as MMP9 (InflammaDry) and tear-film osmolarity can also be helpful adjuncts for diagnosing dry eye and ocular surface disease. More focal topographic irregularities might point to the presence of subtle anterior basement membrane dystrophy, Salzmann's nodules or other corneal pathology. Looking for negative staining at the slit lamp or using the red-free filter can be helpful in identifying these conditions.

IOL Position

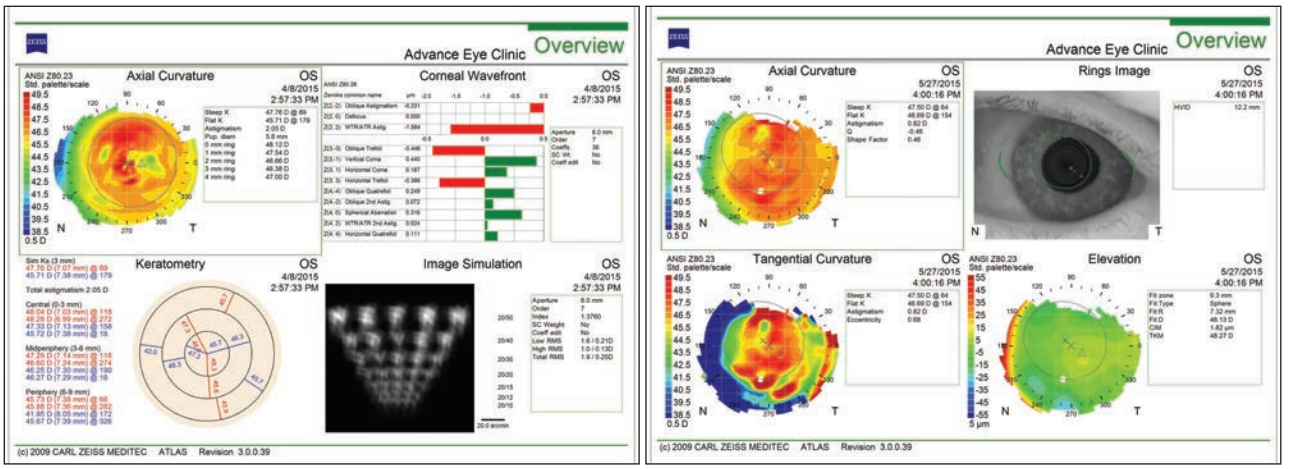
If the residual astigmatism cannot be attributed to the conditions mentioned above, it is time to examine the IOL to see if its position is causing residual refractive error.

If the patient has been implanted with a standard monofocal IOL and she has residual astigmatism, then the surgeon needs to determine whether the patient has residual astigmatism that was expected because of preexisting corneal astigmatism or now has astigmatism not identified by keratometry preoperatively before the monofocal IOL implantation. If none of the previously mentioned causes of astigmatism can be identified, surgeons should examine the placement of the IOL, because tilt with a standard monofocal IOL can induce astigmatism. Several patients have been referred to me for evaluation of postoperative astigmatism only to find that they had one haptic in the bag and one haptic in the sulcus. This was not caught when the implant was placed, and it tilts the IOL, causing postoperative astigmatism in their refraction.

Accurate alignment of toric IOLs inside the eye remains challenging for numerous reasons, and misalignment has significant consequences. For every degree that the lens is off, the patient loses 3.3 percent of astigmatism correction. In other words, if a toric lens is off by 30 degrees, it has no cylindrical effect. Toric IOLs have their own nuances in terms of evaluating for residual astigmatism because they are designed to correct a patient's naturally occurring astigmatism. Measuring the exact axis of astigmatism, as well as aligning a toric IOL to that axis can be somewhat imprecise. If you factor in the unpredictability of surgically induced astigmatism and effective lens position, residual astigmatism is not uncommon after toric IOL placement.

Treatment

If ocular surface disease has been found to be the culprit of residual astigmatism, it can be treated medically. Artificial tears, lid treatments, cyclosporine, punctal occlusion and even steroid drops can be used to control ocular surface inflammation. This is the most common cause of residual astigmatism in patients with standard monofocal IOLs, and treating with lubrication and tears can really help considerably to get back to that preoperative baseline.



Figures 1 and 2. Topographies showing irregularity and 2 D of astigmatism from anterior basement membrane dystrophy (left) and reduction after superficial keratectomy (right).

A recent study found that cyclosporine 0.05% is an effective treatment for dry eye after cataract surgery.[2] The study included 32 newly diagnosed patients with dry-eye syndrome. One week after cataract surgery, these patients received a twice-daily treatment of cyclosporine 0.05% for one eye and normal saline 0.9% for the other. Over time, both groups experienced an increase in Schirmer test 1 and tear-film breakup time. The eyes treated with cyclosporine demonstrated a significant increase in Schirmer test 1 at two months and an increase in TBUT time at two and three months. Additionally, the dry-eye symptom score was significantly reduced in the cyclosporine group.

In cases of anterior basement membrane dystrophy, superficial keratectomy can be very effective in treating the astigmatism. Additionally, a study has found that simple mechanical debridement achieves results that are comparable to those of other procedures used to treat anterior basement membrane dystrophy.[3] This study included 74 eyes of 55 patients who were treated with mechanical epithelial debridement during a 15-year period. Patients' mean age was 74 years, and most (80 percent) were women. Sixty-one eyes experienced visual difficulty before the procedure, and erosion symptoms alone were noted before the procedure in the other 13 eyes. At an early follow-up visit, mean best-corrected visual acuity had improved from 20/44 before surgery to 20/30. At the last follow-up visit (mean: 33 months), mean BCVA was 20/33. The mean refractive spherical equivalent changed -0.6 D (range: -4.75 D to +2 D).

If it is a case of surgically induced astigmatism or missed preoperative posterior corneal astigmatism, limbal relaxing incisions or PRK can be used to treat the residual astigmatism. A study of LRIs performed during cataract surgery found that the effects of LRIs were stable from 10 weeks to three years postoperatively.[4] The study included 20 eyes of 20 patients who underwent small-incision cataract surgery combined with LRIs. Patients' median keratometric astigmatism was 2.1 D measured preoperatively; 1.3 D at two weeks; 1.2 D at 10 weeks, and 1 D at three years postoperatively. No significant differences in keratometric astigmatism were observed between two weeks and 10 weeks postoperatively or between 10 weeks and three years postoperatively. Median surgically induced astigmatism was 2.2 D at two weeks; 2.1 D at 10 weeks; and 1.8 D at three years postoperatively. There was a statistically significant difference in surgically induced astigmatism between two weeks and 10 weeks postoperatively, but not between 10 weeks and three years postoperatively.

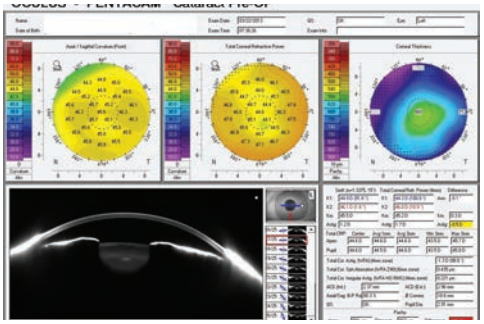


Figure 3. Pentacam showing 0.5 D of additional cylinder contributed by the posterior cornea.

For a standard IOL that is tilted, surgical repair with repositioning of the IOL is required. A recent study found that a tilted scleral-fixated IOL behaves like a toric IOL.[5] Therefore, the astigmatism caused by the position of the scleral-fixated IOL could increase or decrease total astigmatism. This study included 26 eyes of 26 patients. The average amount of tilt was 2.25° ±1.93°, and the average amount of decentration was 359.28 ±194.70 µm. There was a positive and moderate relationship between tilt and astigmatism caused by the position of the IOL; however, there was no relationship observed between decentration and astigmatism caused by the position of the IOL.

For toric IOLs, first and foremost, any medical conditions will need to be treated. These lenses are more likely than standard IOLs to have alignment issues. If a patient has an extreme axial length, a very short eye or a very long eye, the prediction values for toric implants can fall off due to prediction errors of effective lens position and the resulting correction of astigmatism at the lenticular plane. Some of the toric calculators account for axial length, and some do not. Even those that do often use a standard or generalized conversion factor for the degree of astigmatism correction at the corneal plane. If a patient has 1 D of astigmatism at the cornea, it cannot be corrected with 1 D of astigmatism at the lenticular plane. There is a conversion factor that comes into play based on effective lens position that is standardized across most IOLs, regardless of power of the lens. However, if the patient has a very long or a very short eye, the power of toricity may not be sufficient or may be too much and may under- or overcorrect. With toric lenses, it is especially important to consider the posterior cornea. If it wasn't examined preoperatively, the posterior cornea can add or subtract up to 1 D of astigmatism, which can also be the source of residual cylinder.

If a patient with a toric IOL has residual astigmatism, it can generally be corrected by rotating the IOL, laser vision correction, IOL exchange or LRIs. If a toric IOL is not correctly aligned, it will need to be repositioned. We use topography, tomography and keratometry to determine the axis of alignment. Unfortunately, none of these measurements are ever identical, so we always have competing preoperative values, and we often are questioning the exact axis. A recent report found that even toric IOLs that are

(continued on page 55)

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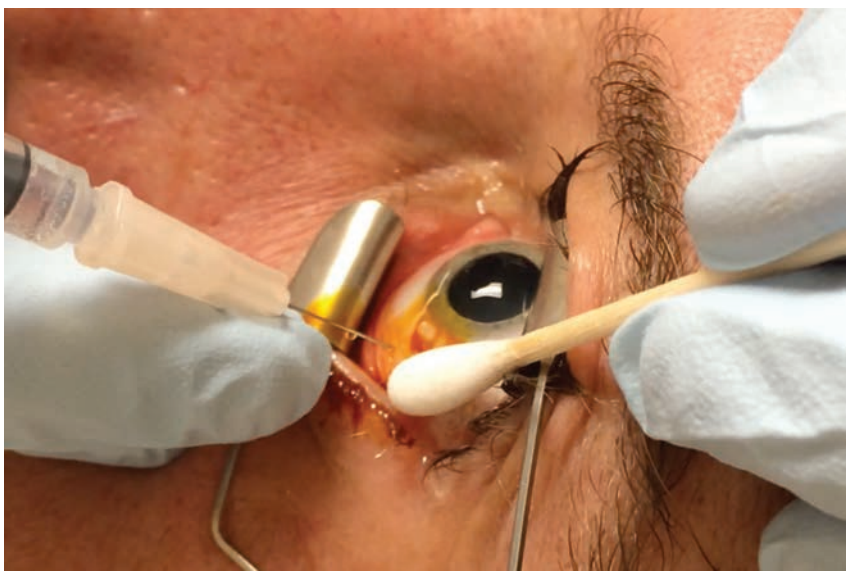
Updated Guidelines for Intravitreal Injection

The protocols for IVT injection continue to evolve as the procedure becomes one of the most-performed in U.S. medicine.

Colin A. McCannel, MD, Harry W. Flynn, Jr., MD, and Emmett T. Cunningham Jr., MD, PhD, MPH

Intravitreal injections have become the most commonly performed medical procedure in the United States, now at nearly twice the rate of cataract surgery. The expanding use of intravitreal triamcinolone acetate, introduced nearly 15 years ago, can be said to have opened the era of widespread intravitreal pharmacotherapy. The introduction of intravitreal anti-VEGF therapy with the approval of pegaptinib (Macugen) in 2004, followed by the off-label use of bevacizumab (Avastin), and approvals of ranibizumab (Lucentis) and aflibercept (Eylea) for expanding indications led to staggering growth in the use of intravitreal injection therapies now seen.

Prior to the approval of Macugen, and in anticipation that the number of intravitreal injections would increase dramatically, an expert panel convened in New York City to establish general guidelines for performing intravitreal injections. The results of this panel meeting were published as a supplement to the journal *Retina* in 2004,[1] and have stood since as consensus guidelines.[1] Since then, a vast body of scientific literature relating to various aspects of the procedure has emerged. In December of 2014, a panel of 16 health professionals with expertise in various aspects of the injection procedure convened to review and revise the intravitreal injection guidelines published in 2004. As part of that effort, each participant reviewed the publications on a particular aspect of the intravitreal injection process, and all reported their findings to the group as the basis for discussion and possible recommendation for revision, or establishment of updated guidelines. The areas of agreement with and without clear consensus are summarized in Tables 1 and 2. Important highlights and general rationale for the recommended changes are summarized here.



• Items of the 2004 recommendations that have been dropped

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Table 1. Areas of General Agreement by Committee Members (2014)*

1. Povidone-iodine (5-10%) should be the last agent applied to the intended injection site before injection. If a gel anesthetic is used, povidone-iodine should be applied both before and after application of gel, as retained gel may prevent povidone-iodine from contacting the conjunctival surface of the injection site.
2. Pre-, peri- or post-injection topical antibiotics are unnecessary.
3. There is no evidence to support the routine use of a sterile drape.
4. Avoid contamination of the needle and injection site by the eyelashes or the eyelid margins.
5. Avoid extensive massage of the eyelids either pre- or post-injection (to avoid meibomian gland expression).
6. Use adequate anesthetic for a given patient (topical drops, gel and/or subconjunctival injection).
7. Use of sterile or nonsterile gloves as consistent with modern office practice, combined with strong agreement regarding the need for handwashing before and after patient contact.
8. Either surgical masks should be used or both the patient and providers should minimize speaking during the injection preparation and procedure to limit aerosolized droplets containing oral contaminants from the patient and/or provider.
9. Monitor IOP both pre- and post-injection.
10. Routine anterior chamber paracentesis is not recommended.

* Reproduced from Avery RL, Bakri SJ, Blumenkranz MS, et al. Retina 2014 Dec; 34 Suppl 12:S1-S18.

or have been significantly altered:

1. Use of a lid speculum is not essential. Unlike 2004, use of a lid speculum is no longer required in the updated 2014 guidelines. However, the panel stressed the importance of paying careful attention to the eyelid margin as a source of possible needle or ocular surface contamination.[3,4] The panel recommended that a lid speculum, manual lid retraction or some similar maneuver be used to keep the eyelid margins away from the injection site and needle during the injection procedure.

2. Routine dilation of the pupil is not essential. There was strong consensus in the 2004 guidelines that the pupil should be dilated to facilitate full examination of the posterior segment following intravitreal injections. The 2014 panel could not achieve agreement on this topic, as many panelists do not dilate the pupil for all injections, while others consider dilation and full post-injection examination to be important. Given the lack of consensus, the recommendation for routine dilation was dropped.

• ***New 2014 recommendations:***

1. Peri-injection antibiotics are not necessary. In 2004, no clear consensus regarding the use of peri-injection antibiotics could be achieved. Since then, a growing body of evidence has emerged that strongly suggests peri-injection antibiotics do not meaningfully lower the risk of post-injection endophthalmitis.[5-9] In addition, there is strong evidence that periodic multi-day administration of topical ophthalmic antibiotics results in the development of, and colonization with, drug-resistant bacteria. Facilitating the colonization of patients with drug-resistant bacteria is generally undesirable, especially since such organisms tend to show increased virulence.[10,11] Thus, the panel did not recommend routine use of pre-, peri- or postinjection antibiotics.

2. Hand washing and glove use are important. Consistent with the modern-day medical practice of universal precautions, hand washing before and after patient contact, as well as the use of sterile or non-sterile gloves during procedures are generally recommended. Although this item was agreed upon nearly uniformly by the panelists, some panelists do not use gloves, citing studies that showed no impact of glove use on endophthalmitis rate.[5,12]

3. Use of a surgical face mask or avoiding talking during the procedure is recommended. In the 2004 guidelines, the topic of droplet contamination was not addressed. Since then, evidence has emerged from multiple studies that streptococcal

Recommended Sequence of Steps for IVT Injection*

1. Take a procedural time-out to verify patient, agent and laterality;
2. Apply liquid anesthetic drops to the ocular surface;
3. Apply povidone-iodine to the eyelashes and eyelid margins (optional, most use 10%);
4. Retract the eyelids away from the intended injection site for the duration of the procedure;
5. Apply povidone-iodine to the conjunctival surface, including the intended injection site (most use 5%);
6. If additional anesthetic is applied, reapply povidone-iodine to the intended injection site immediately prior to injection (most use 5%);
7. Insert the needle perpendicular to the sclera, 3.5 to 4 mm posterior to the limbus, between the vertical and horizontal rectus muscles. Application of a sterile cotton-tip applicator over the injection site immediately following removal of the needle may reduce vitreous reflux.

* Reproduced from Avery RL, Bakri SJ, Blumenkranz MS, et al. Retina 2014 Dec; 34 Suppl 12:S1-S18.

Table 2. Areas with No Clear Consensus by Committee Members (2014)

1. Need for povidone-iodine application to the eyelids, including the eyelashes and eyelid margins. All agreed that when povidone-iodine is applied to the eyelashes and eyelid margins, eyelid scrubbing or eyelid pressure adequate to express material from the meibomian glands should be avoided.
2. Use of an eyelid speculum (some prevent contact between the needle/injection site and the eyelashes and eyelids with manual lid retraction).
3. Need for pupillary dilation and post-injection dilated examination of the posterior segment (although some viewed the return of formed vision as sufficient, others routinely dilate the pupil and examine the posterior segment after injection).
4. Use of povidone-iodine flush (most preferred drops only and saw no benefit to allowing the povidone-iodine to dry before injection).

* Reproduced from Avery RL, Bakri SJ, Blumenkranz MS, et al. Retina 2014 Dec; 34 Suppl 12:S1-S18.

species are responsible for a disproportionate number of cases of endophthalmitis following intravitreal injection compared to endophthalmitis following intraocular surgery.[13,14] The increased rate of *Streptococcus* species is likely from aerosolized droplet contamination from either the practitioners' or patients' oral flora.[15] Thus, it is recommended that clinicians and patients avoid talking during the procedure unless wearing a face mask.

4. Monitoring intraocular pressure both pre- and post-injection is important. Following intravitreal injection, IOP can be assessed by the presence or absence of formed vision, or by IOP measurement. In some patients the IOP elevates acutely to the level that formed vision is not present, suggesting a pressure-induced occlusion of the central retinal artery, and these patients need to be managed accordingly. IOP should be measured before the injection, as recent evidence suggests that chronic intravitreal administration of anti-VEGF agents can result in a sustained elevation in IOP.[16,17]

5. Bilateral injections during the same visit may require special precautions. Some practitioners inject both eyes during the same visit.[18-21] In such situations it is recommended that each eye be treated as a separate procedure, and that when a compounded medication is used, such as bevacizumab, different compounding lots or batches be used for each eye. For commercially packaged unit dose medications, such as ranibizumab and aflibercept, different lots for each eye may not be feasible due to the very large production lot sizes.

6. There is no evidence to support the routine use of a sterile drape. The panel identified no evidence to support routine use of sterile drapes for the injection. In fact, studies not requiring a drape during injection have not reported increased rates of endophthlamitis.[5,22] Moreover, controlled studies addressing the use of sterile drapes in a non-ophthalmic setting found higher rates of infection when adhesive drapes were used.[26]

• Recommendations without change from 2004:

1. The routine use of povidone-iodine as a topical antiseptic remains important. Extensive evidence supports the potent antiseptic properties of povidone iodine.[24,25] There was strong consensus among the group that povidone-iodine solution application is probably the single most important step for reducing the risk of endophthalmitis following IVT injection. Specifically, it was agreed that before injection, povidone-iodine solution (5 to 10%) should be the last agent applied to the intended injection site. In situations that viscous or gel topical anesthetic agents are used, the povidone-iodine solution should be applied to the ocular surface both before and after the viscous agents.[26]

2. Extensive massage of the eyelids either pre- or post-injection should be avoided. If the eyelids and eyelashes are prepped with povidone-iodine solution, this should be done carefully. Excessive pressure may lead to expression of the meibomian glands and contamination of the ocular surface. Generally, the panel felt that the risk of adding a lid and lash prep with povidone-iodine outweighed any potential benefit, and did not recommend this step.

3. Adequate anesthesia is important. The use of topical anesthetics is usually required, whether or not an additional subconjunctival injection of an anesthetic agent is performed. While there are a number of studies comparing various anesthesia techniques for intravitreal injection, no consistently preferred approach has been identified.[29-31] Some panelists preferred localized anesthetic application with a cotton pledget. The panelists unanimously agreed that adequate anesthesia should be used to minimize patient discomfort.

4. Routine anterior chamber paracentesis is not recommended. As was the case in 2004, there was consensus among the 2014 panel that routine anterior chamber paracentesis either before or after the injection is not recommended. In most instances the IOP normalizes rapidly, and performing a paracentesis is not entirely risk-free, as complications such as endophthalmitis can occur.[32,33] However, in select circumstances, paracentesis may be necessary, and should be done at the treating physician's discretion. REVIEW

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Inquires can be directed to Dr. McCannel at CMcCannel@jsei.ucla.edu.

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(continued from page 50)

positioned appropriately intraoperatively can benefit from rotation.[6] The report included three eyes of two patients. Using an online toric IOL calculator, it was determined that IOL rotation would significantly improve astigmatic outcomes. Two months after IOL rotation, residual manifest astigmatism was 0.5 D, 0 D, and 0.75 D in the three eyes, showing that the use of the toric IOL online calculator maximized the uncorrected visual and refractive outcomes.

These online programs (e.g., astigmatismfix.com) that have been developed look at a patient's refraction and the current power and axis of the toric lens and plug that into vector analyses. They can tell surgeons whether there is a new ideal axis of alignment. Perhaps all of your keratometry values were off by 5° or 10°, and you weren't sure which one was the right number. Now, looking at those vector analyses postoperatively, we can determine which one was probably the right number. Plugging these numbers into a calculator, such as the one on the ASCRS website, will help give you a better sense of the ideal axis of the lens and to what degree you are going to reduce the residual astigmatism. REVIEW

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Delivering a Rocky Mountain ARVO

A rundown of the most interesting research in a variety of subspecialties presented at this year's ARVO meeting.

Mark B. Abelson, MD, CM, DSc, FRCSC, FARVO, and ORA Staff, Andover, Mass.

This year's annual meeting of the Association for Research in Vision and Ophthalmology headed west to Denver with the theme of "Powerful Connections." This theme was exemplified throughout the meeting, where clinicians and scientists with diverse specialties but a shared interest in vision come together. One of the central connections highlighted this year was the link between the chemists and materials scientists making inroads in synthesis and construction of new drug-delivery paradigms, and the biologists and clinicians with therapeutics in need of delivery. Despite the annual changing of venue, ARVO is still the singular location for the best in basic and clinical ophthalmic research. Here's a sampling of presentations from this year's meeting. (Unless otherwise specified, all of the abstract citations are from this year: IOVS 2015;56.)

Drug Delivery, A Central Theme

The eye is a unique venue for the pharmacologist: while it affords easy access with topical medications, it's still surprisingly difficult to deliver sufficient concentrations of therapeutics, especially when the need is for extended durations. Exploration into new methods of drug delivery for the treatment of ocular disorders has focused on this limitation, and has taken advantage of an explosion in research into the formulation and manufacture of biomaterials and other delivery-device technologies. A prime example of this is the chemical modification of biopolymers, including collagens and hyaluronic acids for use in drug delivery and for stem cell propagation.[1] Depot forms of a number of drugs have been brought to market in recent years, and it looks like this trend will continue. This year at ARVO, the search for new methods of drug delivery designed to increase efficacy, reduce side effects and increase patient convenience was highlighted.

Several presentations came from Jade Therapeutics, including reports on potential applications of their thiolated carboxymethylated hyaluronic acid films. CMHA chemistry has the advantage of flexibility, both in terms of its physical properties and its delivery potential, since the gels can be easily inserted on-site by a physician. Drug release from the CMHA matrix largely depends on the degradation of the matrix by hyaluronidases (HAase) present in ocular tissue. *(Bowen RC, et al. ARVO E-Abstract 1295)* reported on levels of HAase in ocular tissues; information that is pivotal to future optimization of CMHA matrices for ocular drug delivery. Another report *(Lee WY, et al. ARVO E-Abstract 4139)* investigated different formulations of the CMHA matrix and found that utilizing cross-linker Poly (ethyleneglycol) diacrylate created a film with favorable tensile strength, relaxation modules, durability and flexibility.

Another presentation examined use of CMHA matrices for delivering therapeutic proteins. *(Wirostko B, et al. ARVO E-Abstract 262)* In a model of corneal wound healing, the CMHA film was found capable of delivering recombinant human growth hormone in a controlled, sustained manner both *in vitro* and *in vivo* over a course of days to months. The CMHA matrix shows promise for alternative drug-delivery systems that reduce frequency and increase efficacy of a number of therapeutics for ocular disease. Another similar delivery system involved

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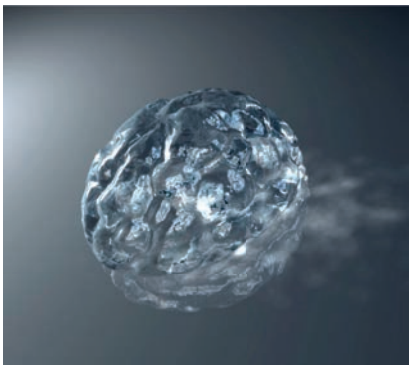
the use of collagen hydrogel implants, in which vancomycin was successfully delivered for prevention of postoperative ocular infection. *(Mondal D, et al. ARVO E-Abstract 4135)*

Hydrogel technology was employed in implanted devices or microparticles. One study used microparticles to deliver a glaucoma therapeutic (OHR1031; Ohr Pharmaceutical, San Diego), testing the release kinetics of the drug *in vitro*. *(Malavia N, et al. ARVO E-Abstract 1296)* Notably, these investigators utilized a dissolvable hydrogel that should yield sustained delivery without the need to recover an empty device. Another implant currently in preclinical evaluations is the ENV905 (Envisia Therapeutics; Research Triangle Park, N.C.), used for delivery of difluprednate for treatment of inflammation and pain associated with ocular surgery. *(Garcia A, et al. ARVO E-Abstract 5897)* The ENV905, which can be placed subconjunctivally or intracamerally, demonstrated in a rabbit model a robust reduction in corneal inflammation over four weeks. This type of delivery would eliminate the need for topical multidose therapies of extended duration.

An interesting application of hydrogel technology utilizes "nanowafer" drug delivery systems. *(Acharya G, et al. ARVO E-Abstract 5032)* In a model of corneal neovascularization, the nanowafer, a transparent disc containing nanoreservoir arrays of the small molecule tyrosine kinase inhibitor Axitinib, was demonstrated to be significantly more effective than b.i.d. drops.

Soft contact lenses are also being used for drug delivery. Using a novel 3-D *in vitro* eye model that mimics physiologic tear flow across the ocular surface, one study confirmed that commercial contact lenses can maintain a sustained drug-release profile for up to 24 hours. *(Phan C-M, et al. ARVO E-Abstract 3085)* Researchers also reported the successful application of dexamethasone-eluting contact lenses



The properties of hyaluronic acid hold huge potential for its use as a lubricant, cell matrix and tissue filler.

for the treatment of ocular inflammation in a rabbit model. *(Ciolino J, et al. ARVO E-Abstract 148)*

Two studies at ARVO 2015 presented new technologies to address the issue of patient compliance in clinical trials. A smartphone-based system for capturing images of conjunctival redness showed a high degree of correlation with measurements made by clinicians. *(Corcoran P, et al. ARVO E-Abstract 3045)* Another study evaluated how the shape of an eye-drop bottle dictates patient compliance by utilizing a novel eye drop application monitor. The monitor creates a log of the number of drops dispensed and how many landed in or outside of the eye. *(Allen M, et al. ARVO E-Abstract 1919)*

AMD and Anti-VEGF Delivery

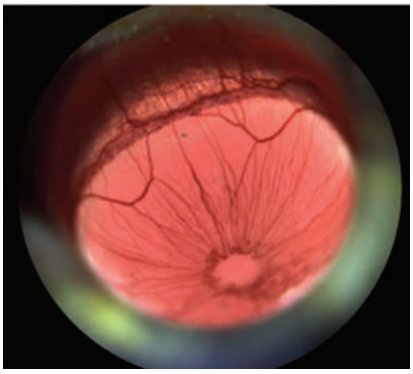
An astonishing amount of research is dedicated to improving the treatment options and visual outcomes of age-related macular degeneration. While vascular endothelial growth factor inhibitors have begun to provide a means of holding off the permanent damage to vision that AMD causes, the necessity of once- or twice-monthly intravitreal injections is a financial and medical burden. Now, however, novel delivery systems are evolving to address this limitation. One fascinating approach involved a system of *de novo* designed cell-penetrating peptide constructs fused to a therapeutic protein transduction domain. *(DeCogan F, et al. ARVO E-Abstract 4147)* This system was shown to successfully transport microgram quantities of macromolecules, such as the very large monoclonal VEGF inhibitors, in a topical eye drop that enables penetration all the way to the posterior segment. Other studies focused on slow-release depots of VEGF-inhibitors. Initial *in vitro* pharmacokinetic work is being done on controlled-release polymer reservoirs of ranibizumab. *(Abe T, et al. ARVO E-Abstract 4146)* A noninvasive electroosmotic delivery of bevacizumab also proved successful and analogous to the efficacy of intravitreal bevacizumab. *(Molokhia S, et al. ARVO E-Abstract 2293)* A polymer nanoparticle system was described in which conjugation of bevacizumab was shown to reduce leakage of the drug into the bloodstream. *(Kong L, et al. ARVO E-Abstract 5029)* This prolonged its retention in the vitreous, making it potentially safer and more effective by reducing systemic exposure and extending ocular residence time. A number of *in vitro* and *in vivo* pharmacokinetic studies examining properties of becacizumab-packaged microparticles were presented, including PK studies of solid-state microparticles within sustained-release hydrogel matrices in both primates and non-primate species. *(Tully S, et al. ARVO E-Abstract 222; Owens G, et al. ARVO E-Abstract 236; and Verhoeven RS, et al. ARVO E-Abstract 230)* If this year's presentations are any indication, a major focus of retinal therapies in the near future will be the refinement of these therapeutic delivery options.

Steroid therapy for retinopathy has not fallen by the wayside, however. A dexamethasone intravitreal implant together with macular grid laser was found effective for retinal vein occlusion *(Massaro D, et al. ARVO E-Abstract 3752)*, allowing clinicians to extend the time between injections.

PRINT technology was used to create biodegradable implants and microparticle suspensions of steroids for six-month, slow-release depots for intravitreal delivery. *(Das S, et al. ARVO E-Abstract 4165)* Release kinetics of loteprednol in a nanoparticle gel was also presented. *(Hirani A, et al. ARVO E-Abstract 5038)* Lastly, topical dexamethasone γ-cyclodextrin nanoparticle eye drops improved visual acuity and decreased macular thickness in patients with DME. *(Ohira A, et al. ARVO E-Abstract 2289)*

With regard to new therapies, effort has been focused on small-molecule therapies to avoid the problems of penetration and absorption of the macromolecule monoclonal VEGF inhibitors. Initial *in vitro* screens included multiple small-molecule, vitamin D receptor agonists *(Merrigan S, et al. ARVO E-Abstract 158)*; combinations of inhibitors of the P13K/Akt/mTOR pathway *(Sasore T, et al. ARVO E-Abstract 2305)*; and an assessment of an isoquinolone sulfonamide derivative that inhibits protein kinase function. *(Sugimoto M, et al. ARVO E-Abstract 150)* In models of neovascularization, intravitreal and systemic IL-18 immunotherapy was effective. *(Campbell M, et al. ARVO E-Abstract 4803)* Pharmacokinetics and initial vascular leakage models were used to successfully assess a topical receptor tyrosine kinase inhibitor formulated via mucus-penetrating particles that allow for enhanced penetration and activity in the back of the eye. *(Schopf L, et al. ARVO E-Abstract 2279)*

Two studies on regorafenib eye drops, which would be a breakthrough topical therapy, presented positive results using this multi-kinase inhibitor. *(Beottger MK, et al. ARVO E-Abstract 2294; Klar J, et al. ARVO E-Abstract 246)* SH-11037, a homoisoflavanone synthetic derivative of cremastranone, significantly suppressed angiogenesis in a murine model. *(Sulaiman RS, et al. ARVO E-Abstract 2470)* Tetramethylpyrazine, a unique small-molecule inhibitor of the chemokine receptor CXCR4 was also found effective. *(Zhuang J, et al. ARVO E-Abstract 2465)* Similarly, oral dosing of a chemokine receptor 3 (CCR3) antagonist effectively suppressed spontaneous neovascularization in mice and laser-induced injury in primates. *(Ng Q, et al. ARVO E-Abstract 2290)* Oral docosahexaenoic acid supplements protected against neovascularization and retinopathy in rat models of AMD *(Ogami S, et al. ARVO E-Abstract 2350)*, and a new RNAi-based agent appears to inhibit both the angiogenesis and fibrosis promoted by periostin. *(Nakama T, et al. ARVO E-Abstract 2280)* A similar strategy was assessed using the anti-pigment derived growth factor aptamer Fovista and aflibercept together in a mouse model. *(Walsh B, et al. ARVO E-Abstract 2298)* A telomerase-derived peptide, GV1001, inhibited neovascularization in a rat model in a dose-dependent fashion. *(Lee EK, et al. ARVO E-Abstract 2291)* The variety of new agents showing promise in preclinical studies bodes well for treatment of retinal proliferative disease.



Increases in vasodilation in mouse models of ocular inflammation can be quantified and used as efficacy measures in preclinical drug assessments. *(Whitlock A, et al. ARVO E-Abstract 4886)*

Clinical Trial Results

Dry AMD continues to be one of the main ocular disorders without significant Food and Drug Administation-approved therapies.[2] In the clinic, BAM114341, a therapy designed to block formation of β-amyloid deposits seen in Alzheimer's disease is being tested in a Phase II study in geographic atrophy secondary to AMD *(Shearn SP, et al. ARVO E-Abstract 2840)*. The authors published the results of the four-month run-in period, in which fundus photography and autofluorescence were used to define pre-specified and patient-specific growth rates of lesions as the unique primary endpoints in this clinical trial. It will be exciting to see the efficacy results of this study, given recent studies linking β-amyloid formation in AMD with other neurodegenerative disorders of peptide misfolding such as Alzheimer's disease.

The one-year results of a Phase I/II combination therapy of low-dose, proton beam irradiation combined with anti-VEGF therapy were published. *(Osmanovic S, et al. ARVO E-Abstract 4906)* This study was initiated based on observed synergies of VEGF inhibition with radiation therapy. While this was only an interim analysis, it's showing that fewer injections were needed in the radiation group, so this might be a means of reducing overall treatment burden. Final Phase II results from the 0.2% squalamine lactate topical therapy in combination with intravitreal ranibizumab for treatment of AMD were presented. *(Slakter JS, et al. ARVO E-Abstract 4805)* Squalamine caused marked improvements in visual acuity gain compared with the VEGF inhibitor alone, though there was no decrease in injection frequency.

Results from the Phase I GEM study were reported to be successful. *(Chandler S, et al. ARVO E-Abstract 2284)* This first-in-human application of a subretinally injected lentiviral vector (RetinoStat) met the primary endpoint, was safe and well-tolerated and patients showed signs of clinical benefit. A humanized single-chain antibody

Post-op relief is affordable for your patients[1-3]

DON'T LET POSTOPERATIVE INFLAMMATION AND PAIN LEAVE A BAD IMPRESSION

3x more cataract patients achieved zero inflammation on postoperative Days 8 and 15 vs placebo
- 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]

- **BETTER** or comparable formulary coverage vs generic prednisolone acetate on some Medicare Part D plans[4-7]
- **NO** therapeutic equivalent to DUREZOL® Emulsion

*Pooled data from placebo-controlled trials in patients undergoing cataract surgery; $P<0.01$ vs placebo.
^Trademark is the property of its owner.

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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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DUREZOL®
(difluprednate ophthalmic emulsion) 0.05%

DUREZOL®
(difluprednate ophthalmic emulsion) 0.05%

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.

Revised: May 2013
U.S. Patent 6,114,319

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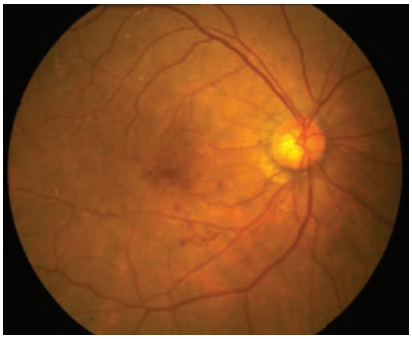
fragment, RTH258, has been tested in the clinic in patients with AMD. This molecule has the advantage of allowing microvolume injections or infusions of 10 µl, leaving room for additional simultaneous treatments or permitting a sustained delivery platform.

Two mineralocorticoid receptor antagonists, spironolactone and eplerenon, were found effective for oral treatment of central serous chorioretinopathy, with the former showing superior efficacy for fast resolution of subretinal fluid and anatomic outcomes. Retinal branch occlusion and DME both received press coverage of their clinical trial results. The 52-week results of aflibercept in the VIBRANT study were positive for treatment of retinal branch occlusion. *(Boyer DS, et al. ARVO E-Abstract 3749)* Studies of DME therapy with aflibercept and bevacizumab showed positive results in pathologic myopia and persistent DME. *(Nassaralla JJ, et al. ARVO E-Abstract 4622; Gillies MC, et al. ARVO E-Abstract 3144)*

Cornea Corner

At ARVO, we always expect to see plenty of new studies in the area of corneal trauma, inflammation and wound healing. This year did not disappoint. Progress in gene-based therapy for inherited disease was demonstrated in a study of corneal clouding associated with MPS1, a condition known historically as Hurler's syndrome. *(Hirsch M, et al. ARVO E-Abstract 260)* The syndrome is due to a genetic defect in iduronidase α-L, a key enzyme in glycosoaminoglycan metabolism. The study tested a viral-based expression of a replacement for IDUA in patient fibroblasts, mouse cornea and human cornea. The goal was to optimize the adeno-associated viral vector for corneal expression of IDUA, and that was demonstrated in all three test tissues. Stromal injections of optimized constructs into wild-type human corneas



Experimental AMD treatments at ARVO include radiation therapy and viral vectors.

ex vivo yielded robust expression of the viral IDUA, providing hope for therapeutic intervention for corneal clouding in children with MPS1 and other varients of mucopolysacharride-associated disorders.

Chronic keratitis, whether from infection, trauma or surgical complication, remains a significant therapeutic challenge. As in years past, there was a wealth of studies, from neurotrophic keratitis to dry eye, aimed at improving therapeutic outcomes for those with corneal disease. One study tested the efficacy of the Rho-kinase inhibitor AMA0076 (Amakem NV, Belgium) in a rabbit model of corneal debridement. *(Defert O, et al. ARVO E-Abstract 5610)* Rho kinases are signal mediators for a host of cellular responses associated with cytoskeletal dynamics and motility.[3] In the past, they have been explored as potential therapies for POAG. More recently their role in cellular inflammation and differentiation has been recognized, and this study aimed to test the ability of Rho kinases to enhance and accelerate the process of corneal wound healing. The study followed four days of healing for untreated animals, AMA0076-treated animals, and a positive comparator of recombinant growth hormone. The ROCK inhibitor and GH treatments were comparable for both re-epithelialization and resolution of corneal haze, and both were superior to control animals. Of note, AMA0076 did not cause the hyperemia that's been associated with other ROCK inhibitors.

Currently, steroids are the primary treatment modality for ocular inflammation, but there is a significant need to improve upon existing treatment regimes and dosing strategies. Implants such as those tested in the Envisia Therapeutics study performed by Garcia, et al, discussed previously, are designed to provide a single-dose treatment via a subconjunctival or intracameral device. *(Garcia, et al. ARVO E-Abstract 5897)* This study tested ENV905, a biopolymer implant designed to deliver therapeutic dosing of difluprednate over a four-week taper, compared with q.i.d. Durezol in a rabbit model of postoperative inflammation. Using slit-lamp exams and Hackett-McDonald scoring, the implants were superior to both placebo implants and to topical steroid.

In a similar strategy, other researchers tested a weekly dosing regimen of cyclosporin delivered using mucoadhesive nanoparticles in a mouse model of dry eye. *(Lui S, et al. ARVO E-Abstract 5036)* This regimen enhanced anti-inflammatory efficacy relative to placebo or to higher doses of CsA.

It's long been thought that dry eye was a condition that was most severe in winter months, but no studies had ever been done to test this. A group from our research firm Ora pooled data from 10 trials and identified 270 patients who had participated in at least one summer study (April to September) and one winter study (November to April), and were randomized to placebo groups in both. *(Ousler G, et al. ARVO E-Abstract 4462)* Both ocular discomfort and dryness symptom scores were significantly higher during the winter months, consistent with the prevailing wisdom. It'll be interesting to see if clinical signs of dry eye such as corneal stain show similar patterns.

The search for new dry-eye therapies continues, and ARVO presented a mix of repurposed products, pipeline products and new chemical enti-

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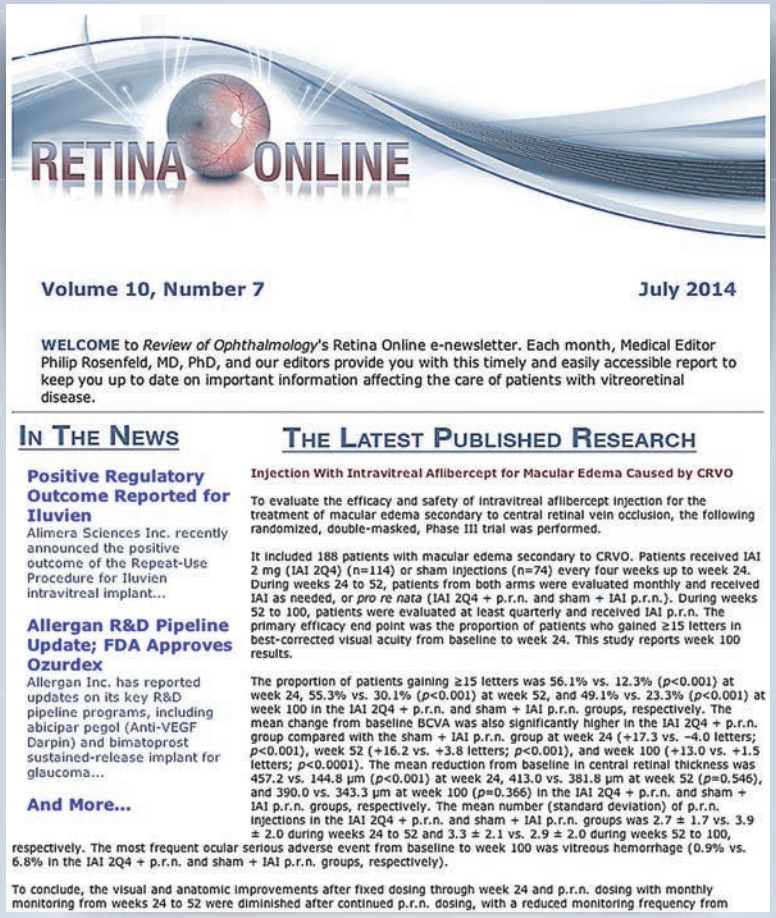

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WELCOME to *Review of Ophthalmology*'s Retina Online e-newsletter. Each month, Medical Editor Philip Rosenfeld, MD, PhD, and our editors provide you with this timely and easily accessible report to keep you up to date on important information affecting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

And More...

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

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ties. One presentation described repurposing of the immunosuppressant rapamycin4 (Rapamune, Pfizer) as a therapy for Sjögren's syndrome, using a non-obese mouse model as a test platform. *(Shah M, et al. ARVO E-Abstract 4810)* After a 12-week treatment of b.i.d. rapamycin, SS markers were all significantly reduced compared to placebo, including lacrimal lymphocytic infiltration and tear cathepsin S activity. Another preclinical trial tested the integrin antagonist GW559090 in a mouse model of dry eye. *(Krauss AH, et al. ARVO E-Abstract 2472)* Integrins are key players in lymphocyte activation and chemotaxis; lifitegrast, a drug for treatment of dry eye currently under FDA review, inhibits another member of the integrin family, lymphocyte function antigen 1.[5]

Another therapeutic approach gaining favor for corneal disease is stem-cell transplantation. One notable study used a mouse model of bacterial inflammation to demonstrate that the local delivery of mesenchymal stem cells is an effective and safe approach for immunomodulation and treatment of ocular inflammation. *(Zhang R, et al. ARVO E-Abstract 942)*

A group of reports on recent advancements in ocular allergy included one study demonstrating the therapeutic potential for PI3K inhibitors. *(Whitlock A, et al. ARVO E-Abstract 4886)* The study used reduction in ocular redness in a mouse model as a reporter for relief of allergic inflammation. Another allergy study used the conjunctival allergen challenge model and an assessment of inflammation based on confocal microscopy. *(Gomes P, et al. ARVO E-Abstract 4892)* In this protocol, comparison of confocal images in placebo treatments and those treated with the antihistamine alcaftadine (Allergan) showed that drug pretreatment reduced inflammatory cell infiltration, a likely mechanism of alcaftadine's long duration of efficacy. Another study reported on the use of MALDI-TOF-MS as a technique for detection of biomarkers for the most severe types of ocular allergy, vernal keratoconjunctivitis and atopic keratoconjunctivitis. *(Leonardi A, et al. ARVO E-Abstract 5875)* This study could prove valuable for these diseases that lack a specific and reliable laboratory test.

Gene Therapies

ARVO always highlights the cutting edge of scientific research, so it was no surprise to see a number of presentations describing the latest progress towards genetically based therapies. One of these reports combined gene-editing CRISPR technology and genetically modified, induced pluripotent stem cells to generate 3-D retina reporter cell lines for the study of photoreceptors. *(Wahlin KJ, et al. ARVO E-Abstract 3596)* Several studies focused on utilizing gene therapy to target the oxidative stress that accompanies a number of retinal diseases. By utilizing a mouse model of retinal pigment epithelium oxidative stress, researchers demonstrated that delivery of genes for antioxidant enzymes can be used as a tool to reverse oxidative stress. *(Biswal MR, et al. ARVO E-Abstract 3189)* In contrast, a different study proposed that targeting of transcription factors regulating hundreds of genes that combat oxidative stress would be more effective than the delivery of antioxidant enzymes. *(Xiong W, et al. ARVO E-Abstract 3188)*

Technological improvements are always on display at ARVO. One example that appeared in several presentations was the automation of ocular redness measurements. *(Rodriguez J, et al. ARVO E-Abstract 340; Finis D, et al. ARVO E-Abstract 4444)* Ocular redness is a key diagnostic indicator in studies of dry eye, and these methods, particularly in combination with devices designed for patient documentation of redness described earlier, can be real game-changers in drug development for ocular inflammation. Two reports from Ora examined blinking under natural conditions using continuous monitoring technology. *(Lane K, et al. ARVO E-Abstract 4447; Harmeling L, et al. ARVO E-Abstract 4486)* These studies continue to advance our understanding of compensatory mechanisms in ocular surface disease.

Another presentation from researchers at Ora examined the differences between corneal fluorescein staining measurements made in research or clinical studies with those in a typical ophthalmic practice. *(Angjeli E, et al. ARVO E-Abstract 336)* While clinicians often visualize staining with a standard slit lamp, protocols used in clinical trials often employ filters, reduce extraneous wavelengths, minimize background light and significantly enhance the image's signal-to-noise ratio. The study compared patient staining with and without low-pass filtration and showed that most measurements made with slit lamps alone underestimate the extent of staining.

As usual, there were far too many interesting discussions, presentations and studies at this year's ARVO meeting to provide a comprehensive summary. Readers would do well to keep this in mind when planning for educational outings in 2016, since a succinct summary of the 2015 ARVO meeting, like those of meetings past, is simply, "You had to be there." REVIEW

Dr. Abelson is a clinical professor of ophthalmology at Harvard Medical School.

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The Many Faces of Coats' Disease

Careful attention must be paid before and after the diagnosis of this mimicker of several ophthalmic diseases.

Edward Y. Chay, MD, and Eric M. Shrier, DO, Brooklyn, N.Y.

Coats' disease is a great mimicker of several severe ophthalmic conditions in children. The most notable of these is retinoblastoma, and diagnostic caution is necessary whenever it is suspected. Coats' mislabeled as retinoblastoma is cited as the most common cause of wrongful enucleation.[1] The variety of signs in Coats' disease can lead to a wide range of other misdiagnoses such as retinopathy of prematurity; familial exudative vitreoretinopathy; hemangioblastoma; lipemia retinalis; ocular toxocariasis; persistent fetal vasculature; Eales' disease; retinal vasoproliferative tumor; idiopathic retinal vasculitis; aneurysms; neuroretinitis; and incontinentia pigmenti.[2]

The typical case is unilateral and progressive and affects males between the ages of 8 and 16 years. However, children as young as 3 weeks[3] and adults[4,5] have been reported to present with Coats' disease. Females are certainly affected, though less frequently.[6] Additionally, bilateral vascular abnormalities are found in about two-thirds of presumed unilateral disease, with peripheral nonperfusion >two disk diameters in contralateral eyes.[7] There is a consensus that Coats' is non-familial, but authors diverge on whether the condition is idiopathic or genetic. Mounting evidence suggests a causative mutation in the NDP gene encoding for norrin, found also in Norrie's disease, resulting in abnormal retinal vasculogenesis.[8] Microscopically this leads to dysfunctional pericytes and vascular endothelial cells, subsequent intraretinal and sub-retinal serosanginous leakage, ischemia, aneurysms and progressively worse sequelae.

Early disease is often asymptomatic and diagnosed during routine examination. A classic finding is the loss of the normal red-reflex. It is replaced by a yellow reflex upon direct ophthalmoscopy and in flash photography as light reflects off of lipid exudation. The most common signs are decreased visual acuity, strabismus and leukocoria. Other signs include pain, nystagmus and heterochromia of the iris. On ophthalmoscopy, retinal telangiectasia, tortuosity, avascularity and aneurysmal dilation of retinal vasculature as well as vascular sheathing may be noted in early disease. More advanced disease may exhibit "light bulb" telangiectasia, named after large yellow exudates adjacent to dilated telangiectatic vessels *(See Figures*

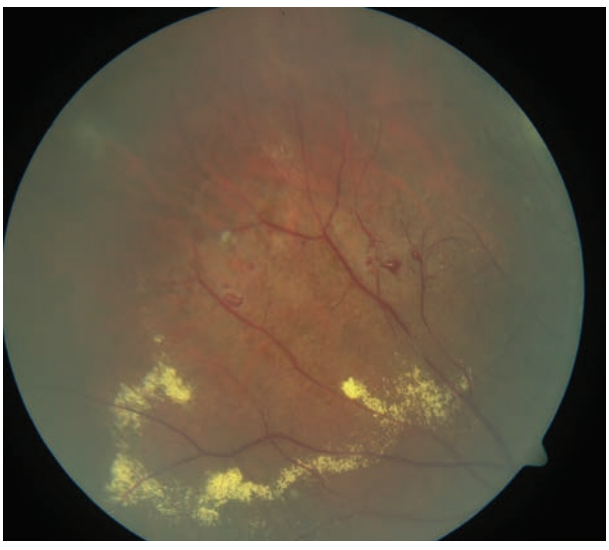

Figure 1. "Light bulb" telangiectasias found in Coats' Disease.

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1 & 2). Ultimately, this disease can progress to macular fibrosis, macular holes, retinal detachment and vitreous hemorrhage. The eye may become blind and painful due to neovascular glaucoma.

Clinical Findings and Diagnosis

Clinical diagnosis based on history and exam alone is not usually sufficient, as other pathologies must be properly ruled out. Even the most experienced observer may not be able to distinguish between retinoblastoma and advanced Coats' disease. There are some clinical clues that may help direct the clinician toward a diagnosis of Coats', however. Familial exudative vitreoretinopathy (FEVR) may present with leukocoria and exudative retinal detachment, but usually is bilateral and associated with more tractional elements. Persistent fetal vasculature (PFV) may also present with leukocoria but lacks exudation, is often associated with central hyaloid canal and a smaller eye, and is usually accompanied by early cataract. Vasoproliferative tumors such as capillary hemangiomas and cavernous hemangiomas may also resemble Coats', but there will usually be an absence of exudation and they occur more commonly in the peripapillary area, whereas Coats' tends to affect the temporal macula and mid-periphery.

Computerized tomography is often used to rule out retinoblastoma, due to calcium content found in solid tumors but not classically present in Coats'. However, CT may miss nearly 50 percent of retinoblastomas that present without calcification,[9] and conversely, Coats' disease can present with intraocular bone formation. Magnetic resonance imaging with gadolinium contrast has been described as superior to CT in ruling out retinoblastoma[10] due to increased contrast in enhancing solid tumors and in demonstrating subretinal exudation of Coats'. Fluorescein angiography is used for assessment of disease progression; early hyperfluorescence with patchy hypofluorescence from exudation can suggest telangiectasia, and "light bulb" dilations aneurysms can signal more advanced, larger vessel disease. Ultrasound is used to help rule out intraocular masses suggestive of retinoblastoma and reveal subretinal opacities representing exudates and retinal detachment from Coats'. Optical coherence tomography is used to detect macular edema, monitor response to treatment and even to perform intraoperative exam under anesthesia.[11] Of note, fine-needle aspiration is not typically recommended if there is risk of retinoblastoma or retinal detachment, but may be potentially used as an adjunct when other testing is equivocal.

Table 1. Coats' Disease Classification System

Stage	VA 20/200 or worse	Eventual enucleation
Stage 1. Retinal telangiectasia only	0%	0%
Stage 2. Telangiectasia and exudation		
A. Extrafoveal exudation	30	0
B. Foveal exudation	66	0
Stage 3. Exudative retinal detachment		
A. Subtotal detachment		
1. Extrafoveal	70	8
2. Foveal	70	0
B. Total detachment	94	11
Stage 4. Total detachment; glaucoma	100	78
Stage 5. Advanced end-stage disease	100	0

Prognosis

In an effort to more clearly describe risk factors for poor outcomes in Coats' disease, Jerry Shields, MD, and coauthors proposed a five-stage classification system.[12] In their retrospective consecutive study of 150 patients, the majority (76 percent of eyes) achieved anatomic improvement or stability, though poor final visual acuity between 20/200 and NLP occurred in 64 percent of eyes and enucleation was necessary in 16 percent of eyes. Significant risk factors for poor visual outcome were postequatorial, diffuse or superior pathology; residual subretinal fluid after treatment; retinal macrocysts; elevated intraocular pressure (over 22 mmHg); and iris neovascularization. Interestingly, age of onset of disease does not appear to correlate with final visual acuity.[13] According to the Shields classification system *(See Table 1)*, the incidence of poor visual outcome (equal to or worse than 20/200) was 0 percent in stage 1 eyes, but jumped to 53 percent in stage 2, 74 percent in stage 3 and 100 percent of stages 4 and 5. Armed with this information, the prudent physician should carefully select candidates for therapy and also manage expectations of children and their parents with various stages of Coats' disease.

Treatment

The Shields study also elucidated the optimal use of different treatment modalities based on stage of disease. The goal for mild disease (Stage 1 or 2) is prevention of retinal detachment, achieved by laser photoablation and cryotherapy for direct treatment of abnormal vasculature. Laser photocoagulation is preferred in mild cases with limited exudation; Amy C. Schefler, MD, and colleagues showed good results with this treat-

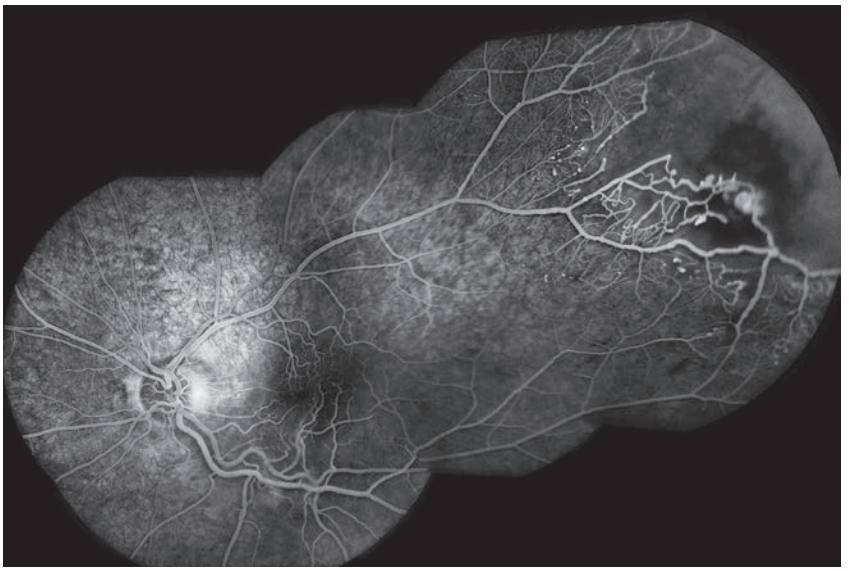

Figure 2. Fluorescein angiogram in the late venous phase demonstrating peripheral "light bulb" aneurysms.

ment modality in 50 percent of their patients[14] and even demonstrated usefulness with subtotal retinal detachment. However, cryotherapy is preferred in mild[15] cases with thicker exudates, in cases where laser photocoagulation is not available and in more advanced cases. Vitreoretinal surgery is typically required in cases of total retinal detachment or significant epiretinal membrane, while enucleation is performed in selected cases with neovascular glaucoma causing intractable pain, nausea and vomiting. There is ongoing research in cyclodiode treatment of these cases, with successful IOP lowering and avoidance of enucleation.[16]

Adjunctive therapy now includes intravitreal triamcinolone and antivascular endothelial growth factor medications. Intravitreal triamcinolone has been shown to help in absorption of subretinal fluid, reducing macular edema[17] and exudates,[18] and improving visual acuity.[19] In a multitude of recent studies, anti-VEGF has also been shown to produce similar results.[20-29] Anti-VEGF agents have a direct impact on vascular leakage and may yield resolution of Stage 3 and 4 disease. The physician must, however, be aware of the potential side effects of these agents, including infection, cataract and IOP elevation due to intravitreal triamcinolone. Emerging studies on the use of intravitreal dexamethasone implant (Ozurdex) as adjunctive treatment are promising.[30] It must be remembered that few studies looked at these treatments in isolation from the mainstays of therapy: cryotherapy and laser photocoagulation. REVIEW

Dr. Chay is an ophthalmology resident and Dr. Shrier is a retina attending, both at SUNY Downstate Medical Center.

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Alternative Surgeries for Uveitic Glaucoma

Studies suggest that alternatives to trabeculectomy and tube shunts may sometimes work very well.

Shan C. Lin, MD, San Francisco

Most ophthalmologists don't encounter uveitic glaucoma very often. When we do, if the uveitic glaucoma hasn't been previously treated, it makes sense to address the glaucoma in a traditional manner first, starting with eye drops to reduce elevated intraocular pressure and therapy to quiet the inflammation. But if we reach maximum medical glaucoma therapy and this is still not effective enough to maintain a safe level of intraocular pressure, then we're forced to consider surgery.

Of course, uveitic glaucoma is a bit different from primary open-angle glaucoma. Among other things, the cause of the glaucoma can be difficult to determine. It could be that preexisting inflammation led to the elevated pressure and glaucoma; or it could be that steroids being used to treat the inflammation led to the glaucoma. The cause may even be a combination of both factors.

When you're treating a patient with uveitic glaucoma and you've reached the point at which surgery is necessary, the first surgery one might consider is trabeculectomy or implantation of a tube shunt. However, uveitis by definition is inflammation in the eye, and inflammation leads to a higher rate of post-surgery failure. Tubes and trabs, for example, have a higher failure rate when used to address uveitic glaucoma than when used to treat primary open-angle glaucoma. Thus, to increase the odds of surgical success we need to try to fight the inflammation with tools such as anti-inflammatory drugs. Ironically, we often use the same steroids that can worsen the glaucoma as a way to help fight the inflammation and reduce the likelihood of surgical failure.

Given that surgical options such as tubes and trabs are more likely to fail in cases of uveitic glaucoma, it's worth considering alternative options. A number of clinicians have looked at the effectiveness of other surgeries in recent years, and although the number of cases in some of their studies has been small—uveitic glaucoma is relatively uncommon, after all—their results suggest that other approaches may be worth considering.

Managing Childhood Uveitis

Goniotomy is a procedure that's considered standard of care for many types of childhood glaucoma. It's often used, for example, to treat congenital glaucoma, which is a maldevelopment of the angle. In this approach the surgeon basically uses a knife to cut away the maldeveloped tissue, opening up what would otherwise be a closed angle. But when childhood glaucoma is associated with uveitis, most surgeons don't usually think of goniotomy as the primary procedure. After all, uveitic glaucoma is an inflammatory disease that causes high pressure through various mechanisms. An inflamed eye may produce more fluid, for example; and inflammation could result in trabeculitis, an inflammation of the trabecular meshwork. But the results of several recent studies suggest that goniotomy is actually a good surgical choice for addressing childhood uveitic glaucoma. In fact, goniotomy may be the best first-line treatment.

One of these studies on goniotomy was published in 2013;[1] it was conducted by Dr. Sharon F. Freedman's group at Duke University School of Medicine. This was a retrospective study of 36 patients

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with juvenile uveitic glaucoma who underwent one or more IOP-lowering surgical procedures; 31 of them had goniotomy as their first procedure. Success was defined as an IOP less than 21 mmHg with controlled inflammation, no need for further IOP-lowering surgery and no devastating complication.

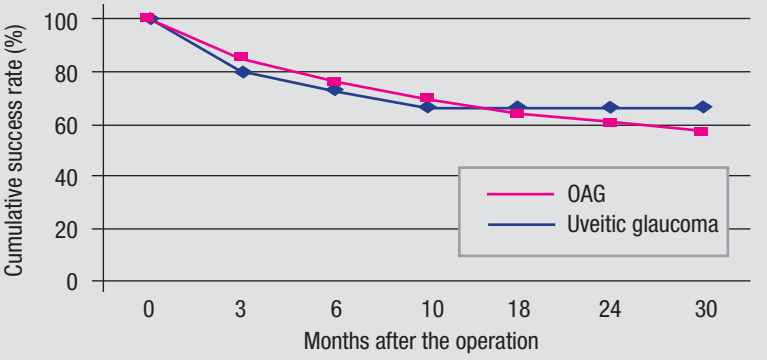
With a mean follow-up of 5.6 years, 15 individuals in that group (48 percent) needed no further procedure to maintain an IOP of less than 21 mmHg with controlled inflammation. Nine others (29 percent) needed a second goniotomy. At 10 years, 69 percent of those treated with one or two goniotomies met the criteria for success. For a childhood form of glaucoma, these results are impressive.

Another retrospective study conducted by Dr. Freedman in 2002 evaluated the success rate of 19 goniotomies performed on 16 eyes of 12 patients whose mean preoperative IOP was 32.3 ±4.6 mmHg.[2] Surgical success was achieved in 12 eyes (75 percent) with a mean postoperative IOP of 12 ±2.5 mmHg. In 10 of them (60 percent), surgical success was achieved after a single goniotomy.

Another retrospective study was conducted several years ago by Ho Ching Lin and colleagues at the Singapore National Eye Center.[3] This study evaluated 54 goniotomies performed by a single surgeon, treating refractory childhood uveitic glaucoma in 40 eyes of 31 patients. The surgery met their definition of success (IOP no greater than 21 mmHg) in 29 eyes (72 percent); 22 of them (55 percent) required no medications to achieve this, while seven others (18 percent) required a mean of 1.6 ±1.1 medications. Factors that led to significantly better outcomes included phakic eyes; fewer peripheral anterior synechiae; no prior surgery; and patient age less than 10 years.

These outcomes suggest that goniotomy is a reasonable option to consider when treating childhood glaucoma associated with uveitis.

Ahmed Valve Efficacy: Open-Angle Vs. Uveitic Glaucoma



In this retrospective, comparative, case-controlled study, 15 eyes with chronic uveitis and 53 eyes with uncontrolled open-angle glaucoma underwent Ahmed glaucoma valve implantation. No significant differences in intraocular pressure were found at three, six, 12, 24, or 30 months. The only complication that differed significantly was tube removal, which occurred more often in the uveitic glaucoma group (p=0.018). (Rachmiel et al, 2008)4

Tube or Trab?

When dealing with surgery for uveitic glaucoma—in adults or children—one question that may arise is whether to perform a trabeculectomy or implant a tube shunt. Unfortunately, the Tube vs. Trabeculectomy study didn't include uveitic glaucoma. However, some inferences related to this question can be drawn from a few small studies that were published in recent years.

One 2008 study conducted at Toronto Western Hospital by Rony Rachmiel, MD, and colleagues was a large retrospective comparison of the success rate of Ahmed shunts in 25 eyes with uveitic glaucoma vs. 53 eyes with primary open-angle glaucoma.[4] They found no significant difference in the success rate of the implants, with the sole exception that there were significantly more tube removals in the uveitic glaucoma group. In my experience, this is related to more frequent exposure of the tube or plate in uveitic patients. But despite this difference, the overall success rate was very similar.

Other studies have also addressed this question:

- In a 1999 study conducted at the Massachusetts Eye and Ear Infirmary,[5] 21 eyes of 19 patients whose uveitis was controlled by immunomodulatory therapy underwent Ahmed valve implantation. With an average follow-up of 24.5 months, all 21 eyes had IOPs between 5 and 18 mmHg; average medications were reduced from 3.5 before surgery to 0.6 after.
- A 2007 retrospective study of 60 eyes of 60 patients, also conducted at the Massachusetts Eye and Ear Infirmary,[6] evaluated the long-term success of Ahmed valves in uveitic glaucoma patients. This study found that at one year vs. four years, 77 percent and 50 percent of eyes, respectively, had an IOP between 5 and 21 mmHg. Excluding eyes that had serious complications lowered the success rates to 57 percent and 39 percent at the two time points.
- A 2002 study conducted at the Bascom Palmer Eye Institute in Miami focused on 24 eyes of 24 uveitic glaucoma patients receiving Baerveldt implants.[7] That study found success rates of 95.8 percent at three

months and 91.7 percent at six, 12 and 24 months. (Success was defined as an IOP between 5 and 21 mmHg, with or without medications, without need for further glaucoma surgery.)

Other Surgical Options

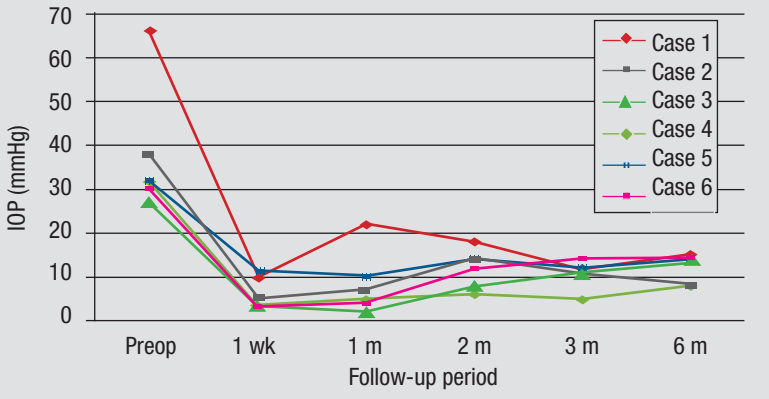
Other studies have provided some information regarding the potential of different surgeries for uveitic glaucoma:

• ***Comparing trabeculectomy, trabeculotomy and Trabectome.*** A 2014 study conducted at Tohoku University Graduate School of Medicine in Sendai, Japan, evaluated 47 eyes of 47 uveitic glaucoma patients who underwent either trabeculectomy, trabeculotomy or Trabectome surgery, with an average of 40 months of follow-up.[8] The success rates for the surgeries (with success defined as an IOP less than 21 mmHg and no need for additional surgery) were: trabeculectomy 83 percent; trabeculotomy 63 percent; and Trabectome 75 percent. Significant risk factors for failure included male sex (p=0.02), age less than 45 years (p=0.0009), nongranulomatous uveitis (p=0.04), and postoperative inflammation (p=0.01).

Interestingly, the Japanese have had a very positive experience with trabeculotomy for adult forms of glaucoma, and they have produced a body of literature that supports this. Most glaucoma specialists in the United States would find that strange. Over here, that procedure is traditionally reserved for children, because studies have shown that after about age 10 it really doesn't work well.

• ***Trabeculodialysis.*** Another relevant study was reported in a poster at the 2015 annual meeting of the American Glaucoma Society. The study was conducted by Andrew Iwach's Glaucoma Research & Education Group in San Francisco (the lead author was Lian Chen, MD).

Bevacizumab as an Adjunct to Trabeculectomy



In this prospective, observational case series, six cases of glaucoma—three of them uveitic glaucoma (cases #3, #4 and #6)—received a subconjunctival injection of bevacizumab at the time of trabeculectomy. All six cases had controlled pressures on no medications at six months. (Choi JY et al, 2010)10

This retrospective study of 10 uveitic glaucoma eyes of 10 patients evaluated the success of using trabeculodialysis to treat the disease, with a 5.7-year follow-up. This procedure is in some ways very similar to goniotomy; the surgeon goes in with a knife and cuts at the level of the trabecular meshwork, essentially unhooking it from its normal insertion. Types of uveitis treated in this study included juvenile rheumatoid arthritis, herpetic uveitis and idiopathic uveitis.

The data showed that trabeculodialysis led to a 70-percent success rate (seven of 10 eyes) without the need for further surgery. Of those seven eyes, four required some medication to maintain the outcome. (The authors note that this surgery has a very favorable safety profile, making it worth considering before attempting a traditional surgery such as trabeculectomy or a tube shunt.) These results are very similar to the results found in the Japanese study, and the surgeries are somewhat similar; both attempt to treat the trabecular meshwork with either a knife or a device such as the Trabectome or a trabeculotome.

• ***Canaloplasty.*** Canaloplasty for uveitic glaucoma is another approach that requires thinking outside the box. A recent retrospective study of 19 eyes of 15 patients, conducted at the University of Montreal, evaluated the effectiveness of this type of surgery for treating herpetic, noninfectious and idiopathic uveitic glaucoma.[9] The surgery consisted of 360 degrees of viscodilation followed by a tension suture. They found that 74 percent of the surgeries were a complete success; 11 percent were a partial success; and 16 percent were failures. There was a low complication rate.

All of the surgical options mentioned here produced reasonably good results. Given the difficulty in treating uveitic glaucoma, success of these surgeries (including some that are relatively new) in the range of 65 to 80 percent success is excellent.

Adjunctive Drugs

As you know, anti-VEGF drugs such as Avastin, Lucentis and Eylea are now being used to treat macular degeneration and diabetic retinopathy. However, there's also a body of literature looking at these agents as adjuncts for glaucoma surgery. Like

mitomycin-C, they can help prevent scarring by preventing new blood vessels from growing, vessels that would bring in more inflammatory factors. Furthermore, they may also directly prevent inflammation.

In terms of uveitic glaucoma, there is one very small prospective observational case series that looked at this possibility; only three eyes in this study had uveitic glaucoma.[10] Nevertheless, the results seem positive enough to warrant further study. Subjects received a subconjunctival injection of 1.25 mg of bevacizumab at the time of trabeculectomy. (Mitomycin was also used as part of the trabeculectomy surgery.) Pressures dropped significantly right after the surgery, and at six months follow-up all pressures were between 8 and 16 mmHg, with functioning blebs and no subjects on IOP-lowering medications. *(See table, facing page.)* Perhaps more interesting, the blebs looked relatively avascular, with mostly white eyes and little inflammation, which is likely attributable to the anti-VEGF drug.

Of course, it's impossible to draw any firm conclusions from such a small sample and short follow-up, but since this is a prospective observational study, I consider these results promising and worthy of further testing. Based on these results, I believe adjunctive use of anti-VEGF drugs may show some promise in the treatment of uveitic glaucoma.

It's also important to note the arrival of new treatments for inflammation, such as tumor necrosis factor inhibitors. These drugs suppress the immune system response to TNF, which appears as part of the inflammatory response, and they can have a profound impact on patients with uveitic glaucoma.

For example, I was following a child with a history of uveitis who had done poorly and was also suffering from glaucoma. Once these anti-TNF drugs became available, he started getting systemic treatment with one of them. His vision improved, his cystoid macular edema got better and his IOP was better controlled, probably because the inflammation was reduced. The drug had a powerful effect on his inflammation status, without the side effects associated with using steroids. For him it was almost a miracle drug.

Steroids, of course, are another challenge when dealing with uveitic glaucoma. They're very good at treating certain diseases, uveitis included, and they can help to prevent scarring after surgery. However, they can also cause elevated pressure and cataracts. Using steroids therefore becomes a tricky balance for the uveitis specialist and glaucoma specialist, because steroids can be both friend and foe.

Certainly after the surgical treatment of glaucoma with a filtering procedure, heavy use of steroids is recommended. At that point, even if steroid use is the cause of the glaucoma, you've treated the elevated pressure in a very definitive way, at least in the short term. You've created a hole in the eye, and the pressure's likely to be around 10 mmHg the next day. Steroids are favorable in this situation because they can help prevent uveitic inflammation, which can cause more failure. Certainly when treating primary open-angle glaucoma with a trabeculectomy it's been shown that pretreating with steroids leads to a better surgical outcome. (Of course, over the long haul as the inflammation is controlled, the surgeon should taper the steroids appropriately to avoid continued high pressures and steroid glaucoma.)

Broadening Our Options

Uveitic glaucoma definitely comes with some unique challenges. For example, when treating other forms of glaucoma, factors such as age make a difference in our approach to treatment. Older patients don't scar as much as younger patients, which can affect our choice of surgical options, such as how much mitomycin to use during surgery. But factors such as age matter less when you're managing uveitic glaucoma, in part because the uveitis is a major driving force behind the scarring, overriding the reduction in scarring you would normally find in an older individual.

This is part of the reason it's worth considering options besides the standard choices such as trabeculectomy and tube shunts. An uncommon form of glaucoma such as uveitic glaucoma is difficult to study because of the small number of patients most practices encounter; it will be difficult for many groups to do prospective, randomized, controlled trials involving uveitic glaucoma. Nevertheless, there are surgical alternatives, and the evidence—albeit limited—suggests that they may work as well, or better, than the traditional options. REVIEW

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Laser Treatment for Post-PK Astigmatism

Expert tips for using both excimer and femtosecond technology to deal with troublesome post-transplant cylinder.

Walter Bethke, Managing Editor

Penetrating keratoplasty can be a great help to the vision of many patients, but can also induce a great amount of postop astigmatism due to the biomechanical forces present in the new graft. Surgeons say that, though these patients' astigmatism will never be as easy to treat as an untouched cornea, you can often get them to a point at which they can comfortably wear thinner spectacles or tolerate contact lenses. Here are their tips for accomplishing this.

Define the Problem

Before you attack the astigmatism, surgeons say it's important to find out the exact nature of the cylinder first. Also, don't proceed with corrective refractive surgery until the sutures are out and the vision has proven to be stable.

"Is the astigmatism the result of the sutures being strong in one section or has the graft slipped in another area?" asks London surgeon Sheraz Daya. "If it's slipped, then that needs to be fixed first. This is because, if you decide to do laser surgery, invariably, the area that's slipped is the area in which you're going to have to do laser to reshape it by doing a lift. That could be a problem, because it's probably a weak spot in terms of how the graft has adhered. If you start thinning that area out further, it will keep lifting off and you can get ectasia in that area.

"Also, see if there's a step in the incision," Dr. Daya adds. "Home in on the negative axis of astigmatism, and determine if the graft is apposed properly 100 percent or if it's only been sutured partially, which has the potential for further slippage. I'll do an [ocular coherence tomography] exam using Visante in the negative axis to see if there's anything I'm missing. I'll then look at the steep axis. If it's steep because it's fibrosed, that's good; I'm much more comfortable that the graft is going to stay stable after I do laser surgery on it."

The Excimer Approach

Surgeons say PRK or LASIK can be helpful in many patients, even if it only "debulks" their astigmatism down to a normal level.

Majid Moshirfar, MD, co-director of the cornea and refractive surgery division and professor of ophthalmology at the University of California, San Francisco Medical Center, says he alters his approach based on the level of astigmatism. For high astigmatism post-PK, in the range of 8 to 12 D or more, he will consider performing a wedge resection and placing compression sutures. "But for patients with lower levels of astigmatism, I think an ablative procedure is a good option," he says. "With LASIK, we now have the ability to make flaps inside the diameter of the donor graft, a capability we didn't have with the microkeratome," he says. "Now, we make a 7.3- to 7.5-mm flap inside the donor. To perform LASIK in such a patient, I'll usually mark the donor-host interface so I know where the edge of it is. Then I center the procedure not necessarily on the apex of the cornea or the center of the pupil. Often it's the center of the donor. Then I dock the femtosecond laser and program a very thin flap located within the graft. We're very happy with the results from this."

If the surgeon chooses to go the surface-ablation route, surgeons say to be sure to use mitomycin-C in

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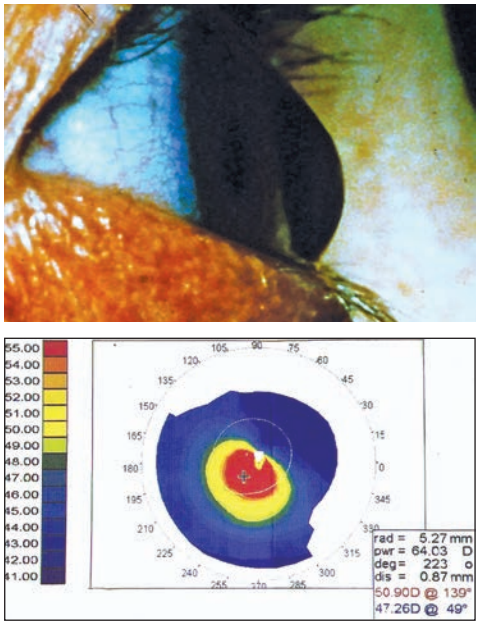
these patients. "You need to use mitomycin-C in the post-PK patient undergoing PRK because he's at a higher risk for haze and scar formation," says Charleston, W.V., corneal specialist Heather Skeens. "Also, they're at risk for regression of the treatment, so the mitomycin is critical. The other aspect that's important is to note that the topographic astigmatism and the astigmatism in the refraction are often different. If you treat the patient based on the refraction only, you will usually end up with an undercorrection. So, take into account the topographic astigmatism, because it will usually be higher, and understand that you may need to fudge a little toward the topographic astigmatism when planning the treatment." In her PRK protocol, Dr. Skeens debrides the epithelium with alcohol in a corneal well for 20 seconds, with a treatment zone of about 6 mm. For the mitomycin application, she soaks a corneal pledget in 0.02% mitomycin-C and then applies it to the cornea for 20 seconds. She then removes the pledget and rinses the eye with a bottle of balanced salt solution.

In terms of the limits of PRK and LASIK, surgeons say you can usually correct, at most, 5 to 6 D. However, they're quick to add that going from something like 8 D down to 2 D can make a big difference for these patients. "Even though we'd like to, we don't often get 20/20 vision in these patients," says Dr. Daya. "There are too many variables involved. But if you can reduce the refractive error to a low level where they can get into thin spectacles, that's a success. You also want to make sure that they stay stable."

Dr. Skeens says one of the biggest limitations is that these laser interventions aren't usually covered by insurance. "The patient's physician can send a letter to the insurance company to try to get preapproval to get it covered," she says. "Initially, the physician has to demonstrate that the patient either doesn't do well with a hard contact lens, or can't put the contact lens in his eye because of dexterity issues. You also have to demonstrate that the rest of the eye is healthy, the retina's healthy, et cetera, and that there will be a positive change in vision. Even with these being satisfied, it's hard to get an insurance company to cover it, and often ends up being a cash-pay procedure."



Some surgeons say patients who have undergone PK for keratoconus (top) or ectasia (bottom) may do better with a PRK for their postop astigmatism.

The Femtosecond Alternative

Surgeons are getting more comfortable with nomograms for corneal incisions created by a femtosecond laser, and say these can be a good option in certain post-PK patients.

"For levels of astigmatism in the 6- to 8-D range, where the myopia component is equivalent or less than the astigmatism, I think the excimer laser doesn't give that good of a result," says Dr. Moshirfar. "This is because at that level of corneal astigmatism, in most cases, the irregularity and non-orthogonal nature of the astigmatism is such that ablative procedures won't be good enough. For this middle range of astigmatism—greater than 4 D but not more than 8 D—I think femtosecond relaxing incisions can be very useful to the surgeon. The key with these incisions is that you need to know how to place them correctly. You can't make them concentric with respect to the limbus or to the graft. You need to place them relative to the corneal apex. For these cases, I determine the steep axis, then mark the apex of the cornea with a marking pen. I then dock the cornea with the femtosecond laser platform, then place the arcuate incisions. I determine the number of degrees for the incisions based on the anterior keratometry of the topography. I usually bring these incisions all the way to the epithelium so that, later on, I can go in with my Colibri forceps and open them. I don't usually open the incisions in the OR; instead I will wait a day or two, see the patients in the clinic and decide if opening them is necessary. Ninety-nine percent of the time, I open them."

Dr. Daya says the post-PK patient is one instance where intrastromal femtosecond incisions can actually have a significant effect. "If there's not that much fibrosis in the graft-host interface, I'll do one clock hour per diopter," he says. "So, for 6 D, it will be two quadrants of three clock hours—that's the maximum incision size and number you can do on the hardware. However, in these corneas you will get more than 1 D per clock hour; because when you're in the middle of the cornea or in the graft, there are no vessels, the wound healing is poor and the magnitude of effect is quite high. Often, it doesn't look like it's had much of an effect on the first day. But wait a month and it will have changed a lot." REVIEW

What I Teach My **Fellows**

Our series continues with one of the leading retina surgeon's key messages to new ophthalmologists.

By Steve Charles, MD

Be a compassionate, ethical doctor first, ophthalmologist second and vitreoretinal surgeon third.

Retinal patients often have glaucoma, often mismanaged or unrecognized by their primary ophthalmologist or optometrist, as unbelievable as this might seem. Ocular surface disorders are incredibly common and affect vision, not just comfort, as well OCT imaging quality.

Many vitreoretinal surgeons have missed a lymphoma by performing a misdirected uveitis workup seeking vaguely connected autoimmune disorders. A central retinal artery occlusion or branch retinal artery occlusion needs carotid and aortic valve ultrasonic imaging to detect atherosclerotic plaque, however minor, and consideration of anticoagulation by an internist.

It is unacceptable to miss an aneurysm, choroidal metastases or papilledema; you must think about the patient not just the eye or retina. Communicate with a neurosurgeon, cardiologist or oncologist directly. To avoid delays and prevent crucial medical problems being overlooked, resist the habit of just ordering tests and instead, "order doctors."

Visualization is essential in vitreoretinal surgery but not an argument to do a phaco-vit in a majority of cases.

Today's patients expect near-perfect refractive outcomes. Don't dabble in cataract surgery; if you cannot see well enough to perform high-quality vitreous surgery, send the patient for cataract surgery before performing macular surgery. Phaco-vit surgery does not produce consistent, precise refractive outcomes that patients want and deserve.

Vitrectomy does not cause cataract; it causes rapid progression of pre-existing nuclear sclerosis. Do not hesitate to do a lensectomy in inflammatory, proliferative vitreoretinopathy, complex trauma or uveitis cases. Do not leave capsule, touch iris or implant an intraocular lens in severe uveitis vitrectomy cases. Contact-based macular visualization produces better lateral and axial resolution (modulation transfer function) than non-contact visualization (BIOM, Oculus, or ReSight, Carl Zeiss) by eliminating all corneal asphericity. Contact-based wide angle-visualization provides 10 degrees greater field of view than non-contact and better resolution.

This article has no commercial sponsorship.


Vitreoretinal surgery is not an extreme sport or fame game.

Surgery is not about making a show-and-tell video or doing combined procedures, endoscopy or intraoperative optical coherence tomography; it is about focusing on the primary surgical goal—restoring or preserving vision. Overly aggressive posterior vitreous detachment creation causes many iatrogenic retinal breaks and excessive use of silicone oil.

Linear thinking produces bad outcomes; multi-branching algorithms are essential for problem solving.

Understanding, concept-based learning is essential and is far more effective and utilizable than rote memorization, content-based learning. Vitreoretinal surgeons should understand the physics behind surgical fluidics and imaging, the physical chemistry of silicone oil, gas and liquid perfluorocarbon, and the biology of angiogenesis and apoptosis. The surgeon must learn how to set up and operate all vitreoretinal machines to avoid mistakes and dependence on the OR staff.

There is no standard approach or "gold standard" in medicine.

Technology, techniques and bioscience rapidly evolve and the surgeon must evolve in parallel. Vitbuckles are obsolete; they produce poor refractive outcomes, pain and strabismus; are not cost effective because of long operating times; and definitely not minimally invasive.

Lifetime learning is essential to the practice of medicine.

It is not just about CME hours, it is about attending many meetings every year, interacting with trusted colleagues, incessant reading, learning the science behind diseases and therapeutic tools. Lifetime learning helps patients and is inherently interesting, not drudgery.

Surgery is not about making a show-and-tell video … it is about restoring vision.

Surgical goals and techniques are diagnosis-dependent.

The highest possible cutting rates should be used for all tasks and all cases except for dense fibrous tissue after the vitreous has been removed. Virtually all macular surgery patients require brilliant blue assisted internal limiting membrane peeling using ILM forceps peeling; the indications include epimacular membrane, partial and full thickness macular holes, vitreomacular schisis and vitreomacular traction syndrome.

Indocyanine green can be toxic and should be replaced by brilliant blue for ILM staining; triamcinolone particulate marking is not specific for ILM. Peripheral vitreous shaving is not indicated for macular surgery patients but retinal detachment patients with or without PVR require removal of the majority of peripheral vitreoretinal traction.

Scissors delamination skills are essential for diabetic traction retinal detachment surgery even though 25/27 ga. conformal and foldback cutter delamination using high cutting rates allows the surgeon to safely remove substantial epiretinal membrane. Endophotocoagulation is preferable to laser indirect ophthalmoscope for retinopexy and panretinal photocoagulation in a vitrectomy setting. Endophotocoagulation is better than diathermy for hemostasis because it reduces collateral damage and is non-contact. Reoperation for PVR or epimacular membrane in patients with silicone oil should be performed "under" oil, not by removing oil and reinjecting it. Operation under oil is a subset of interface vitrectomy; vitrectomy under PFO and vitrectomy under air are crucial parts of the surgeon's technique repertoire. Medium-term perfluoro-n-octane (two weeks) is ideal for all inferior retinal detachments including phakic eyes, PVR, primary rhegmatogenous retinal detachments, inferior, nasal and temporal giant breaks.

Play by the rules of coding and billing but do not obsess over finances.

Income will come if the focus is on hard work and high quality, ethical, compassionate patient care. REVIEW

Dr. Charles is a clinical professor of ophthalmology at the University of Tennessee Hamilton Eye Institute. Contact him at: Charles Retina Institue, 6401 Poplar Ave., Ste 190, Memphis, Tenn. 38119. scharles@att.net

Dry-eye Disease and Reduced Cell Density

A cross-sectional control study done by researchers from the Massachusetts Eye and Ear Infirmary, evaluating corneal endothelial cell density in patients with dry-eye disease compared to an age-matched control group, found significant reduction in corneal ECD in dry-eye disease patients that correlates with clinical severity.

This study involved 90 eyes of 45 patients with moderate to severe dry-eye disease (aged 53.7 ±9.8 years) and 30 eyes of 15 normal controls (aged 50.7 ±9.8 years). All subjects had a complete ophthalmic evaluation, including symptom assessment using the Ocular Surface Disease Index and corneal fluorescein staining. In addition, laser scanning *in vivo* confocal microscopy was performed to measure the density of the following parameters in the central cornea: endothelial cells; sub-basal nerves; and sub-basal immune dendritic cells.

Corneal ECD was significantly lower in the dry-eye disease group (2,595.8 ±356.1 cells/mm^2) than in the control group (2,812.7 ±395.2 cells/mm^2; p=0.046). The dry-eye disease group showed significantly lower corneal sub-basal nerve density (17.1 ±6.9 mm/mm^2) compared to the control group (24.7 ±4.4 mm/mm^2; p<0.001). Dendritic cell density was significantly higher in the dry-eye group than in the controls (111.7 ±137.3 vs. 32 ±24.2 cells/mm^2; p=0.002). There were statistically significant correlations between corneal ECD and dry-eye severity parameters including the OSDI score (r_s=-0.26; p=0.03) and corneal fluorescein staining (r_s=-0.28; p=0.008).

Am J Ophthalmol 2015;159:1022-1026.
Kheirkhah A, Saboo U, Abud T, Dohlman T, et al.

OCT-3 to Evaluate Temporal Retinal Thickness

A prospective study evaluating temporal macular retinal thickness using optical coherence tomography-3-generated superior-to-inferior retinal thickness (S/I RT) ratios successfully reproduced the structural damage in eyes with early and advanced glaucoma field defects.

Forty normal eyes, 40 eyes with early glaucomatous visual field defects and 33 eyes with advanced visual field defects were included in this study. All participants underwent complete ocular and visual field examinations and OCT-3 imaging on the same day. A 3x3-mm area temporal to the foveal reflex was scanned with the OCT-3 using six horizontal, equally spaced raster lines. Retinal thickness was evaluated at points 500 µm apart for each line and S/I RT ratio computed between similar points above and below the fovea for each patient. One-way ANOVA was used to compare S/I RT ratio between the normal, early and advanced glaucoma eyes.

Average retinal thickness increased progressively as points temporal to the fovea were scanned. There was a statistically significant difference between the average superior and inferior retinal thickness at points 1,500, 2,000 and 2,500 µm temporal to the fovea in both early and advanced glaucoma eyes (p<0.05) with corresponding significant differences in the S/I RT ratios when compared with the normal participants (p<0.017). This suggests OCT-3 can complement optic disc scanning protocols in diagnosing glaucoma at an early age.

J Glaucoma 2015;24:257-261.
Sihota R, Naithani P, Sony P, Gupta V.

Using Omega-3s to Improve Contrast Sensitivity in MGD

Indian researchers at the World Cornea Congress presented results from a study concluding that oral supplementation with omega-3 fatty acids significantly improves contrast sensitivity under both photopic and mesopic testing conditions in patients with moderate meibomian gland dysfunction. Tear-film stability was also improved significantly with omega-3 FA supplementation, although no effect was seen on aqueous tear production.

Utilizing a prospective study design, 60 patients with moderate MGD

were allocated alternately to treatment and control groups. Both groups received warm compresses, lid massage and artificial tear substitutes. The treatment group also received oral supplements of 1.2 g omega-3 FA per day. All parameters were recorded at baseline and at 12 weeks, including Ocular Surface Disease Index scores, contrast sensivity testing at three, six, 12 and 18 cycles per degree, tear breakup time, Schirmer test I without anesthesia, corneal and conjunctival staining scores and meibum quality and expressibility.

At the end of 12 weeks, significant improvement in contrast sensitivity was seen in the treatment group in seven of the eight testing conditions (three, six, 12 and 18 CPD photopic and six, 12 and 18 CPD mesopic), whereas in the placebo group, significant improvement was only seen in three of the eight testing conditions (three CPD photopic; six and 18 CPD mesopic). Ocular Surface Disease Index, tear breakup time, ocular surface staining and meibum quality and expressibility improved significantly in both groups, but more so in the treatment group. Schirmer scores showed no significant improvement in either group.

Cornea 2015;34:637-643.

Malhotra C, Singh S, Chakma P, Jain A.

Sustained IOP Rise After Intravitreal Anti-VEGF

An analysis of current literature evaluating sustained and delayed elevation of IOP in patients receiving intravitreal anti-VEGF therapy for neovascular age-related macular degeneration suggests that it is likely a multifactorial process. Within the literature, the incidence of sustained elevation of IOP in patients with neovascular AMD varied from 3.45 percent to 11.6 percent and few patients required surgical management to control IOP. Possible risk factors associated with sustained and delayed elevation of IOP include, but are not limited to, history of glaucoma; phakia; history of glucocorticoid use; and/or extended treatment duration. There are multiple theories explaining the pathogenesis of sustained elevation of IOP, including microparticle obstruction of the trabecular meshwork, intraocular inflammation and transient elevation of IOP. The lack of an effect in some studies may be due to a small cumulative number of injections and/or short follow-up periods; small study size may also be a limiting factor, as this may be a rare event.

Although there may be insufficient data to conclusively determine that intravitreal injection of VEGF inhibitors results in sustained elevation of IOP, the current body of literature supports this theory. Further studies to prospectively investigate sustained elevation of IOP in large, randomized control trials might lead to better understanding of the long-term adverse events associated with intravitreal anti-VEGF.

Retina 2015;35:841-858.

Dedania V, Bakri S.

Comparative Cost-Effectiveness Of Glaucoma Treatments

New York doctors assessed the cost-effectiveness of the 350-mm^2 Baerveldt implant (tube) insertion and trabeculectomy with mitomycin-C with maximal medical treatment, showing that–assuming a willingness to pay $50,000 per quality-adjusted life-years (QALYs)–tube insertion and trabeculectomy are cost-effective compared with medical treatment alone. Trabeculectomy, however, is cost-effective at a substantially lower cost per QALY compared with tube insertion.

The doctors utilized a Markov cohort model with a five-year time horizon to study a hypothetical cohort of 100,000 patients who required glaucoma surgery. The main outcomes and measures were QALYs gained, costs from the societal perspective and the incremental cost-effectiveness ratio of medical treatment, tube insertion and trabeculectomy. Costs were identified from the Centers for Medicare & Medicaid *Current Procedural Terminology* and Ambulatory Payment Classification reimbursement codes and *Red Book* medication costs. The QALYs were based on visual field and visual acuity outcomes. The hypothetical societal limit to resources was included, using a willingness-to-pay threshold of $50,000 per QALY. Costs and utilities were discounted at 3 percent per year. Uncertainly was assessed using deterministic sensitivity analyses.

The mean costs for medical treatment, tube insertion and trabeculectomy were $6,172, $10,075 and $7,872; these amounts resulted in a cost difference of $1,700 (95 percent confidence interval; $1,644 to $1,770) for medical treatment vs. trabeculectomy, $3,904 (95 percent CI; $3,858 to $3,953) for medical treatment vs. tube insertion and $2,203 (95 percent CI; $2,121 to $2,261) for trabeculectomy vs. tube insertion. The mean five-year probability of blindness was 4 percent for both surgical procedures and 15 percent for medical treatment. The utility gained after medical treatment, tube insertion and trabeculectomy was 3.10, 3.38 and 3.30 QALYs, respectively. The incremental cost-effectiveness ratio was $8,289 per QALY for trabeculectomy vs. medical treatment; $13,896 per QALY for tube insertion vs. medical treatment; and $29,055 per QALY for tube insertion vs. trabeculectomy. The cost-effectiveness of each surgical procedure was most sensitive to early and late surgical failure rate and was minimally affected by adverse events, rate of visual field progression or medication costs.

JAMA Ophthalmol 2015;133:560-567.

Kaplan R, de Moraes C, Cioffi G, Al-Aswad L, et al.

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A toddler's earlier accidental trauma leads to complications, prompting a referral to Wills and eventual surgical intervention.

Jinali Patel, MD, Leon Noel, MD, and Alex V. Levin, MD, MHSc

Presentation

A 17-month-old Caucasian male presented for evaluation of a cyst on his left iris. The cyst had been forming on the inferior aspect of his iris over the past several weeks, causing superotemporal displacement of the pupil. The patient's parents had noted their son to have worsening vision and photophobia in the left eye, causing difficulty in compliance with recommended patching of the right eye.

Medical History

The patient was otherwise healthy and with normal development. There was no relevant medical history. He was not taking medications. Family history was noncontributory.

Nine months prior to presentation, the patient sustained an accidental traumatic injury to the left eye, caused by a kitchen knife piercing the left eye. The knife dropped from his mother's hand while she was cutting cooked chicken sprinkled with pepper. The patient presented two days after the initial injury when he developed redness of the left eye. Exam at this time revealed a 4-mm superotemporal, full-thickness, corneal laceration with a peaked pupil and iris prolapse. The anterior chamber was otherwise normal. The ruptured globe was repaired at an outside facility with five interrupted 10-0 nylon sutures. He healed well after his surgery and patching of the right eye was initiated. Six months after initial repair, an inferior iris cyst was noted, prompting a referral to Wills Eye for further evaluation.

Examination

Ocular examination demonstrated a visual acuity of central, steady and maintained OD and central, steady, not-maintained OS. The right eye was normal. The left pupil was reactive but miotic, crescent-shaped and superotemporally displaced. There was no relative afferent pupillary defect. Examination under anesthesia revealed two remaining sutures superotemporally within the cornea. A large, translucent inferior iris cyst measuring 8 mm x 6 mm was noted. Its roof was abutting the corneal endothelium *(See Figure 1)*. The posterior iris pigmented epithelium was stretched and thin and contained one white foreign body. A cilia was found to be embedded in the iris superotemporally, just below a small iris hole. Gonioscopy revealed two superotemporal peripheral anterior synechiae with prominent vascularization of the angle. Dilated retinal examination with scleral depression was within normal limits.

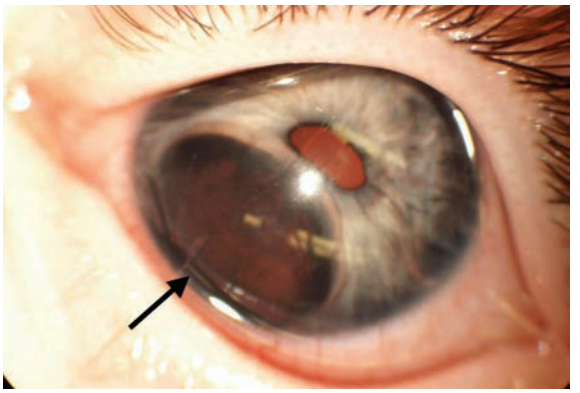

Figure 1. RetCam photograph of the left eye showing a large inferior iris cyst (arrow) causing superior displacement of the pupil.

What is your differential diagnosis? What further workup would you pursue? Please turn to p. 80

Diagnosis, Workup and Treatment

The patient underwent surgical unroofing of the iris cyst. Intraoperatively, three white foreign bodies were noted at the base and rim of the cyst, which were surgically excised and sent for pathologic evaluation. A black foreign body was removed from the iris surface above the pupil. Unfortunately, the specimens were too small to survive processing. The cilia was also removed.

Histopathologic inspection of the anterior cyst wall revealed nonkeratinized squamous epithelium, consistent with the lining of an epithelial cyst and resembling corneal or limbal epithelium. A small segment of basement membrane was also visualized and could represent Descemet's membrane.

Postoperatively, the patient was started on topical and a short course of oral steroids. The cyst has not recurred at one month follow-up.

Discussion

Iris cysts comprise 21 percent of all iris tumors and can be categorized as iris pigment epithelial (IPE) cysts, stromal cysts or epithelial downgrowth cysts. IPE cysts are the most common iris tumor found in children, accounting for 28 percent of iris lesions. Iris cysts in children are more commonly found at the pupillary margin, when compared to the mid-zonal region, which is more common in adults. Pupillary IPE cysts are usually asymptomatic and remain stable without need for intervention.[1] Rarely, they may be associated with vascular aneurysm due to mutation in the ACTA2 gene.

In a 1998 review of cystic iris lesions in children, it was found that only four of 57 iris cysts occurred from secondary causes. Of these four cases, two represented post-traumatic, epithelial ingrowth cysts, as was the case in our patient, while the other two arose from intraocular tumors. Both cases of post-traumatic, epithelial ingrowth cysts were managed with surgical excision. This is in contrast to the management of primary pupillary IPE cysts in children, which are generally observed.[2]

Stromal cysts, which are less common than IPE cysts, tend to enlarge progressively and can grow large enough to fill the anterior chamber and occlude the pupil. Due to their natural clinical course, stromal cysts usually require surgical intervention, which can include aspiration, excision, laser therapy or injection of absolute alcohol to induce sclerosis.[3]

Review of the literature reveals a case of a recurrent IPE cyst in a child after penetrating ocular trauma. On the third and final attempt at surgical excision, retained foreign body material from the initial injury was identified. As there was no subsequent recurrence after complete removal of the cyst with the foreign body, it was thought that the recurrence of the cyst was due to the retained material.[4] Many cases of iris cysts after traumatic injuries are associated with retained cilia. A case of intraocular cilia and iris cyst remained asymptomatic for one year after injury until it presented as an intense uveitic reaction, which promptly resolved with removal of the cilia and iris cyst.[5] Additionally, such iris cysts have been reported to occur as long as four years from the initial injury and inoculation of the cilia into the anterior chamber.[6] Retained cilia are relatively inert and are rarely associated with infection. While cilia can be well-tolerated in the anterior chamber without adverse effects, the risk for iris cysts formation, uveitis and endophthalmitis is not negligible.[6,7]

We believe the cyst in our patient was due to retained foreign bodies, perhaps chicken and pepper, and the deposition of epithelial cells in the anterior chamber at the time of injury. When possible and safe to do so, primary repair of anterior chamber penetrating injuries should include consideration of possible foreign bodies by gonioscopy, ultrasound biomicroscopy and/or irrigation of the anterior chamber to ensure complete inspection and avoidance of retained foreign bodies.[7] If a cyst develops postoperatively, missed retained foreign body should again be considered.

Once iris cysts due to foreign bodies occur, they are best managed with surgical excision with complete removal of the inciting foreign body. Attempts at YAG laser photocoagulation are often unsuccessful.[6,8]

The diagnosis of retained foreign body should always be kept in mind for patients who have had penetrating trauma, even years after injury. REVIEW

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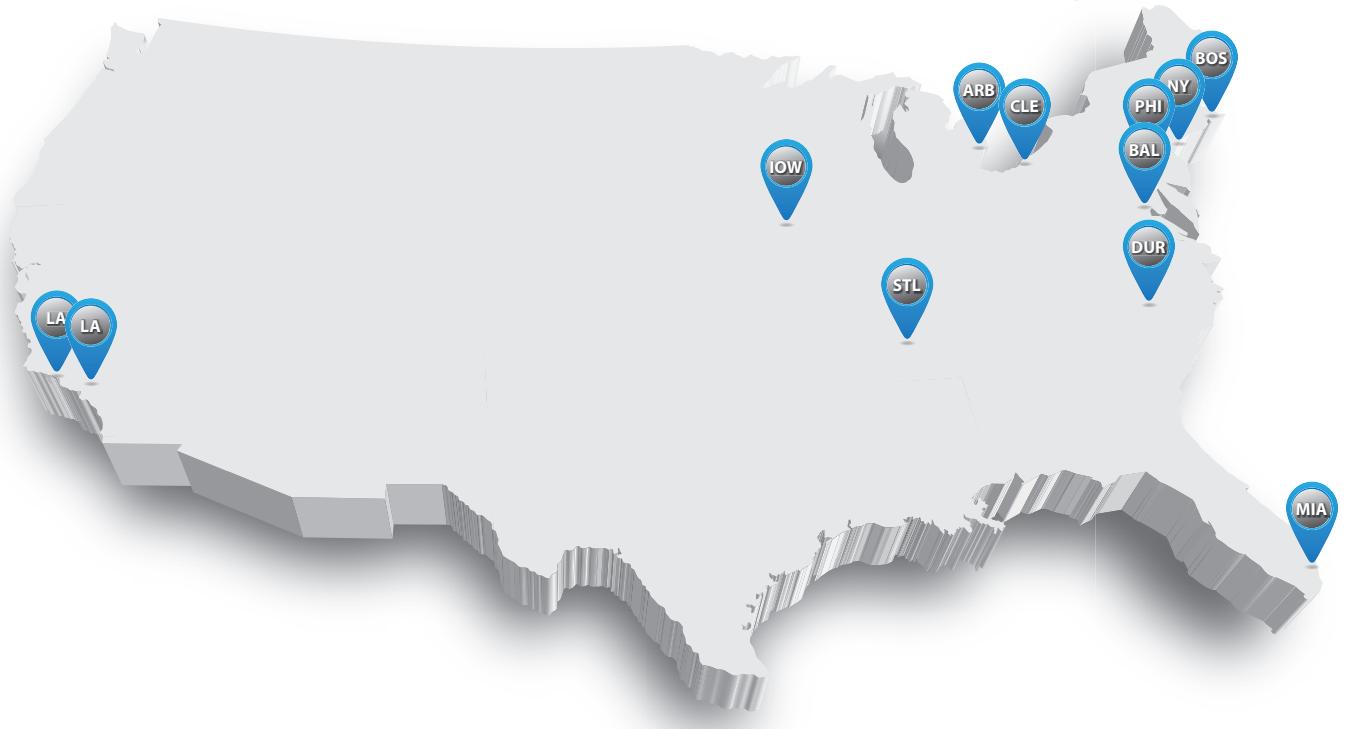

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