REVIEW® of Ophthalmology

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SATURDAY APRIL 26

10:00 am – 10:45 am
Innovative Technologies and Excellent Outcomes in Laser Cataract Surgery
Johnny Gayton MD – Moderator
William Culbertson MD,
Burkhard Dick MD, PhD

11:00 am – 11:45 am
***iDesign® Dx* System: A Science Story of Innovation**
Dan Neal PhD – Moderator
Stephen Coleman MD, Sandy Feldman MD

2:00 pm – 2:45 pm
Optimizing Premium IOL Outcomes with Laser Cataract Surgery
Mark Blecher MD – Moderator
Subba Gollamudi MD, Keith Walter MD

3:00 pm – 3:45 pm
Surgical Pearls for Challenging Cataracts: Video Case Presentations
David Chang MD – Moderator
Marjan Farid MD, Cynthia Matossian MD

SUNDAY APRIL 27

10:00 am – 10:45 am
Deliver the Best Refractive Outcomes to Build a Successful Business
Steven Schallhorn MD – Moderator
Derek Cunningham OD, FAAO, James Loden MD

11:00 am – 11:45 am
Astigmatism Correction and Outcomes with Toric IOLs
Kevin Waltz MD – Moderator
Ike Ahmed MD, Tal Raviv MD

12:00 pm – 12:45 pm
Clinical Pearls for Success with Premium IOLs
Kerry Assil MD – Moderator
Rex Hamilton MD, Jeff Martin MD

2:00 pm – 2:45 pm
Customized Premium Lens Outcomes Combined with a New Preloaded Delivery System
Doug Koch MD – Moderator
Daniel Chang MD, Oliver Findl MD

3:00 pm – 3:45 pm
Routine and Challenging Cases in Laser Cataract Surgery
Shachar Tauber MD – Moderator
Juan Batlle MD, Barry Seibel MD

MONDAY APRIL 28

10:00 am – 10:45 am
Practice Integration and Patient Adoption Pearls for Laser Cataract Surgery
George Waring IV MD – Moderator
James Khodabakhsh MD, Paul Mann MD

11:00 am – 11:45 am
Premium Lens Design for High Quality Visual Outcomes with a New Preloaded Delivery System
David Hardten MD – Moderator
Daniel Black MD, Daniel Chang MD

12:00 pm – 12:45 pm
Phaco Techniques and Fluidics Measurement in Laser Cataract Surgery
Jason Jones MD – Moderator
Robert Rivera MD, William Wiley MD

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Abbott Medical Optics

REVIEW NEWS
Volume XXI • No. 4 • April 2014

Researchers Progress Toward Eye Drop for Retinal Disease

Drugs used to treat blinding disorders could be successfully administered by eye drops rather than unpleasant and expensive eye injections, according to new research led by University College London scientists that could be a breakthrough for the millions worldwide suffering from age-related macular degeneration and other eye disorders.

One in five people over 75 have AMD. The research findings are significant due to growing patient numbers and an increasing demand for the eye injections that halt the progression of the disease.

The research, demonstrated in animal models and published in nanotechnology journal *Small*, demonstrates that it is possible to create formulations of tiny nanoparticles loaded with the AMD drug Avastin and deliver significant concentrations to the back of the eye. Lead author Professor Francesca Cordeiro (UCL Institute of Ophthalmology) said: "The development of eye drops that can be safely and effectively used in patients would be a magic bullet—a huge breakthrough in the treatment of AMD and other debilitating eye disorders.

"The current treatment of injecting drugs into the eye is uncomfortable, detested by patients and often needs repeated monthly injections in hospital for as long as 24 consecutive months. It's impossible to exaggerate the relief patients would feel at not having to experience injections into their eyes."

Britain's National Health Service is currently overburdened with patients who need repeat eye injections and the numbers are set to rise exponentially over the next 10 years. Demand is high, and injections are difficult to administer, time-consuming and very expensive. The treatment also carries a risk of infection and bleeding, increased by the frequency of recurrent injections into the eyes. In the United States, well over 1 million ocular injections were given in 2010. In the UK, 30,500 injections were estimated to have been given in 2008—a 150-fold increase in 10 years.

It was previously thought that drugs used to treat AMD such as Avastin and Lucentis have molecules that are simply too large to be effectively transported in an eye drop. First author Dr. Ben Davis (UCL Institute of Ophthalmology) added: "There is significant interest in the development of minimally invasive systems to deliver large drug molecules across biological barriers, including the cornea of the eye.

"We have shown in experimental models a formulation system to get substances including Avastin across the barriers in the eye and transport them across the cells of the cornea. In theory, you could customize the technology for different drugs such as Lucentis … as it is a smaller molecule than Avastin so likely to be delivered effectively via this method.

"All the components we used are safe and well-established in the field, meaning we could potentially move quite quickly to get the technology into trials in patients—but the timescales are dependent on funding." The paper includes functional data showing that the Avastin administered stops the blood vessels from leaking and forming new blood vessels.

This technology has been patented by UCL's technology transfer company UCL Business and the researchers are seeking commercial partners to accelerate development.

Eye May Reveal Early Alzheimer's

Investigators at the Cedars-Sinai Regenerative Medicine Institute have discovered eye abnormalities that may help reveal features of early-stage Alzheimer's disease. Using a novel laboratory rat model of Alzheimer's disease and high-resolution imaging techniques, researchers correlated variations of the eye structure, to identify initial indicators of the disease.

"Detecting changes in the brain that indicate Alzheimer's disease can be an extremely challenging task," said Shaomei Wang, MD, PhD, lead author of the study and an associate professor in the Regenerative Medicine Institute and Department of Biomedical Sciences. "By using the eye as a window to brain activity and function, we may be able to diagnose patients sooner and give them more time to prepare for the future. Options may include earlier enrollment in clinical trials, developing support networks and dealing with any financial and legal matters."

Using both animal models and postmortem human retinas from donors

with Alzheimer's disease, researchers found changes in the retinal pigment epithelial layer and in the thickness of the choroidal layer. Changes in these two regions were detected using sophisticated, state-of-the-art imaging and immunological techniques.

With high-resolution, microscopic imaging and visual acuity measurements, investigators were able to monitor tissue degeneration in the cell layer and vascular layer at the back of the eye, as well as decline in visual function, that were strongly associated with Alzheimer's disease.

"Greater magnitude in these eye abnormalities may mean a greater chance of a patient having Alzheimer's disease," said Alexander Ljubimov, PhD, director of the Eye Program within the Regenerative Medicine Institute and study co-author. "We found that a rat model showed similar signs to the human ailment in the eye. If true in a larger number of humans, these findings may be used to study Alzheimer's disease mechanisms and test potential drugs."

Though additional research is needed to investigate the mechanisms of these ocular changes in relation to changes in the brain, investigators hope to ultimately aid early diagnosis of Alzheimer's disease by studying the most approachable part of the central nervous system: the eye. Cedars-Sinai has been at the cutting edge of studies on the eye and Alzheimer's disease with a previous report showing amyloid plaques, a hallmark of Alzheimer's disease, also build up in the eye using a similar animal model of the disease.

Finding in Canine Eye Linked to Retinal Diseases

In humans, the fovea is critically important to viewing fine details. Densely packed with cone photo receptor cells, it is used while reading, driving and gazing at objects of interest. Some animals have a similar feature in their eyes, but researchers believed that among mammals the fovea was unique to primates—until now.

University of Pennsylvania vision scientists report that dogs, too, have an area of their retina that strongly resembles the human fovea. What's more, this retinal region is susceptible to genetic blinding diseases in dogs just as it is in humans.

"It's incredible that in 2014 we can still make an anatomical discovery in a species that we've been looking at for the past 20,000 years and that, in addition, this has high clinical relevance to humans," said William Beltran, an assistant professor of ophthalmology in Penn's School of Veterinary Medicine and co-lead author of the study with Artur Cideciyan, research professor of ophthalmology in Penn's Perelman School of Medicine.

"It is absolutely exhilarating to be able to investigate this very specialized and important part of canine central vision that has such unexpectedly strong resemblance to our own retina," Dr. Cideciyan added.

The paper was published in the journal *PLoS ONE*.

It is known that dogs have an area centralis, a region around the center of the retina with a relative increase in cone photoreceptor cell density. But dogs lack the pit formation that humans have, and, before this study, it was believed that the increase in cone photoreceptor cell density didn't come close to matching what is seen in primates. Prior to this study, the highest reported density in dogs was 29,000 cones per square millimeter compared to more than 100,000 cones per square millimeter seen in the human and macaque foveas.

It turns out that previous studies in dogs had missed a miniscule region of increased cell density. In this study, while examining the retina of a dog with a mutation that causes a disease akin to a form of X-linked retinal degeneration in humans, the Penn researchers noticed a thinning of the retinal layer that contains photoreceptor cells.

Zeroing in on this region, they examined retinas of normal dogs using advanced imaging techniques, including confocal scanning laser ophthalmoscopy, optical coherence tomography and two-photon microscopy. By enabling the scientists to visualize different layers of the retina, these techniques allowed them to identify a small area of peak cone density and then estimate cone numbers by counting the cells in this unique area.

Based on their observations, the researchers found that cone densities reached more than 120,000 cells per square millimeter in a never-before-described fovea-like region of the area centralis, a density on par with that of primate foveas.

They also recognized that the "output side" of this cone-dense region corresponded with an area of dense retinal ganglion cells, which transmit signals to the brain.

Human patients with macular degeneration experience a loss of photoreceptor cells at or near the fovea, resulting in a devastating loss of central vision.

To see whether the fovea-like region was similarly affected in dogs, the Penn researchers used the same techniques they had employed to study normal dogs to examine animals that had mutations in two genes (BEST1 and RPGR) that can lead to macular degeneration in humans.

In both cases, the onset of disease affected the fovea-like region in dogs in a very similar way to how the diseases present in humans, with central retinal lesions appearing earlier than lesions in the peripheral retina.

"Why the fovea is susceptible to early disease expression for certain hereditary disorders and why it is spared un-

der other conditions is not known," Dr. Cideciyan said. "Our findings, which show the canine equivalent of a human genetic disease affecting an area of the retina that is of extreme importance to human vision, are very promising from the human point of view. They could allow for translational research by allowing us to test treatments for human foveal and macular degenerative diseases in dogs."

The fact that dogs have a fovea-like area of dense photoreceptor cells may also indicate that dogs are seeing more acutely than once suspected.

"This gives us a structural basis to support the idea that dogs might have a higher visual acuity than has been measured so far," Dr. Beltran said. "It could even be the case that some breeds have an especially high density of cells and could be used as working dogs for particular tasks that require high-level sight function."

Lifestyle Changes Can Spare Visual Impairment

A physically active lifestyle and occasional drinking are associated with a reduced risk of developing visual impairment, according to a study published online in March in *Ophthalmology*.

Visual impairment is associated with a poorer quality of life and, when severe, loss of independence. In 2020, the number of people in the United States with visual impairment is projected to increase to at least 4 million. This is a 70-percent increase from 2000 and is due to the growing aging population and prevalence of age-related eye diseases.

To help determine ways to decrease the growing burden of visual impairment, researchers from the University of Wisconsin School of Medicine and Public Health examined the relationships between the incidence of visual

impairment and three modifiable lifestyle behaviors: smoking, drinking alcohol and staying physically active. The research was conducted as part of the Beaver Dam Eye Study, a long-term population-based cohort study from 1988 to 2013 of nearly 5,000 adults aged 43 to 84 years.

The researchers found that over 20 years visual impairment developed in 5.4 percent of the population and varied based on lifestyle behaviors as follows:

• Physically active persons (regular activity three or more times a week): Over 20 years, 6.7 percent of sedentary persons and 2 percent of physically active persons developed visual impairment. After adjustment for age, these figures show a 58-percent decrease in odds of developing visual impairment in physically active persons compared to those who were sedentary.

• Occasional drinkers (those who have consumed alcohol in the past year, but reported fewer than one serving in an average week): Over 20 years, 11 percent of non-drinkers (people who have not consumed alcohol within the past year) developed visual impairment while 4.8 percent of occasional drinkers did so. After adjustment for age, these figures show a 49-percent decrease in odds of developing visual impairment in those who were occasional drinkers compared to those who consumed no alcohol.

• While the odds were higher in heavy drinkers and smokers compared to people who never drank heavily and never smoked, the associations were not statistically significant.

While the study provides risk estimates of associations of lifestyle factors with the incidence of visual impairment, the researchers caution that a limitation to their study is that the findings may be due, in part, to unmeasured factors related to both lifestyle behaviors and development of visual impairment. The data does not prove that these lifestyle behaviors are directly responsible for increased risk.

"While age is usually one of the most strongly associated factors for many eye diseases that cause visual impairment, it is a factor we cannot change," said Ronald Klein, MD, MPH, lead researcher of the study. "Lifestyle behaviors like smoking, drinking and physical activity, however, can be altered. So, it's promising, in terms of possible prevention, that these behaviors are associated with developing visual impairment over the long term. However, further research is needed to determine whether modifying these behaviors will in fact lead to a direct reduction in vision loss." REVIEW

ThromboGenics®

JETREA™
(ocriplasmin)
Intravitreal Injection, 2.5mg/mL

The FIRST AND ONLY pharmacologic treatment for symptomatic VMA

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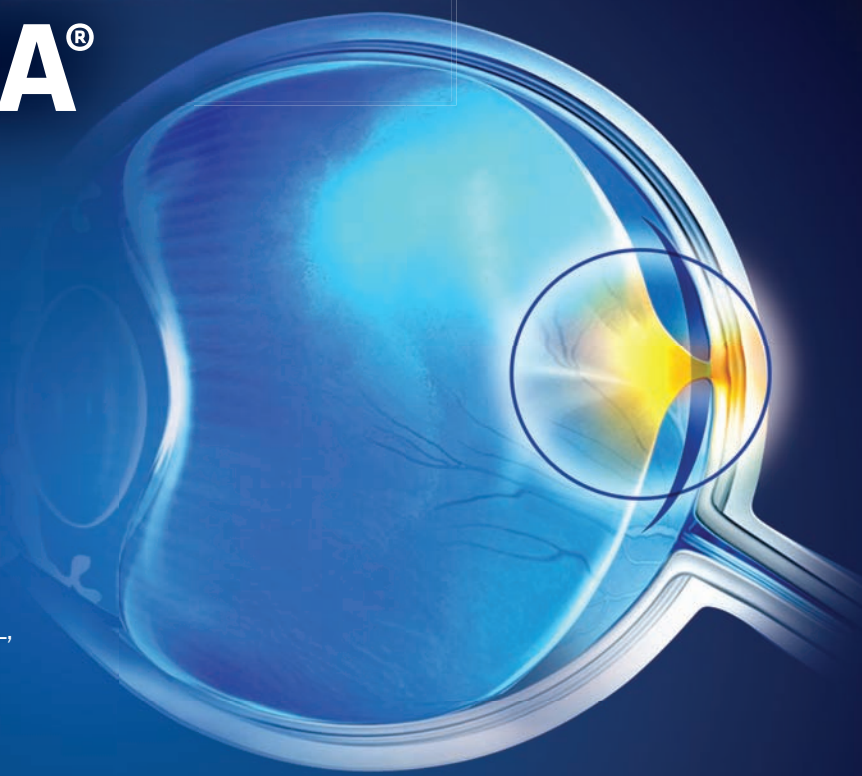

Indication

JETREA® (ocriplasmin) Intravitreal Injection, 2.5 mg/mL, is a proteolytic enzyme indicated for the treatment of symptomatic vitreomacular adhesion (VMA).

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- A decrease of ≥3 lines of best-corrected visual acuity (BCVA) was experienced by 5.6% of patients treated with JETREA® and 3.2% of patients treated with vehicle in the controlled trials. The majority of these decreases in vision were due to progression of the condition with traction and many required surgical intervention. Patients should be monitored appropriately.
- Intravitreal injections are associated with intraocular inflammation/infection, intraocular hemorrhage, and increased intraocular pressure (IOP). Patients should be monitored and instructed to report any symptoms without delay. In the controlled trials, intraocular inflammation occurred in 7.1% of patients injected with JETREA® vs 3.7% of patients injected with vehicle. Most of the post-injection intraocular inflammation events were mild and transient. If the contralateral eye requires treatment with JETREA®, it is not recommended within 7 days of the initial injection in order to monitor the post-injection course in the injected eye.
- Potential for lens subluxation.
- In the controlled trials, the incidence of retinal detachment was 0.9% in the JETREA® group and 1.6% in the vehicle group, while the incidence of retinal tear (without detachment) was 1.1% in the JETREA® group and 2.7% in the vehicle group. Most of these events occurred during or after vitrectomy in both groups.
- Dyschromatopsia (generally described as yellowish vision) was reported in 2% of all patients injected with JETREA®. In approximately half of these dyschromatopsia cases, there were also electroretinographic (ERG) changes reported (a- and b-wave amplitude decrease).

Adverse Reactions

- The most commonly reported reactions (≥5%) in patients treated with JETREA® were vitreous floaters, conjunctival hemorrhage, eye pain, photopsia, blurred vision, macular hole, reduced visual acuity, visual impairment, and retinal edema.

Please see Brief Summary of full Prescribing Information on adjacent page.

VISIT JETREACARE.COM OR SCAN QR CODE FOR REIMBURSEMENT AND ORDERING INFORMATION

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JETREA.COM

JETREA™
(ocriplasmin)
Intravitreal Injection, 2.5 mg/mL

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

Please see the JETREA® package insert for full Prescribing Information.

1 INDICATIONS AND USAGE
JETREA is a proteolytic enzyme indicated for the treatment of symptomatic vitreomacular adhesion.

2 DOSAGE AND ADMINISTRATION
2.1 General Dosing Information
Must be diluted before use. For single-use ophthalmic intravitreal injection only. JETREA must only be administered by a qualified physician.

2.2 Dosing
The recommended dose is 0.125 mg (0.1 mL of the diluted solution) administered by intravitreal injection to the affected eye once as a single dose.

2.3 Preparation for Administration
Remove the vial (2.5 mg/mL corresponding to 0.5 mg ocriplasmin) from the freezer and allow to thaw at room temperature (within a few minutes). Once completely thawed, remove the protective polypropylene flip-off cap from the vial. The top of the vial should be disinfected with an alcohol wipe. Using aseptic technique, add 0.2 mL of 0.9% w/v Sodium Chloride Injection, USP (sterile, preservative-free) into the JETREA vial and gently swirl the vial until the solutions are mixed.

Visually inspect the vial for particulate matter. Only a clear, colorless solution without visible particles should be used. Using aseptic technique, withdraw all of the diluted solution using a sterile #19 gauge needle (slightly tilt the vial to ease withdrawal) and discard the needle after withdrawal of the vial contents. Do not use this needle for the intravitreal injection.

Replace the needle with a sterile #30 gauge needle, carefully expel the air bubbles and excess drug from the syringe and adjust the dose to the 0.1 mL mark on the syringe (corresponding to 0.125 mg ocriplasmin). THE SOLUTION SHOULD BE USED IMMEDIATELY AS IT CONTAINS NO PRESERVATIVES. Discard the vial and any unused portion of the diluted solution after single use.

2.4 Administration and Monitoring
The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include the use of sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad spectrum microbiocide should be administered according to standard medical practice.

The injection needle should be inserted 3.5 - 4.0 mm posterior to the limbus aiming towards the center of the vitreous cavity, avoiding the horizontal meridian. The injection volume of 0.1 mL is then delivered into the mid-vitreous.

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

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

Each vial should only be used to provide a single injection for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, and injection needles should be changed before JETREA is administered to the other eye, however, treatment with JETREA in the other eye is not recommended within 7 days of the initial injection in order to monitor the post-injection course including the potential for decreased vision in the injected eye.

Repeated administration of JETREA in the same eye is not recommended *[see Nonclinical Toxicology]*.

After injection, any unused product must be discarded.

No special dosage modification is required for any of the populations that have been studied (e.g. gender, elderly).

3 DOSAGE FORMS AND STRENGTHS
Single-use glass vial containing JETREA 0.5 mg in 0.2 mL solution for intravitreal injection (2.5 mg/mL).

4 CONTRAINDICATIONS
None

5 WARNINGS AND PRECAUTIONS
5.1 Decreased Vision
A decrease of ≥ 3 line of best corrected visual acuity (BCVA) was experienced by 5.6% of patients treated with JETREA and 3.2% of patients treated with vehicle in the controlled trials *[see Clinical Studies]*.

The majority of these decreases in vision were due to progression of the condition with traction and many required surgical intervention. Patients should be monitored appropriately *[see Dosage and Administration]*.

5.2 Intravitreal Injection Procedure Associated Effects
Intravitreal injections are associated with intraocular inflammation / infection, intraocular hemorrhage and increased intraocular pressure (IOP). In the controlled trials, intraocular inflammation occurred in 7.1% of patients injected with JETREA vs. 3.7% of patients injected with vehicle. Most of the post-injection intraocular inflammation events were mild and transient. Intraocular hemorrhage occurred in 2.4% vs. 3.7% of patients injected with JETREA vs. vehicle, respectively. Increased intraocular pressure occurred in 4.1% vs. 5.3% of patients injected with JETREA vs. vehicle, respectively.

5.3 Potential for Lens Subluxation
One case of lens subluxation was reported in a patient who received an intravitreal injection of 0.175 mg (1.4 times higher than the recommended dose). Lens subluxation was observed in three animal species (monkey, rabbit, minipig) following a single intravitreal injection that achieved vitreous concentrations of ocriplasmin 1.4 times higher than achieved with the recommended treatment dose. Administration of a second intravitreal dose in monkeys, 28 days apart, produced lens subluxation in 100% of the treated eyes *[see Nonclinical Toxicology]*.

5.4 Retinal Breaks
In the controlled trials, the incidence of retinal detachment was 0.9% in the JETREA group and 1.6% in the vehicle group, while the incidence of retinal tear (without detachment) was 1.1% in the JETREA group and 2.7% in the vehicle group. Most of these events occurred during or after vitrectomy in both groups. The incidence of retinal detachment that occurred pre-vitrectomy was 0.4% in the JETREA group and none in the vehicle group, while the incidence of retinal tear (without detachment) that occurred pre-vitrectomy was none in the JETREA group and 0.5% in the vehicle group.

5.5 Dyschromatopsia
Dyschromatopsia (generally described as yellowish vision) was reported in 2% of all patients injected with JETREA. In approximately half of these dyschromatopsia cases there were also electroretinographic (ERG) changes reported (a- and b-wave amplitude decrease).

6 ADVERSE REACTIONS
The following adverse reactions are described below and elsewhere in the labeling:

- Decreased Vision *[see Warnings and Precautions]*
- Intravitreal Injection Procedure Associated Effects *[see Warnings and Precautions and Dosage and Administration]*
- Potential for Lens Subluxation *[see Warnings and Precautions]*
- Retinal Breaks *[see Warnings and Precautions and Dosage and Administration]*

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

Approximately 800 patients have been treated with an intravitreal injection of JETREA. Of these, 465 patients received an intravitreal injection of ocriplasmin 0.125 mg (187 patients received vehicle) in the 2 vehicle-controlled studies (Study 1 and Study 2).

The most common adverse reactions (incidence 5% - 20% listed in descending order of frequency) in the vehicle-controlled clinical studies were: vitreous floaters, conjunctival hemorrhage, eye pain, photopsia, blurred vision, macular hole, reduced visual acuity, visual impairment, and retinal edema.

Less common adverse reactions observed in the studies at a frequency of 2% - < 5% in patients treated with JETREA included macular edema, increased intraocular pressure, anterior chamber cell, photophobia, vitreous detachment, ocular discomfort, iritis, cataract, dry eye, metamorphopsia, conjunctival hyperemia, and retinal degeneration.

Dyschromatopsia was reported in 2% of patients injected with JETREA, with the majority of cases reported from two uncontrolled clinical studies. In approximately half of these dyschromatopsia cases there were also electroretinographic (ERG) changes reported (a- and b-wave amplitude decrease).

6.2 Immunogenicity
As with all therapeutic proteins, there is potential for immunogenicity. Immunogenicity for this product has not been evaluated.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy: Teratogenic Effects
Pregnancy Category C. Animal reproduction studies have not been conducted with ocriplasmin. There are no adequate and well-controlled studies of ocriplasmin in pregnant women. It is not known whether ocriplasmin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. The systemic exposure to ocriplasmin is expected to be low after intravitreal injection of a single 0.125 mg dose. Assuming 100% systemic absorption (and a plasma volume of 2700 mL), the estimated plasma concentration is 46 ng/mL. JETREA should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers
It is not known whether ocriplasmin is excreted in human milk. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when JETREA is administered to a nursing woman.

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

8.5 Geriatric Use
In the clinical studies, 384 and 145 patients were ≥ 65 years and of these 192 and 73 patients were ≥ 75 years in the JETREA and vehicle groups respectively. No significant differences in efficacy or safety were seen with increasing age in these studies.

10 OVERDOSAGE
The clinical data on the effects of JETREA overdose are limited. One case of accidental overdose of 0.250 mg ocriplasmin (twice the recommended dose) was reported to be associated with inflammation and a decrease in visual acuity.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
No carcinogenicity, mutagenicity or reproductive and developmental toxicity studies were conducted with ocriplasmin.

13.2 Animal Toxicology and/or Pharmacology
The ocular toxicity of ocriplasmin after a single intravitreal dose has been evaluated in rabbits, monkeys and minipigs. Ocriplasmin induced an inflammatory response and transient ERG changes in rabbits and monkeys, which tended to resolve over time. Lens subluxation was observed in the 3 species at ocriplasmin concentrations in the vitreous at or above 41 mcg/mL, a concentration 1.4-fold above the intended clinical concentration in the vitreous of 29 mcg/mL. Intraocular hemorrhage was observed in rabbits and monkeys.

A second intravitreal administration of ocriplasmin (28 days apart) in monkeys at doses of 75 mcg/eye (41 mcg/mL vitreous) or 125 mcg/eye (68 mcg/mL vitreous) was associated with lens subluxation in all ocriplasmin treated eyes. Sustained increases in IOP occurred in two animals with lens subluxation. Microscopic findings in the eye included vitreous liquefaction, degeneration/disruption of the hyaloideo-capsular ligament (with loss of ciliary zonular fibers), lens degeneration, mononuclear cell infiltration of the vitreous, and vacuolation of the retinal inner nuclear cell layer. These doses are 1.4-fold and 2.3-fold the intended clinical concentration in the vitreous of 29 mcg/mL, respectively.

14 CLINICAL STUDIES
The efficacy and safety of JETREA was demonstrated in two multicenter, randomized, double masked, vehicle-controlled, 6 month studies in patients with symptomatic vitreomacular adhesion (VMA). A total of 652 patients (JETREA 464, vehicle 188) were randomized in these 2 studies. Randomization was 2:1 (JETREA:vehicle) in Study 1 and 3:1 in Study 2.

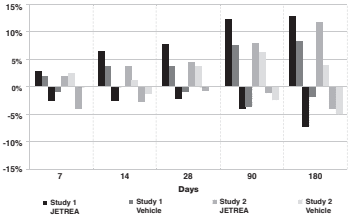
Patients were treated with a single injection of JETREA or vehicle. In both of the studies, the proportion of patients who achieved VMA resolution at Day 28 (i.e., achieved success on the primary endpoint) was significantly higher in the ocriplasmin group compared with the vehicle group through Month 6.

The number of patients with at least 3 lines increase in visual acuity was numerically higher in the ocriplasmin group compared to vehicle in both trials, however, the number of patients with at least a 3 lines decrease in visual acuity was also higher in the ocriplasmin group in one of the studies (Table 1 and Figure 1).

Table 1: Categorical Change from Baseline in BCVA at Month 6, Irrespective of Vitrectomy (Study 1 and Study 2)

Study 1			
	JETREA	Vehicle	Difference
	N=219	N=107	(95% CI)
≥ 3 line Improvement in BCVA			
Month 6	28 (12.8%)	9 (8.4%)	4.4 (-2.5, 11.2)
> 3 line Worsening in BCVA			
Month 6	16 (7.3%)	2 (1.9%)	5.4 (1.1, 9.7)
Study 2			
	JETREA	Vehicle	Difference
	N=245	N=81	(95% CI)
≥ 3 line Improvement in BCVA			
Month 6	29 (11.8%)	3 (3.8%)	8.1 (2.3, 13.9)
> 3 line Worsening in BCVA			
Month 6	10 (4.1%)	4 (5.0%)	-0.9 (-6.3, 4.5)

Figure 1: Percentage of Patients with Gain or Loss of ≥ 3 Lines of BCVA at Protocol-Specified Visits



16 HOW SUPPLIED/STORAGE AND HANDLING
Each vial of JETREA contains 0.5 mg ocriplasmin in 0.2 mL citric-buffered solution (2.5 mg/mL). JETREA is supplied in a 2 mL glass vial with a latex free rubber stopper. Vials are for single use only.

Storage
Store frozen at or below -4˚F (-20˚C). Protect the vials from light by storing in the original package until time of use.

17 PATIENT COUNSELING INFORMATION
In the days following JETREA administration, patients are at risk of developing intraocular inflammation/infection. Advise patients to seek immediate care from an ophthalmologist if the eye becomes red, sensitive to light, painful, or develops a change in vision *[see Warnings and Precautions]*.

Patients may experience temporary visual impairment after receiving an intravitreal injection of JETREA *[see Warnings and Precautions]*. Advise patients to not drive or operate heavy machinery until this visual impairment has resolved. If visual impairment persists or decreases further, advise patients to seek care from an ophthalmologist.

Manufactured for:
ThromboGenics, Inc.
101 Wood Avenue South, 6th Floor
Iselin, NJ 08830

U.S. License Number: 1866

Version 1.0
Initial U.S. Approval: 2012
ThromboGenics U.S. patents: 7,445,775; 7,547,435; 7,914,783 and other pending patents.

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REVIEW

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* Haigis W, Mlynski J,
Comparative axial length measurements using optical and acousticbiometry in normal persons and in patients with retinal lesions, White Paper, Carl Zeiss Meditec, 2009

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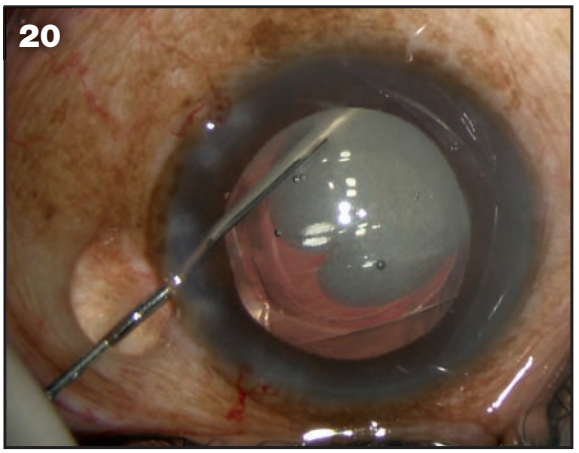

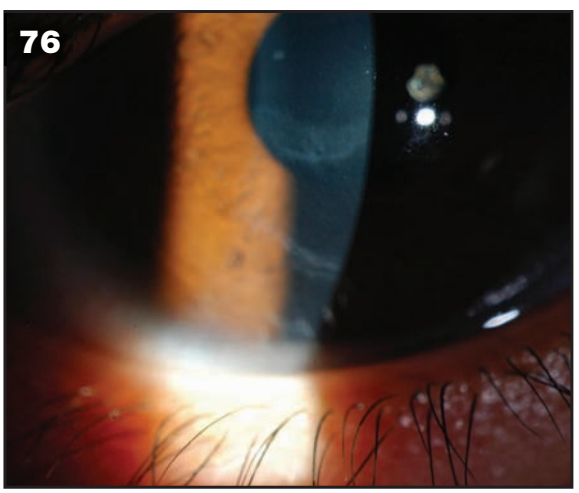

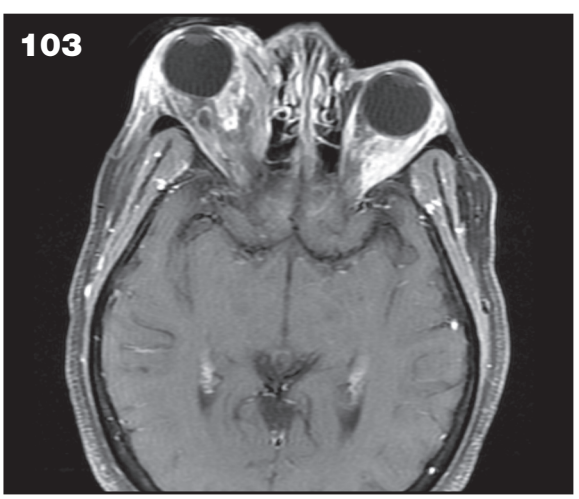

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This product should not be used in patients with a history of hypersensitivity to Bacitracin.

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Please see adjacent page for full prescribing information.

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

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

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

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

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REVIEW® of Ophthalmology

Bring Generic Rules Into the 21st Century

It's generally estimated that generics account for more than 80 percent of drugs prescribed in the United States. With the continuing pressure on health-care costs, it's in the government's (and everyone's) interest to encourage the use of generics that provide safe and equivalent, lower-cost treatment options to that of branded drugs that have gone off-patent.

This month, Dr. Malik Y. Kahook joins us to address the topic of generics, providing both a concise outline of the current regulatory environment around generics, and some very practical advice on helping patients and physicians navigate the "through the looking glass" world of generic drug rules and regulations.

One of the key contributors to the concern about generic drug safety involves labeling. With good intentions (as always) rules were created decades ago that required that a generic drug carry the exact same label as the innovator drug that it copies, effectively prohibiting generic drugmakers from updating safety data on their labels unless such changes are made on the original drug's label.

Compounding the problem is a 2011 Supreme Court ruling that the FDA's restriction on label changes by generic manufacturers meant that those companies could not be held liable for failure to warn patients about risks. One study revealed that safety-related label changes may occur a median of 10 to 13 years after a drug's approval, and as long as many decades after approval. As the original drug has often exited the market, it's up to the generic manufacturer to monitor safety; and that's just not happening.

Dr. Kahook takes the optimistic road: "Fortunately, this issue has come to the attention of the FDA. In November 2013, the FDA proposed a rule that would permit generic drug manufacturers to update their labels if they receive information about potential safety concerns. If passed, this will go a long way toward ensuring safety for our patients."

The legislation was scheduled for review in a House of Representatives early in April. Lining up against the FDA will be the Generic Pharmaceutical Association, which charges that the change will add unnecessary costs, needlessly confuse patients with labeling changes, and lead insurers to decline to cover generic drug companies against liability risks.

Throw in the increasingly common news reports of unsafe imported generics, and you see real reason for concern about what your patients are actually doing once your prescription walks out the door.

Donna McCune, CCS-P, COE, CPMA

2014 Physician Quality Reporting System

National Quality Strategy Domains, Qualified Clinical Data Registry options and other changes you should know about.

Q Does the Physician Quality Reporting System continue in 2014? Is there still an opportunity to receive a bonus for participating?

A The PQRS does continue in 2014. Providers who successfully participate are eligible to receive a 0.5-percent bonus for all services paid under the Medicare Physician Fee Schedule.

Q Are the requirements for successful participation in 2014 different than in prior years?

A Yes. Successful participation has always relied on providers performing services described as "quality measures" and submitting codes to support their performance of these measures. One change for 2014 is the categorization of quality measures into National Quality Strategy domains. Successful reporting relies on reporting quality measures from three separate domains. The six domains are:

- Patient Safety;
- Person and Caregiver-Centered Experience and Outcomes;
- Communication and Care Coordination;
- Effective Clinical Care;
- Community/Population Health; and
- Efficiency and Cost Reduction.

Another change is the number of measures that must be reported to secure a bonus. In 2014, providers must report at least nine measures covering a minimum of three NQS domains. The instructions indicate that if fewer than nine measures covering at least three NQS domains apply, physicians may report one to eight measures covering one to three NQS domains.

Q What quality measures apply to ophthalmologists?

A The 2014 measures for eye disease, carried over from the 2013 program, are:

- *Primary Open Angle Glaucoma (POAG): Optic Nerve Evaluation* (#12)
- *Age-related Macular Degeneration (AMD): Dilated Macular Examination* (#14)
- *Diabetic Retinopathy: Documentation of Presence or Absence of Macular Edema and Level of Severity of Retinopathy* (#18)
- *Diabetic Retinopathy: Communication With the Physician Managing Ongoing Diabetes Care* (#19)
- *Diabetes: Eye Exam* (#117)
- *Age-Related Macular Degeneration (AMD): Counseling on Antioxidant Supplement* (#140)
- *Primary Open-Angle Glaucoma (POAG): Reduction of Intraocular Pressure (IOP) by 15%* or *Documentation of a Plan of Care* (#141)

Practices interested in measures that are not ophthalmic specific may also consider the following measures for reporting in 2014:

- *Documentation of Current Medications in the Medical Record* (#130)
- *Preventive Care and Screening:*

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Tobacco Use: Screening and Cessation Intervention (#226)
- *Melanoma: Continuity of Care–Recall System* (#137) (Registry only
- *Melanoma: Coordination of Care* (#138) (Registry only)
- *Biopsy follow up* (#265) (Registry only)

Q Are there quality measures related to cataract surgery?

A Yes. In 2012, a "Cataracts Measures Group" was added to the program. A measures group is a subset of four or more measures that have a particular clinical condition or focus in common. The Cataracts Measures Group may only be reported through a registry. The measures group is made up of the following measures.
- *Cataracts: 20/40 or Better Visual Acuity within 90 days Following Cataract Surgery* (#191)
- *Cataracts: Complications within 30 Days Following Cataract Surgery Requiring Additional Surgical Procedures* (#192)
- *Improvement in Patient's Visual Function within 90 Days Following Cataract Surgery* (#303)
- *Patient Satisfaction within 90 Days Following Cataract Surgery* (#304)

When reporting this group, all applicable measures must be completed for each patient being reported. Successful reporting of the Cataract Measures Group requires reporting for 20 or more patients.

Q If a provider reports fewer than nine measures, will there be a reduction to the Medicare reimbursement in 2016?

A Maybe. Physicians who submit fewer than nine measures or three NQS domains are subject to a review process called "Measure Applicability Validation." This process allows the Centers for Medicare & Medicaid to determine whether the provider should have reported additional measures and/or measures covering additional NQS domains. If the MAV review done by CMS determines that the provider accurately submitted data and that no additional measures and/or NQS domains applied, the penalty is averted and the provider may be entitled to the PQRS bonus.

Q Is there another option to avoiding the 2016 penalty when reporting PQRS in 2014?

A Fortunately, yes. Eligible professionals may avoid a penalty in 2016 by successfully reporting three measures in 2014. If fewer than three measures apply, report one or two measures for at least 50 percent of Medicare fee-for-service patients. By reporting less than three, physicians may be subject to the MAV process discussed above. If the MAV process determines that three or more measures applied, but only one to two measures were reported, it would result in the physician receiving a 2-percent penalty in 2016.

Q What are the different ways to report PQRS measures to CMS?

A Measures may be reported by individual providers or as a group practice. Some, not all, measures may be submitted on claims filed to Medicare. Some measures are eligible to be reported via electronic health records. Providers may choose to utilize a "registry" to report on their behalf. In 2014, a new type of registry is added for the purpose of reporting: a Qualified Clinical Data Registry option. A QCDR is a CMS-approved entity that has self-nominated and successfully completed a qualification process.

Those who want to report as a group practice must request this option from CMS and be approved to report in this manner. Reporting through an EHR also requires that the EHR vendor be approved by CMS to report via this method.

Q Are providers required to report on every Medicare patient meeting the quality measure description?

A No. Each measure must be reported for at least 50 percent of the Medicare Part B fee-for-service patients seen during the reporting period for providers submitting PQRS measures on their Medicare claims. For those utilizing a registry, the reporting threshold for the registry has been reduced to 50 percent in 2014. The previous threshold for the registry was 80 percent.

Q Is the PQRS program likely to continue beyond 2014?

A Yes, it is. The PQRS program is slated to link to the EHR bonus program and the value based performance modifier program. Reporting of quality measures is a priority for CMS as they consider the future payment systems for health-care providers.

Q Will providers be penalized for nonparticipation?

A Yes, there will be a penalty. Providers who did not participate in 2013 will see a 1.5-percent reduction to their Medicare reimbursement in 2015. Penalties in 2016 will depend on the provider's level of participation and successful reporting in 2014. REVIEW

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


Can Surgeons Stop the Drops?

A look at recent attempts to replace postop eye drops with injections and the pros and cons of this approach.

Walter Bethke, Managing Editor

Though cataract surgeons successfully prescribe postop drops every day, some physicians would rather remove the onus of compliance with drops from the patients and instead administer a compounded intraoperative anti-inflammatory/antibiotic injection themselves. The reasoning is, with an infusion of drug, you're not beholden to patients' adherence to the drop schedule, it's more convenient for the patient and the surgeon's staff, and it might save the patient some money. Other surgeons, however, are wary of compounded drugs and wonder if an injection/infusion is the same as a drop regimen. Here, we'll look at two recent protocols for intraoperative injections, with cataract surgeons discussing the pros and cons of injections vs. drops.

TriMoxi/TriMoxiVanc

San Diego-based Imprimis Pharmaceuticals is currently in the process of finalizing an agreement with Randoph, N.J., compounder Pharmacy Creations to provide Imprimis' formulations of intraoperative injections of triamcinolone/moxifloxacin and triamcinolone/moxifloxacin/vancomycin. James Lewis, MD, of Elkins Park, Pa., uses a trans-zonular infusion of both TriMoxi and TriMoxiVanc and has noticed some advantages. "We no longer have problems with compliance or corneal toxicity from the drops," he says. "We also save the patients a good deal of money. But, more important, we save them aggravation from such issues as: 'Will my insurance pay for the drops? Will I have to call to get a generic because the brand is too much? Do I have to go from a b.i.d. branded drug to a q.i.d. generic? Will the generic work well? Will it sting? What if I travel somewhere and don't have the bottle with me; can I get another one at a pharmacy?' Probably the biggest thing is that patients simply don't like the mess of putting in eye drops, and can have difficulties with physically administering them. Family members can do it for them, but unless they live with the patient it's a two- to four-time-a-day obligation for a month. The infusion does away with all of this."

John Saharek, vice president of commercialization for Imprimis' ophthalmology division, says the company is trying to close the deal with Pharmacy Creations by the end of March 2014, though the pharmacy can currently ship to "many of the Eastern Seaboard states," he says. Though the company hasn't established prices for the formulation yet, physicians in one of the states served by Pharmacy Creations can currently get a TriMoxi compound from the pharmacy for $40 and a TriMoxiVanc for $45, with a prescription.

DuoCat

Researchers at the Brazilian Ocular Pharmacology and Pharmaceutical Technology Research group have developed an injectable compound that combines an anti-inflammatory and an antibiotic in microsphere form. In the group's studies, they combined triamcinolone and ciprofloxacin for the microsphere injection.

"The microspheres are placed with a sub-Tenon's injection immediately after surgery to create a time-release system," explains Jose Cardillo, MD, who was lead author on one of the DuoCat studies. "In the beginning our main goal was to keep patients out of unnecessary eye drops but, after researching the method, we proved pharmacoki-

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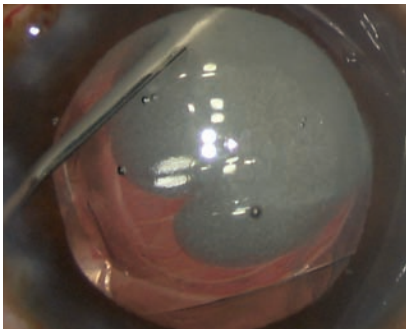
netically in a study of a single drop vs. this system that the microsphere injection can reach a higher level of antibiotic in the anterior chamber and the vitreous."[1]

To compare the system to drops in humans in a double-masked, controlled trial, the researchers randomized 135 cataract patients to two groups: Group 1 consisted of 67 patients treated after surgery with prednisolone 1% and ciprofloxacin 3% eye drops four times daily (week 1), three times daily (week 2), twice daily (week 3), and once daily (week 4) along with 0.3% ciprofloxacin drops four times daily (weeks 1 and 2); Group 2 consisted of 68 patients treated at the end of surgery with a sub-Tenon's injection of 25 mg triamcinolone and 2 mg ciprofloxacin in biodegradable microspheres. At the end of four weeks, there were no significant differences between the groups in terms of anterior chamber cell and flare at any visit, and no patient developed an infection.[2]

Dr. Cardillo and his co-workers met with the U.S. Food and Drug Administration about possible approval of the post-cataract system in the United States, but the agency required proof that the system prevented endophthalmitis, a process that would take millions of patients, owing to the already-low incidence of endophthalmitis. Such a trial was beyond his group's resources and, right now, the researchers say they may need a corporate partner to take the idea further. "We know it works clinically and may be an important method for the patient," Dr. Cardillo says. "We maybe need a company to purchase the idea—not actually the product but the idea—and help us develop it in a more commercial way."

The Pros and Cons

Though many surgeons would be interested in intraoperative injection/infusion, they have some questions about the modality, too.



James Lewis, MD

Some surgeons infuse an antibiotic/steroid compound through the zonules and into the posterior chamber at the end of the case.

• ***Compounding pharmacy fears.*** Probably chief among ophthalmologists' concerns about any intraocular injection or infusion is the quality of the compounder who made it. Their concerns are well-founded: The passage of the 2012 Drug Quality and Security Act came in the wake of the deaths of 49 people out of 751 confirmed or probable fungal meningitis cases that were linked to drugs compounded at the New England Compounding Center. In addition, there have been cases of endophthalmitis linked to anti-VEGF injections that were mixed at compounding facilities.

Imprimis' Mr. Saharek says that Pharmacy Creations complies with both the mandatory state regulations and the more stringent regulations of the Pharmacy Compounding Accreditation Board, which mandates, among other things, an on-site inspection. "We have a pharmacy that's PCAB-accredited, which is one of the higher standards in terms of compounding pharmacies," he says. In the future, Imprimis' compounding facility may also require further voluntary oversight by the FDA if the drugs in its compounds are included on an FDA list of agents, since the company would ultimately like to achieve "outsourcing facility" status. As an outsourcing facility, the site would be subject to spot checks by the agency, but would also be able to produce compounded injections that surgeons could store at their offices and use as-needed without having to submit a prescription. "Regardless of whether the drugs are on the FDA list," Mr. Saharek says, "the state and PCAB oversight are pretty stringent requirements."

• ***Pharmacokinetics.*** There's also the question of how long an injection would last vs. daily drops. Though TriMoxi and TriMoxiVanc haven't been specifically studied in trials for duration, surgeons who have injected them and similar compounds say they appear to last long enough.

Warwick, R.I., surgeon Paul Koch used a compounded intraocular steroid and antibiotic for cataract surgery for two years until one of the agents he used, Tequin (gatifloxacin), was taken off the market. "I believe when the studies were done back [when I used it] the injection's duration wasn't as long as drops', but it was long enough," he says. "It was fine. Speaking of antibiotics, there actually is no evidence that antibiotic eye drops, either preop or postop, affect the rate of infection after surgery. The only studies that show elements that can effect endophthalmitis rates are draping the lids, preop Betadine and opening the posterior capsule. There are a lot of studies that show that using antibiotics reduces the bacterial load on the surface of the eye, but that hasn't translated into a reduction of the rate of endophthalmitis. However, intracameral antibiotics have shown a decrease in endophthalmitis based on the European studies.

"With regard to steroids and nonsteroids being used in surgery, yes, there is an effect there with the injection," Dr. Koch says. "When we were doing the injections, we found that 94 percent of patients had enough steroid onboard to recover from the procedure very quickly and 6 percent had to have supplemental steroid eye drops after surgery for rebound iritis or any sort of discomfort." He says the Kenalog left patients' vision blurry for a couple of days since they injected it

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into the anterior chamber.

• ***Steroid responders.*** Surgeons who use postop drops will occasionally have a patient who has an intraocular pressure spike from the steroid, and can just discontinue the drop and maybe initiate pressure-lowering therapy. But what if the steroid responder had steroid injected directly into the eye?

"We were concerned about that as well," says Dr. Koch. "But in the two years we were doing it, we never had to face that situation. So whether it's a real concern and we were just fortunate or the doses we were using didn't matter, I don't know. We looked at that closely. We did see pressure rises on the first day, and sometimes we thought it was the Kenalog blocking trabecular meshwork. We studied it and found that the rate of the elevated pressure with the irrigation was exactly the same as our postop rate without the irrigation; we were just more cognizant of it when the Kenalog was in the eye."

• ***Standard of care?*** Though Drs. Cardillo and Koch point out that the use of steroid and antibiotic drops after cataract surgery is actually an off-label use, there's still the impression in the specialty that it's become the standard of care. This impression could hurt a surgeon who performs a steroid/antibiotic injection in a patient who then develops a problem. "The problem is there are so many people who say using two or three drops is a standard of care and are willing to get paid to testify that way," says Dr. Koch. "And the person who's not doing it is on the defensive, even if they may be completely correct. I think that is shying a lot of people away from using it, though I think that's incorrect." REVIEW

1. Cardillo JA, Paganelli F, Melo Jr L, The Brazilian Ocular Pharmacology and Pharmaceutical Technology Research Group. Subconjunctival Delivery of Antibiotics in a Controlled-Release System. Arch Ophthalmol 2010;128:1:81-87.
2. Paganelli F, Cardillo J, Melo L, The Brazilian Ocular Pharmacology and Pharmaceutical Technology Research Group. A single intraoperative sub-tenon's capsule injection of triamcinolone and ciprofloxacin in a controlled-release system for cataract surgery. Invest Ophthalmol Vis Sci 2009;50:7:3041-3047.

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Taking Femto Cataract To the Next Level

Walter Bethke, Managing Editor

Surgeons detail the manual techniques that complement femtosecond laser surgery.

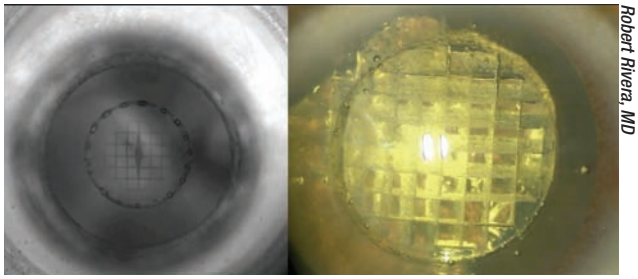
Though much has been made of the exacting nature of incisions, capsulotomies and fragmentation performed by femtosecond lasers in cataract surgery, an oft-overlooked aspect of using the laser is how it affects the surgeon's other, more manual techniques, such as phaco or nuclear chopping. Along these lines, surgeons say that once you start using the femtosecond for your cataract cases, you'll notice differences—some subtle, some very noticeable—in how you approach each step. Here, cataract experts well-versed in using the femtosecond laser for their cases explain how using the new device has led them to change their techniques to get the best results.

Incision Decisions

Even before they were cleared for cataract surgery, femtosecond lasers were making corneal incisions. Surgeons note, though, that these incisions behave differently from manual ones in certain situations.

"For me, the incisions created by the femtosecond are good," says Greenville, N.C., surgeon Karl Stonecipher, who works with the Alcon LenSx device. "However, on some patients, such as those with previous RK, there can be a parallax effect that causes the new incisions to not end up where I want them. On these patients, I'll do these incisions manually because I can see a little bit better that way, and I can get the new incisions placed between the RK incisions. Or, alternately, I can do a scleral tunnel if I feel there are too many RK incisions."

Harvey Uy, MD, a Lensar system user from Manila, Philippines, says the cornea's condition may influence the choice of incision. "It's very important to pay attention to how much corneal arcus or circus senilis is present," he says. "This grayish-white ring of fatty material, often in the periphery, builds up over the years. Because of



Robert Rivera, MD

Robert Rivera, MD, says the Catalys laser's cuboidal fragments make for efficient nuclear removal in later steps of the surgery.

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CAUTION: United States Federal Law restricts this device to sale and use by or on the order of a physician or licensed eye care practitioner.

INDICATION: The LenSx® Laser is indicated for use in patients undergoing cataract surgery for removal of the crystalline lens. Intended uses in cataract surgery include anterior capsulotomy, phacofragmentation, and the creation of single plane and multi-plane arc cuts/incisions in the cornea, each of which may be performed either individually or consecutively during the same procedure.

RESTRICTIONS:

- Patients must be able to lie flat and motionless in a supine position.
- Patient must be able to understand and give an informed consent.
- Patients must be able to tolerate local or topical anesthesia.
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Contraindications:

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- Conditions which would cause inadequate clearance between the intended capsulotomy depth and the endothelium (applicable to capsulotomy only)
- Previous corneal incisions that might provide a potential space into which the gas produced by the procedure can escape
- Corneal thickness requirements that are beyond the range of the system
- Corneal opacity that would interfere with the laser beam
- Hypotony or the presence of a corneal implant
- Residual, recurrent, active ocular or eyelid disease, including any corneal abnormality (for example, recurrent corneal erosion, severe basement membrane disease)
- History of lens or zonular instability
- Any contraindication to cataract or keratoplasty
- This device is not intended for use in pediatric surgery.

WARNINGS: The LenSx® Laser System should only be operated by a physician trained in its use.
The LenSx® Laser delivery system employs one sterile disposable LenSx® Laser Patient Interface consisting of an applanation lens and suction ring. The Patient Interface is intended for single use only. The disposables used in conjunction with ALCON® instrument products constitute a complete surgical system. Use of disposables other than those manufactured by Alcon may affect system performance and create potential hazards.
The physician should base patient selection criteria on professional experience, published literature, and educational courses. Adult patients should be scheduled to undergo cataract extraction.

PRECAUTIONS:

- Do not use cell phones or pagers of any kind in the same room as the LenSx® Laser.
- Discard used Patient Interfaces as medical waste.

AES/COMPLICATIONS:

- Capsulotomy, phacofragmentation, or cut or incision decentration
- Incomplete or interrupted capsulotomy, fragmentation, or corneal incision procedure
- Capsular tear
- Corneal abrasion or defect
- Pain
- Infection
- Bleeding
- Damage to intraocular structures
- Anterior chamber fluid leakage, anterior chamber collapse
- Elevated pressure to the eye

ATTENTION: Refer to the LenSx® Laser Operator's Manual for a complete listing of indications, warnings and precautions.

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INTENDED USES: The VERION™ Reference Unit is a preoperative measurement device that captures and utilizes a high-resolution reference image of a patient's eye in order to determine the radii and corneal curvature of steep and flat axes, limbal position and diameter, pupil position and diameter, and corneal reflex position. In addition, the VERION™ Reference Unit provides preoperative surgical planning functions that utilize the reference image and preoperative measurements to assist with planning cataract surgical procedures, including the number and location of incisions and the appropriate intraocular lens using existing formulas. The VERION™ Reference Unit also supports the export of the high-resolution reference image, preoperative measurement data, and surgical plans for use with the VERION™ Digital Marker and other compatible devices through the use of a USB memory stick.

The VERION™ Digital Marker links to compatible surgical microscopes to display concurrently the reference and microscope images, allowing the surgeon to account for lateral and rotational eye movements. In addition, the planned capsulorhexis position and radius, IOL positioning, and implantation axis from the VERION™ Reference Unit surgical plan can be overlaid on a computer screen or the physician's microscope view.

CONTRAINDICATIONS: The following conditions may affect the accuracy of surgical plans prepared with the VERION™ Reference Unit: a pseudophakic eye, eye fixation problems, a non-intact cornea, or an irregular cornea. In addition, patients should refrain from wearing contact lenses during the reference measurement as this may interfere with the accuracy of the measurements.

Only trained personnel familiar with the process of IOL power calculation and astigmatism correction planning should use the VERION™ Reference Unit. Poor quality or inadequate biometer measurements will affect the accuracy of surgical plans prepared with the VERION™ Reference Unit.

The following contraindications may affect the proper functioning of the VERION™ Digital Marker: changes in a patient's eye between preoperative measurement and surgery, an irregular elliptic limbus (e.g., due to eye fixation during surgery, and bleeding or bloated conjunctiva due to anesthesia). In addition, the use of eye drops that constrict sclera vessels before or during surgery should be avoided.

WARNINGS: Only properly trained personnel should operate the VERION™ Reference Unit and VERION™ Digital Marker.

Only use the provided medical power supplies and data communication cable. The power supplies for the VERION™ Reference Unit and the VERION™ Digital Marker must be uninterruptible. Do not use these devices in combination with an extension cord. Do not cover any of the component devices while turned on.

Only use a VERION™ USB stick to transfer data. The VERION™ USB stick should only be connected to the VERION™ Reference Unit, the VERION™ Digital Marker, and other compatible devices. Do not disconnect the VERION™ USB stick from the VERION™ Reference Unit during shutdown of the system.

The VERION™ Reference Unit uses infrared light. Unless necessary, medical personnel and patients should avoid direct eye exposure to the emitted or reflected beam.

PRECAUTIONS: To ensure the accuracy of VERION™ Reference Unit measurements, device calibration and the reference measurement should be conducted in dimmed ambient light conditions. Only use the VERION™ Digital Marker in conjunction with compatible surgical microscopes.

ATTENTION: Refer to the user manuals for the VERION™ Reference Unit and the VERION™ Digital Marker for a complete description of proper use and maintenance of these devices, as well as a complete list of contraindications, warnings and precautions.

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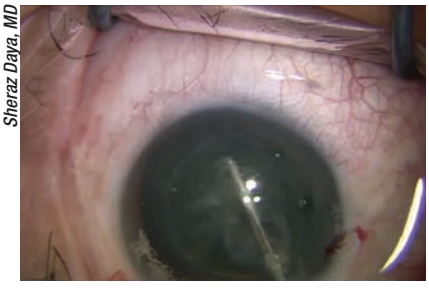
the ring's color, it interferes with the laser treatment in that area and can deflect the laser energy. If you create some portion of your femtosecond incision along a thick band of circus senilis, therefore, the energy will often be deflected and you'll have an incomplete corneal incision that will be hard to open. In these cases, you can move the incision anterior to the circus location and you'll be more likely to have a complete incision. In other cases, you may just be better off using a knife for the incision."

Dilation Issues

Some surgeons have noticed a tendency for the pupil to constrict after the initial femtosecond steps, such as the anterior capsulotomy. Here's how you can address this if it occurs.

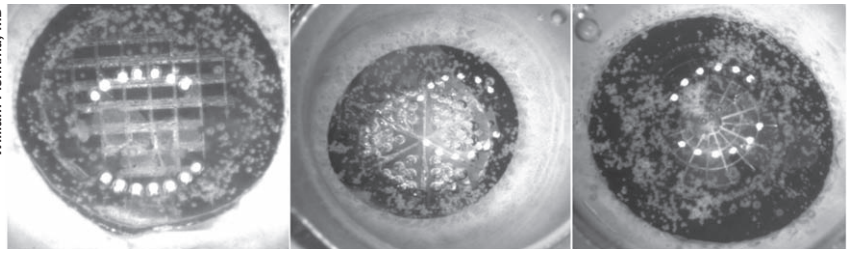
"There tends to be a pupil constriction reaction when the pupil isn't too big to begin with," says Dr. Uy. "Then, when you create your femtosecond capsulorhexis close to the pupil edge, this causes some inflammation that makes the pupil constrict some more. To try to avoid this, preoperatively it helps to add an NSAID to your usual dilation regimen. Also, if you have any control over where to place the capsulorhexis, then you may want to try to put the laser anterior capsulotomy so it's farther away from the iris, or maybe make the rhexis a little smaller if it helps avoid iris constriction. In rare instances, we've had to use some kind of pupil expanding technique."

Sheraz Daya, MD



With translenticular hydrodissection, the surgeon cracks the nucleus and irrigates at the same time, creating a safe fluid wave.

William Fishkind, MD



Tucson, Ariz., ophthalmologist William Fishkind says femto-fragmentation can soften a nucleus so that it's one grade lower in hardness when the surgeon attempts to remove it.

Tucson, Ariz., ophthalmologist William Fishkind says that if a surgeon is having a problem with the pupil coming down after the laser, epinephrine in the infusion bottle is one option. "The other is compounded phenylephrine and lidocaine, mixed much like Shugarcaine used to be," he says. "Introduce 0.2 cc at the beginning of the case. That keeps the pupil dilated throughout the case."

Hydrodissection

Surgeons say that, in some patients, using hydrodissection in conjunction with the femtosecond laser can be challenging due to the buildup of a gas bubble behind the lens nucleus as a result of the photodisruption. Experts say that simply blasting a fluid wave behind the lens when this gas bubble is present can actually result in a torn posterior capsule.

"There's a fusion between the cortex and the capsule that locks the fluid in," explains London, England's Sheraz Daya, MD, who performs procedures with the Bausch + Lomb Victus laser. "Then, upon the injection of fluid, the capsule breaks. During one case, I was breaking up the lens with a hydrodissection cannula and inadvertently released fluid from the cannula. I noticed it produced a good fluid wave and the lens was mobilized. I then noticed I could deliberately reproduce this in other cases as well, and I use it regularly now. I call the technique translenticular hydrodissection, and Bausch + Lomb has developed a cannula for the maneuver that chops the lens and irrigates at the same time."

Dr. Fishkind says a surgeon can also hydrodissect in multiple locations. "You have to be careful to hydrodissect in multiple sections because the fluid will sometimes find a plane breaking through the various laser cuts," he says. "So, for the right eye for example, you inject superiorly, superonasally, then directly across from your entry point, then infero-nasally, then inferiorly. Just gently inject the fluid and you'll find that it separates things better than just going in two places. Injecting in multiple places gets the fluid to separate the cortex from the capsule in more areas, and really helps the I/A at the end of the case, too. The material will be much less adherent."

Fragmentation and Phaco

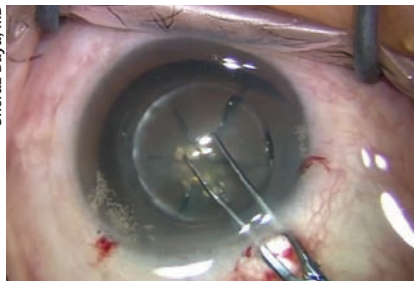
Surgeons say one of the benefits of using a femtosecond laser for cataract surgery is that the laser allows you to soften up the nucleus before you even get into the bag to begin your dividing, flipping or cracking maneuvers. Here are the femto-fragmentation patterns that surgeons say work best, and how to follow them with the best techniques to remove the nuclear material.

Draper, Utah, surgeon Robert Rivera says his work with the AMO Catalys has taught him that the hardness of the lens will partially dictate the pattern he uses to break it up. "The patterns the laser creates can be customized in terms of the number

of quadrants, sextants or octants," Dr. Rivera says. "But the really special way it treats the nucleus is it lets you create a fragmentation pattern that uses smaller fragments if the lens is harder or more mature and larger fragments if it's softer. These are little cuboidal fragments resembling french fries. Being able to create small segments is beneficial as it allows us to back off on the amount of phaco energy/cumulative dispersed energy that we have to use: We've found that novice users can decrease phaco energy by 70 percent, and those who have used it longer can reduce it by upwards of 95 percent."

Dr. Stonecipher uses eight concentric cylinders and six radial chops in what he calls the spider-web pattern. "This is the same technique that Robert Cionni uses," he explains. "It allows me to bowl out the center into little pixelated pieces and bring in that outer shell. I still can chop, so if I want to chop the lens like in an old-fashioned phaco I can do that. And, in some cases, I'll do a Brown flip technique and flip the lens right up into the phacoemulsification and it will fall apart into my ultrasound handpiece.

"My approach depends on how the lens presents itself to me," Dr. Stonecipher continues. "If it's easily rotated and divides easily, I do divide and conquer. If I get part of it out and the rest isn't completely broken up, I may do a chop. If it spins easily and flips and collapses in on itself, I'll use the Brown technique. And, in some of these dense lenses, such as white cataracts and dense brunescent cataracts, I'll take out the bowl, push into the center and get the epinuclear shell later. In those last cases, I'm trying to protect the endothelium, such as in patients with Fuch's dystrophy." Dr. Daya also thinks six segments is ideal. "I just use six segments," he says. "Four are quite bulky to remove, but if you have too many fragments they can start to fly around and can strike the endothelium."



Sheraz Daya, MD

Manually removing the capsulotomy tissue can help ensure there are no tags.

Dr. Fishkind says the pre-fragmentation with the laser allows the surgeon to reduce his phaco settings in many cases. "Because the nucleus is softened and pre-chopped, it's easier to go in with lower power, lower aspiration and lower vacuum," he says. "It's kind of easier to get into the center of the nucleus and find one of the pre-established clefts in the pie cuts and crack it as if you're doing a cracking procedure. Then, once you've cracked it into its different pie shapes, you can do a gentle phaco. These segments come out in pieces or chunks; so you lift one up and remove a chunk at the plane of the iris. A vertical chopping technique is not quite as organized as it used to be, because as the segments are lifted up the chunks just come up and then break. You grasp them with aspiration and don't need very much power to emulsify whatever chunks are coming to you. This is because the chunks are smaller than what you'd get with a normal chopping technique. Also, there are multiples of them because there are a couple of concentric circles, so they fracture into circles as well as pie shapes. The harder the nucleus, the more defined the chunks."

Using the femtosecond for cataract procedures has led Dr. Rivera to use more venturi-based phaco. "This turns out to be more efficient in removing those smaller cuboidal fragments," he says. "Besides the instrumentation itself, the fact that I can stay in position two in phaco rather than applying ultrasound position three more aggressively is a huge change. We used to have to apply position three aggressively to ultrasonically emulsify the cataract, but now that's not the case."

Dr. Uy says he's developed an instrument with ASICO for use as the surgeon's second instrument in his off-hand that helps during phaco. "On one side of the instrument is a nucleus manipulator with a ball-tipped chopper without any sharp edges," he explains. "I've found you don't really need a sharp edge to break up the cataract because the femtosecond has already broken it up for you. This allows you to manipulate the nuclear fragments better; I've found it's safer to go around the equator to do a sort of horizontal chopping maneuver. The ball tip also allows you to more safely lift up the posterior plate. Since it's not sharp, there's no danger of going through the soft cortex and puncturing the posterior capsule. The other side of this combination instrument is like a paddle, which you can use to direct small nuclear fragments to the tip of the phaco handpiece."

Different nuclei might require different approaches, says Dr. Uy. "When you have an extremely hard cataract, such as dark brown or black ones, sometimes I prefer to concentrate the laser energy and simply create chops in the nucleus rather than try to fragment it completely," he says. "Sometimes, such a lens is very hard and the laser energy won't do much inside of it, so we just want to concentrate on creating three planes. This will allow us to minimize the laser energy and focus on opening up those three planes.

"If you have a posterior polar cataract, you generally want to avoid any prechopping," Dr. Uy continues. "In such a case, we like to do a more routine divide-and-conquer technique. For those cases you can use a pie or a cube pattern with two or three chops, followed by a more gentle divide-and-conquer pattern. If there's zonular laxity or dialysis, you'll want to do more

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CONTRAINDICATIONS

Asthma, COPD: COMBIGAN® is contraindicated in patients with bronchial asthma; a history of bronchial asthma; severe chronic obstructive pulmonary disease.

Sinus bradycardia, AV block, Cardiac failure, Cardiogenic shock: COMBIGAN® is contraindicated in patients with sinus bradycardia; second or third degree atrioventricular block; overt cardiac failure; cardiogenic shock.

Neonates and Infants (Under the Age of 2 Years): COMBIGAN® is contraindicated in neonates and infants (under the age of 2 years).

Hypersensitivity reactions: Local hypersensitivity reactions have occurred following the use of different components of **COMBIGAN®**. **COMBIGAN®** is contraindicated in patients who have exhibited a hypersensitivity reaction to any component of this medication in the past.

WARNINGS AND PRECAUTIONS

Potentiation of respiratory reactions including asthma: COMBIGAN® contains timolol maleate; and although administered topically can be absorbed systemically. Therefore, the same types of adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions including death due to bronchospasm in patients with asthma have been reported following systemic or ophthalmic administration of timolol maleate.

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

In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, **COMBIGAN®** should be discontinued.

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

Potentiation of vascular insufficiency: COMBIGAN® may potentiate syndromes associated with vascular insufficiency. **COMBIGAN®** should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans.

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

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

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

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

Ocular Hypersensitivity: Ocular hypersensitivity reactions have been reported with brimonidine tartrate ophthalmic solutions 0.2%, with some reported to be associated with an increase in intraocular pressure.

Contamination of topical ophthalmic products after use: There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

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

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

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. **COMBIGAN®:** In clinical trials of 12 months duration with **COMBIGAN®**, the most frequent reactions associated with its use occurring in approximately 5% to 15% of the patients included: allergic conjunctivitis, conjunctival folliculosis, conjunctival hyperemia, eye pruritus, ocular burning, and stinging. The following adverse reactions were reported in 1% to 5% of patients: asthenia, blepharitis, corneal erosion, depression, epiphora, eye discharge, eye dryness, eye irritation, eye pain, eyelid edema, eyelid erythema, eyelid pruritus, foreign body sensation, headache, hypertension, oral dryness, somnolence, superficial punctate keratitis, and visual disturbance.

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

Brimonidine Tartrate (0.1%-0.2%): Abnormal taste, allergic reaction, blepharoconjunctivitis, blurred vision, bronchitis, cataract, conjunctival edema, conjunctival hemorrhage, conjunctivitis, cough, dizziness, dyspepsia, dyspnea, fatigue, flu syndrome, follicular conjunctivitis, gastrointestinal disorder, hypercholesterolemia, hypotension, infection (primarily colds and respiratory infections), hordeolum, insomnia, keratitis, lid disorder, nasal dryness, ocular allergic reaction, pharyngitis, photophobia, rash, rhinitis, sinus infection, sinusitis, taste perversion, tearing, visual field defect, vitreous detachment, vitreous disorder, vitreous floaters, and worsened visual acuity. **Timolol (Ocular Administration):** *Body as a whole:* chest pain; *Cardiovascular:* Arrhythmia, bradycardia, cardiac arrest, cardiac failure, cerebral ischemia, cerebral vascular accident, claudication, cold hands and feet, edema, heart block, palpitation, pulmonary edema, Raynaud's phenomenon, syncope, and worsening of angina pectoris; *Digestive:* Anorexia, diarrhea, nausea; *Immunologic:* Systemic lupus erythematosus; *Nervous System/Psychiatric:* Increase in signs and symptoms of myasthenia gravis, insomnia, nightmares, paresthesia, behavioral changes and psychic disturbances including confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss; *Skin:* Alopecia, psoriasiform rash or exacerbation of psoriasis; *Hypersensitivity:* Signs and symptoms of systemic allergic reactions, including anaphylaxis, angioedema, urticaria, and generalized and localized rash; *Respiratory:* Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), dyspnea, nasal congestion, respiratory failure; *Endocrine:* Masked symptoms of hypoglycemia in diabetes patients; *Special Senses:* diplopia, choroidal detachment following filtration surgery, cystoid macular edema, decreased corneal sensitivity, pseudopemphigoid, ptosis, refractive changes, tinnitus; *Urogenital:* Decreased libido, impotence, Peyronie's disease, retroperitoneal fibrosis.

Postmarketing Experience: Brimonidine: The following reactions have been identified during post-marketing use of brimonidine tartrate ophthalmic solutions in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to brimonidine tartrate ophthalmic solutions, or a combination of these factors, include: bradycardia, depression, iritis, keratoconjunctivitis sicca, miosis, nausea, skin reactions (including erythema, eyelid pruritus, rash, and vasodilation), and tachycardia. Apnea, bradycardia, hypotension, hypothermia, hypotonia, and somnolence have been reported in infants receiving brimonidine tartrate ophthalmic solutions. **Oral Timolol/Oral Beta-blockers:** The following additional adverse reactions have been reported in clinical experience with ORAL timolol maleate or other ORAL beta-blocking agents and may be considered potential effects of ophthalmic timolol maleate: *Allergic:* Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress; *Body as a whole:* Decreased exercise tolerance, extremity pain, weight loss; *Cardiovascular:* Vasodilatation, worsening of arterial insufficiency; *Digestive:* Gastrointestinal pain, hepatomegaly, ischemic colitis, mesenteric arterial thrombosis, vomiting; *Hematologic:* Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura; *Endocrine:* Hyperglycemia, hypoglycemia; *Skin:* Increased pigmentation, pruritus, skin irritation, sweating; *Musculoskeletal:* Arthralgia; *Nervous System/Psychiatric:* An acute reversible syndrome characterized by disorientation for time and place, decreased performance on neuropsychometrics, diminished concentration, emotional lability, local weakness, reversible mental depression progressing to catatonia, slightly clouded sensorium, vertigo; *Respiratory:* Bronchial obstruction, rales; *Urogenital:* Urination difficulties.

DRUG INTERACTIONS

Antihypertensives/Cardiac Glycosides: Because **COMBIGAN®** may reduce blood pressure, caution in using drugs such as antihypertensives and/or cardiac glycosides with **COMBIGAN®** is advised. **Beta-adrenergic Blocking Agents:** Patients who are receiving a beta-adrenergic blocking agent orally and **COMBIGAN®** should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended. **Calcium Antagonists:** Caution should be used in the co-administration of beta-adrenergic blocking agents, such as **COMBIGAN®**, and oral or intravenous calcium antagonists because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, co-administration should be avoided. **Catecholamine-depleting Drugs:** Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension. **CNS Depressants:** Although specific drug interaction studies have not been conducted with **COMBIGAN®**, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered. **Digitalis and Calcium Antagonists:** The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time. **CYP2D6 Inhibitors:** Potentiated systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g., quinidine, SSRIs) and timolol. **Tricyclic Antidepressants:** Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with **COMBIGAN®** in humans can lead to resulting interference with the IOP-lowering effect. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines. **Monoamine oxidase inhibitors:** Monoamine oxidase (MAO) inhibitors may theoretically interfere with the metabolism of brimonidine and potentially result in an increased systemic side-effect such as hypotension. Caution is advised in patients taking MAO inhibitors which can affect the metabolism and uptake of circulating amines.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C: Teratogenicity studies have been performed in animals.

Brimonidine tartrate was not teratogenic when given orally during gestation days 6 through 15 in rats and days 6 through 18 in rabbits. The highest doses of brimonidine tartrate in rats (1.65 mg/kg/day) and rabbits (3.33 mg/kg/day) achieved AUC exposure values 580 and 37-fold higher, respectively, than similar values estimated in humans treated with **COMBIGAN®**, 1 drop in both eyes twice daily.

Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day [4,200 times the maximum recommended human ocular dose of 0.012 mg/kg/day on a mg/kg basis (MRHOD)] demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1,000 mg/kg/day (83,000 times the MRHOD) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses 8,300 times the MRHOD without apparent maternotoxicity.

There are no adequate and well-controlled studies in pregnant women; however, in animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. Because animal reproduction studies are not always predictive of human response, **COMBIGAN®** should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers: Timolol has been detected in human milk following oral and ophthalmic drug administration. It is not known whether brimonidine tartrate is excreted in human milk, although in animal studies, brimonidine tartrate has been shown to be excreted in breast milk. Because of the potential for serious adverse reactions from **COMBIGAN®** in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: COMBIGAN® is not recommended for use in children under the age of 2 years. During post-marketing surveillance, apnea, bradycardia, hypotension, hypothermia, hypotonia, and somnolence have been reported in infants receiving brimonidine. The safety and effectiveness of brimonidine tartrate and timolol maleate have not been studied in children below the age of two years.

The safety and effectiveness of **COMBIGAN®** have been established in the age group 2-16 years of age. Use of **COMBIGAN®** in this age group is supported by evidence from adequate and well-controlled studies of **COMBIGAN®** in adults with additional data from a study of the concomitant use of brimonidine tartrate ophthalmic solution 0.2% and timolol maleate ophthalmic solution in pediatric glaucoma patients (ages 2 to 7 years). In this study, brimonidine tartrate ophthalmic solution 0.2% was dosed three times a day as adjunctive therapy to beta-blockers. The most commonly observed adverse reactions were somnolence (50%-83% in patients 2 to 6 years) and decreased alertness. In pediatric patients 7 years of age or older (>20 kg), somnolence appears to occur less frequently (25%). Approximately 16% of patients on brimonidine tartrate ophthalmic solution discontinued from the study due to somnolence.

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

OVERDOSAGE

No information is available on overdosage with **COMBIGAN®** in humans. There have been reports of inadvertent overdosage with timolol ophthalmic solution resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

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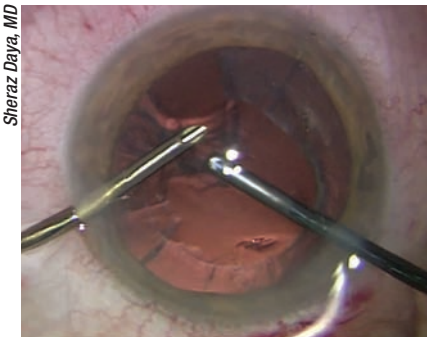
fragmentation so that you don't have to apply as much ultrasound energy to disassemble the nucleus; you won't have to perform as many maneuvers, just a standard divide and conquer technique. With these cases you also should have hooks ready to support the capsule.

"Finally, a white cataract is one situation where you won't be able to do much, if any, nuclear fragmentation," Dr. Uy continues. "The femtosecond is important in these cases, even if you just use it for the capsulorhexis, in order to avoid rupturing the anterior capsule and causing a tear in the posterior capsule that results in the Argentinian-flag sign."

Dr. Fishkind says an instrument that was on the market 10 or 15 years ago—but which never found a niche—would actually be ideal for femto-phaco. "There used to be a phaco and I/A tip that came in either 0.3- or a 0.5-mm size that never worked for anything," Dr. Fishkind says. "But now, it would be nice to use in femtosecond cases because you could use the 0.5-mm size to remove the nuclear fragments and then use the 0.3-size for the cortex. With a 0.3-mm I/A tip, for instance, if you grabbed the capsule with it, it wouldn't tear it. And 0.5-mm I/A tips will take bigger chunks of nucleus and hopefully make things more stable and decrease the risk of tearing the capsule. The other helpful instrument is the rounded Dewey tip. This is a safer phaco tip that's not very aggressive for traditional phaco. However, it lends itself to laser phaco where you don't need as much power and you're removing pieces of material that are already fragmented."

Cortex Challenges

Though some surgeons say they've been able to perform femtosecond cataract surgery with minor modifications to their technique, almost all acknowledge that the removal of cortical material is noticeably more challenging than it was with just mechanical and manual phacoemulsification. They've developed ways to counteract this difficulty, though.



Sheraz Daya, MD

Surgeons say a second instrument can sometimes make cortical cleanup easier.

"The removal of cortical remnants will be one of the biggest learning curves for the surgeon," says Dr. Stonecipher. "In a manual technique, the cortical pieces are frilly and able to be grabbed easily. In the spots where that femtosecond capsulotomy is performed, however, that capsular-cortical adhesion is tighter. So, if I can't quite get the cortex to dissect, I'll start at the posterior capsule and take the cortex up to the back of the anterior capsule as opposed to starting at the top and taking it down. Sometimes, I'll put the machine on polish mode or low-vacuum mode. That way I'll work my way backwards if I'm finding it challenging to separate the cortex. I will also tend to use a sideport incision with a bimanual technique. I'll take the aspiration off and put it on a little instrument, which is just a cannula, and bring it in through the sideport to remove any superior cortex. Also, the sub-incisional cortex can be really hard to get in these cases, so coming in from a different angle helps."

Dr. Fishkind also says the cortical removal can be confounding, and offers his advice. "There aren't any tails you can grasp," he says. "There are no pieces that are sitting out above the capsule that you can grasp and easily maneuver. It's kind of severed along the capsulorhexis so it's very smooth. You have to go under the anterior capsule, with the I/A tip pointed up, and with linear vacuum. Go in with zero aspiration and zero vacuum and come up under the anterior capsule, gently increasing either aspiration or vacuum—depending on how you've set your machine—with the linear foot pedal until you grasp the cortex and pull it down and centrally to get it away from the anterior capsule. Leave the sub-incisional cortex for last.

"You can usually get the sub-incisional cortex with a sleeved, 45-degree I/A tip from the main incision with maybe a little difficulty," Dr. Fishkind adds. "But, if you're stuck you can switch to a bimanual approach to get the sub-incisional cortex."

Dr. Uy says that, though removing the cortex may be tough, you should try to remain gentle. "There's a tendency with the femtosecond procedure for cortex to be coagulated and adhere to the anterior capsulorhexis," he says. "So, you have to be gentle with removing cortex there. It helps if you have a plastic tip or a sleeve instead of metal so you don't inadvertently cause an enlargement of a capsular tag, and so a nick won't expand to become a tear."

Dr. Fishkind says he hopes more work with femtosecond cataract surgery will lead to concrete improvement in results. "My theory about what separates laser cataract surgery from manual surgery isn't just the wow factor for surgeons," he says, "rather it's that it can soften hard nuclei and make them easier to remove so, theoretically, it should be able to remove all nuclei. By doing that—by making this removal easier—it should be safer. And, if femtosecond cataract surgery is safer there would be fewer torn capsules. And if there are fewer torn capsules it would be a wonderful improvement in the safety of cataract surgery." REVIEW

Making the Most of High-tech Biometry

Christopher Kent, Senior Editor

Today's advanced technology calls for a well-informed user in order to optimize results. Here's help.

As cataract surgery patient expectations grow, so does the need for better outcomes. Those improved outcomes depend, in turn, on ever-more accurate measurements of the eye. Today's measuring technology is impressive, but the biggest gains in accuracy have been the result of insights from astute doctors and researchers about the nature of the eye and the limitations of the measuring tools.

Here, four surgeons review the latest thinking on how best to use today's cutting-edge technology to achieve the outstanding results your patients are expecting.

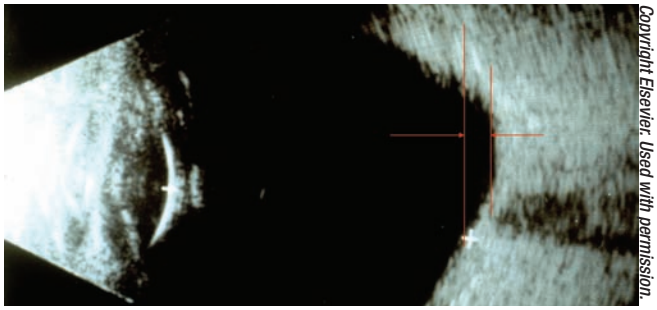
Measuring Axial Length

Certainly the most significant change in the measurement of axial length has been the shift from ultrasound to laser interferometry, or optical biometry. "Today, more than 80 percent of the surgeons I talk to are using optical biometry to measure axial length for lens power calculation," says Jack T. Holladay, MD, MSEE, FACS, clinical professor of ophthalmology at Baylor College in Houston. "That means they're using either the Lenstar or the IOLMaster, the latter being the original optical biometer on the market. About 90 percent of eyes can be measured using optical biometry; only a dense, central cataract will force the surgeon to rely on ultrasound to make the measurement."

"Biometry is not just about measuring from the tear film to the back of the eye any more," notes Michael E. Snyder, MD, who practices at the Cincinnati Eye Institute and is a volunteer assistant professor at the University of Cincinnati School of Medicine. "It's measuring all of the different interfaces that we encounter between the tear film and the back of the eye. For example, the Lenstar uses laser interferometry to measure corneal thickness, anterior chamber depth (defined as the distance from the front of the cornea to the front of the lens), aqueous depth (the distance from the back of the cornea to the front of the lens) and lens thickness. The current version of the IOLMaster gives interferometry of the axial length and also measures anterior chamber depth, although it does this using optical mechanisms rather than laser interferometry. It does not currently provide lens thickness or pachymetry."

Dr. Snyder notes that these measurements have become increasingly useful. "Latest-generation IOL power formulas such as Olsen's formula now incorporate lens thickness and anterior chamber depth, increasing their ac-

curacy," he says. "Also, having measurements such as corneal pachymetry can be clinically useful. Sometimes a patient who's in the clinic for a cataract consult has a high pressure reading. If the laser biometry measurements have already been obtained, I can review the pachymetry; if the cornea is thicker than average, I know the measurements made by applanation tonometry are going to be higher than the actual pressure."



Optical biometry measures to the fovea; ultrasound measures to the posterior pole. In long eyes (> 26 mm), the distance from the anterior corneal vertex to the posterior pole is an average of 0.8 mm longer than the distance to the foveola. That's sufficient to produce a refractive surprise when used to determine the power of an intraocular lens.

Dr. Holladay notes that optical biometry has two advantages over ultrasound. "The first is that it measures to the fovea because the patient is fixating on a target when you take the measurement," he says. "Ultrasound measures to the posterior pole, which is the longest part of the eye, a little more nasal. In long eyes, that's clearly not the right measurement, because the foveal measurement would be much shorter. It makes far more sense to measure the optical axial length than the anatomic axial length.

"The other big advantage of optical biometry is that it takes retinal thickness into account," he continues. "Ultrasound only measures to the internal limiting membrane, which is the anterior part of the retina. The photoreceptors are deep in the retina, so you have to add about 200 µm to an ultrasound measurement in order to account for retinal thickness—and retinal thickness can vary from 160 to 400 µm, so 200 µm is just a guesstimate. With optical biometry, you're measuring the actual thickness of the retina to the point you want. These two factors have led to a significant improvement in our axial length measurement when using optical biometry."

Refining Axial Measurement

Dr. Holladay notes that the precise measurement of axial length is not a simple feat, and it continues to be refined. "About two years ago, Doug Koch and Li Wang wrote an article showing that optical biometry has one of the same problems we encounter using ultrasound for this measurement," he says. "Historically, the ultrasound measurement has assumed an average velocity for the sound as it travels through the different media—cornea, aqueous, vitreous and lens—usually 1,555 meters per second. In reality, the velocity of sound through each of those media is different.

"Using an average velocity to calculate the distance traveled may provide an accurate result in an average eye, but it can confound the measurement in a very long or short eye," he continues. "The same thing is true of the index of refraction when measuring with optical biometry; the index of refraction is different for the cornea, the aqueous, the vitreous and the lens. Just as ultrasound used an average sound velocity, the IOLMaster and Lenstar use an average index of refraction. However, in long eyes the light spends a much smaller percentage of the time traveling through the lens than in an average eye, and the result is an overestimation of the axial length in long eyes.

"What Drs. Koch and Wang's article showed," he says, "was that the average being used produces an accurate measurement in an average eye with a 4.7-mm thick lens and an axial length of about 23.5. However, the measurement in a long eye might say the axial length is 33 mm when it's really only 32. That incorrect measurement will cause you to underpower the IOL and get a significant hyperopic surprise."

Dr. Holladay explains that to compensate for this, Drs. Wang and Koch developed a conversion adjustment for the axial length in eyes over 25 mm that can be plugged into the Holladay I or II, SRK/T or Hoffer Q formulas to correct for the error. "It's called the Wang-Koch axial length adjustment over 25 mm," he says. "It tells you what axial length to put into the formula to come up with the target refraction you're aiming for. Currently, none of the instruments are making this correction for you, so using the Wang-Koch conversion formula is the best way to avoid hyperopic errors today. We've incorporated it into our Holladay IOL Consultant program [at hicsoap.com] as well, to help ensure that surgeons using the IOL Consultant get the right lens power for extremely long eyes."

Dr. Holladay adds that ultrasound still has a place in the measurement of axial length. "Ten percent of patients cannot have accurate optical biometry measurements," he points out. "You have to be able to see the macula to get a good measurement. If you can't see it, neither can the instrument. You can't even get a good optical biometry measurement in a patient who has a 3- to 4-mm, dense posterior subcapsular cataract, because it blocks the center pathway. The light then takes an oblique path around the cataract and ends up giving you a longer-than-actual length. Basically, if you find you're

getting a low signal-to-noise ratio, you should be suspicious of your measurement and switch to ultrasound."

Keratometry Considerations

"We used to think of keratometry as strictly guiding us in the selection of the implant lens power," says Dr. Snyder. "Today, keratometry also helps us determine what kind of astigmatism we're dealing with and whether we want to adjust for it. We have to make sure our measurements account for astigmatism, because patients now expect both power and astigmatic accuracy. They certainly need to be offered the option of having their astigmatism corrected.

"So how do we measure the astigmatism?" he continues. "Do we measure it using topography, automatic keratometry or manual keratometry? All of these approaches become important if we're planning on correcting astigmatism because they provide different pieces of the puzzle. I like using the keratometry from the Lenstar to identify the astigmatic axis. Then, I like to qualitatively look at topography to make sure there's no irregularity, which could give me artifactual results or perhaps cause me to eliminate consideration of certain lenses. Of course, if the eye has had previous refractive surgery we need to look at other components as well."

One issue when measuring with keratometry is that each instrument measures the cornea somewhat differently, altering the result. "Manual keratometry still measures a 3.2-mm ring; the IOLMaster measures a 2.5-mm ring; the Lenstar averages a 2.35-mm and 1.65-mm ring measurement together," says Dr. Holladay. "They all give a different measurement of the same cornea, although in a normal person, the differences would be insignificant—less than a quarter-diopter. That's not the case, however, if the cornea has undergone surgery such as LASIK. LASIK treatments are not constant across the treated zone; the postop cornea will be a little flatter in the center than at the periphery. So the smaller-diameter instrument will measure a flatter K; the bigger-diameter instrument will measure a steeper K.

Different instruments and manual keratometry may give different K-readings for the same eye, in part because they measure different widths. No one width is necessarily superior. Consistently using one instrument and developing a personal constant based on those readings will optimize your outcomes.

"However, no one of those measurement diameters is necessarily any better for measuring the power on a specific patient than another," he continues. "That's why you have to personalize things. If you put your postop refractions in after surgery and personalize your lens constant for the instrument you're using, over time your constant will adjust for the bias of your particular instrument."

These differences can also affect the astigmatic axis reading. "From a purist perspective, the closer you measure to the center, the more accurate you ought to be," says Dr. Snyder. "After all, when we use our eyes we're looking through the center of the cornea. The problem is that none of the current devices is very good at measuring right at the center. They all make assumptions based on the average shape of a cornea. This is especially problematic in terms of determining the astigmatic axis.

"For example, manual keratometry is basically measuring two single points on the cornea at the 3-mm optical zone that are 90 degrees apart," he continues. "So if you have a tiny variation or some mild irregular astigmatism where one of those two points happens to fall, it can induce a very meaningful artifact. For that reason, I'm not a fan of manual keratometry, except as a double-check. I know that some people still consider manual keratometry to be the gold standard, but I personally do not.

"The IOLMaster measures six points and uses those six points to mathematically compute a best-fit oval," he says. "The longest axis of that oval is presumed to be the correct axis. But those six points are 60 degrees apart, and this is supposed to determine the axis down to a single degree. The Lenstar has 32 points in two separate concentric circles. This should be more precise, simply because the number of data points is greater. My clinical experience seems to bear this out.

"Some will suggest using corneal topography for this purpose, since it measures hundreds or thousands of data points," he adds. "As it turns out, that creates a different problem. Astigmatism is very seldom 100 percent regular from the center of the cornea out to the periphery. So the question then becomes, at what distance from the center do you measure the axis? Maybe the axis is at 20 degrees at 2 mm from the center, 18 degrees at 5 or 6 mm out and 12 degrees at 7 mm out. Which axis do you pick? One way to proceed would be to use the points closest to the center, since that's the

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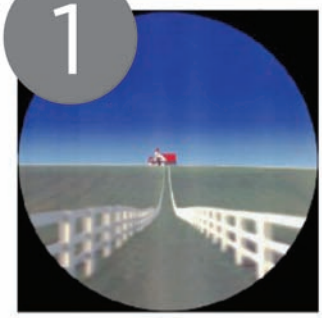
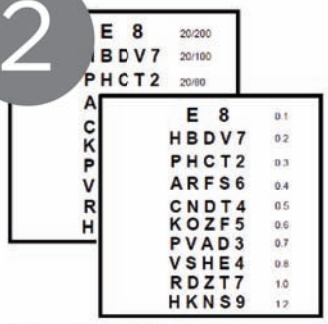


Accurate objective measurement

2



Subjective VA measurement for far & near distance

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Glare Test

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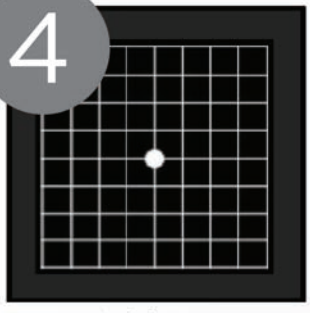

Grid Test

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Contrast Test

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part of the cornea our central vision passes through. That's a good premise, but then you're basing the axis on a small number of data points again."

The Cassini Device

Terrence P. O'Brien, MD, professor of ophthalmology and director of the Refractive Surgery Service at Bascom Palmer Eye Institute of the Palm Beaches in Miami, has for several months been using a new device that has recently become available: the Cassini corneal shape analyzer (from i-Optics in Westboro, Mass.). The instrument's design is reminiscent of a placido topographer, but it uses red, green and yellow LEDs, each one positioned in a unique relationship to four of its neighbors, to project light onto the cornea. Ray-tracing is used to measure the position of each reflected light. According to the company, the multiple colors being used, along with their asymmetric positioning, prevent errors if reflections are smeared or overlapping.

"Keratometry has been around a long time," notes Dr. O'Brien. "It works reasonably well, especially in normal eyes with normal ocular surfaces, but it's difficult to get accurate, robust information when measuring more irregular or aberrated corneas. This new instrument with its point-source color LED topography has a lot of potential to give us faster and more accurate corneal measurements than the existing placido disc or Scheimpflug imaging technologies we've been using. In our recent experience, it's given us more accurate and repeatable measurements of topography. We also believe it's improving our outcomes, although it's early. We plan to look at that in a prospective manner, especially for post-LASIK and more irregular eyes, where it seems to make the most difference.

"Most ophthalmologists are familiar with placido disc topography, as

The Cassini corneal shape analyzer uses multi-colored LEDs in asymmetric patterns to prevent reflection analysis errors and improve precision.

well as more advanced topographers that use both placido and Scheimpflug technology such as the Galilei system and the Pentacam," he continues. "Placido-based technology gives us a large number of data points describing the corneal surface, and is typically accurate to within about 0.25 D. However, because placido technology uses concentric rings, it's easier to measure changes in the radial direction than in any other direction, and source-image mismatches can be a problem.

"This new technology, with its 700 red, yellow and green LED point sources, provides us with more robust imaging," he says. "The point sources and distinct colors help make sure that there's no source-image mismatch, and that, combined with its image processing software, makes it especially useful in corneas that are less regular. These are the corneas we most often encounter in eyes that have had prior corneal surgeries, especially LASIK or PRK. The other thing is that the new device has been more repeatable when measuring abnormal eyes. In these eyes, other instruments often yield a range of results when taking multiple measurements.

"We've found that for normal eyes, all of these technologies work great," he adds. "But as the corneal curvature is increased in post-LASIK eyes, the differences among the devices become more apparent, favoring the new device."

Dr. O'Brien points out a few other advantages of the LED-based instrument. "Cassini's proprietary image capture and processing are really fast," he says. "As a result, the image and data are not affected by motion artifacts that can happen if the patient is looking around or has microsaccadic eye movements. We can typically get a good image very rapidly, even in older, less cooperative patients. Also, the 700 points cover a wider swath of the corneal surface than placido. One of the limitations of keratometry is that you're measuring a small section of the cornea, and with conventional keratometry you're even missing some of the central cornea. In addition, with some of the placido-based topographers artifacts can occur because of shadows from an eyelash, the nose or even facial features such as high cheekbones. The technology used in the new device is less prone to those kinds of artifacts."

Dr. O'Brien adds that the Cassini has recently been synchronized with the TrueVision 3-D system. "That's especially nice to have when implanting a toric IOL," he notes. "After using the Cassini to measure for a toric IOL, the link allows the TrueVision system to project a virtual image of the astigmatism and where the toric IOL should be aligned onto our surgical view. So instead of using less-than-precise handmade ink marks after measuring with super-expensive, accurate devices, this allows the surgeon to know exactly where to put the toric IOL. I think that's a big advantage."

Dr. O'Brien adds that despite the advantages of the LED device, he finds it most useful to combine the information from multiple instruments. "Each technology has advantages in terms of getting the most information

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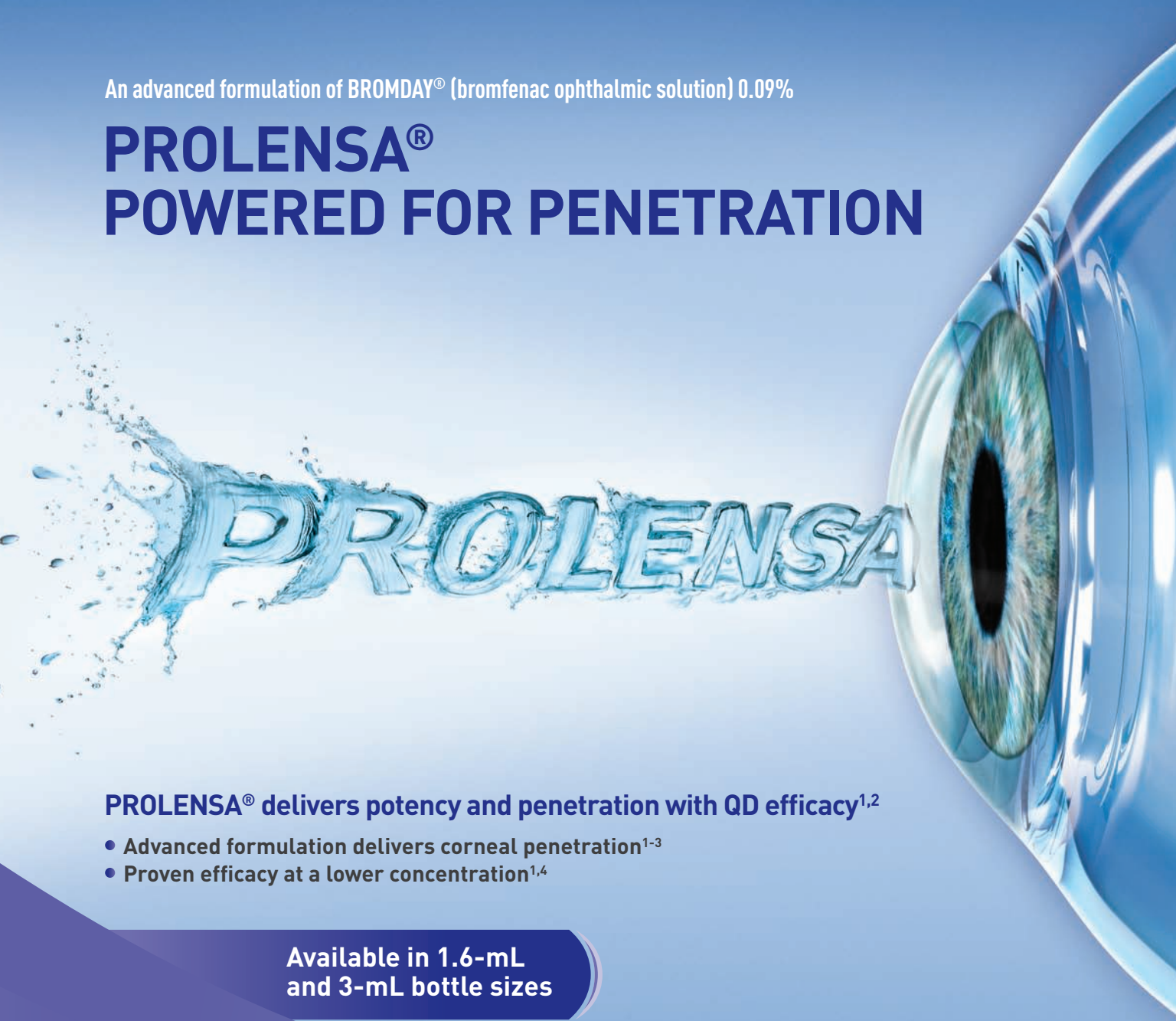

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IMPORTANT RISK INFORMATION ABOUT PROLENSA®

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

Dosage and Administration
Instill one drop into the affected eye once daily beginning 1 day prior to surgery, continued on the day of surgery, and through the first 14 days post surgery.

Please see brief summary of full 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 ^{14}C-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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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.

PROLENSA®
(bromfenac ophthalmic solution) 0.07%

Brief Summary

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Recommended Dosing

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

Use with Other Topical Ophthalmic Medications

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

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Sulfite Allergic Reactions

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

Slow or Delayed Healing

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

Potential for Cross-Sensitivity

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

Increased Bleeding Time

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

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

Keratitis and Corneal Reactions

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

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

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

Contact Lens Wear

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

ADVERSE REACTIONS

Clinical Trial Experience

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

The most commonly reported adverse reactions following use of PROLENSA 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, 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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Improving Diagnostic Capability with the iDesign Dx

Another newly available instrument that may improve surgeons' ability to analyze the cornea is the iDesign Dx from Abbott Medical Optics. The iDesign Dx system uses advanced wavefront-sensing technology to capture five optical measurements in one three-second scan. According to the company, the device can measure corneal shape, curvature and power; wavefront data; refraction; and pupil diameter under different lighting conditions—all in a single scan.

Steven C. Schallhorn, MD, in private practice in San Diego and the chief medical director for Optical Express in the United Kingdom, has used the iDesign Dx for several months. (He has also used the related iDesign Advanced WaveScan Studio, approved in Europe, for two years.) "Many practitioners have replaced manual keratometry with placido-based topography units with well-developed algorithms that can quantify irregular astigmatism," he notes. "However, these also have limitations such as failure to directly capture skew rays, and lack of accuracy in all cases. A full gradient topographer, such as that available on the iDesign Dx, has the potential for increased accuracy by covering the central cornea and capturing both the x and y slopes for each spot. This data is then used to reconstruct corneal elevation, much like Shack-Hartmann sensor methods. The result is accuracy within 0.25 D.

"Most significant to topography and wavefront technology is the degree of resolution, as higher resolution improves our ability to measure ocular aberrations with accuracy, precision and greater dynamic range," he adds. "The iDesign Dx uses five times as many lenslets as the WaveScan system, providing highly accurate spatial, angular and temporal registration of measurements. Microscopically precise measurements with a high dynamic range will improve the ability of clinicians to measure optical aberrations with great detail and accuracy, thus improving their patient outcomes."

—CK

about shape and astigmatism and the precise location of astigmatism when screening corneas," he says. "Each one also has limitations. We've found that combining them gives the most information to help with surgical planning, or to help us understand patient dissatisfaction. For example, in post-LASIK or PRK eyes, the Cassini device allows us to measure higher levels of aberration than placido technology, which is helpful in understanding why someone isn't happy with the quality of his vision. At the same time, adding Scheimpflug to the Cassini gives us more information about the posterior corneal curvature, the anterior chamber depth and so forth."

Choosing the Right Toricity

One problem with using toric IOLs to correct astigmatism—which more surgeons are doing every year—is that a number of factors affect how much toricity in the lens is needed to offset the astigmatism in the optical system of the eye. "Determining the right amount of astigmatism to correct via the IOL has turned out to be more of a challenge than originally anticipated," notes Dr. Holladay. "For example, the first toric calculators that appeared a few years ago used a constant multiplier of about 1.5 to compute the toricity needed in the IOL, based on the astigmatism in the cornea. So if you had 1 D of corneal astigmatism, they would put 1.5 D of cylinder in the IOL, independent of the power of the lens, the K-readings or the A-constant. As it turns out, the needed correction is not a constant. It varies, depending on the spherical equivalent power of the IOL, the K-readings and the distance of the IOL from the cornea.

"For example, suppose you're dealing with a normal eye that has a 44-D cornea and a 22-D IOL at the normal depth," he says. "In that situation, you would indeed need a 3-D lens to correct 2 D of corneal astigmatism. But if you have a 34-D IOL, you'll only need about 2.4 D of correction to offset the 2 D of corneal astigmatism, and if you have a 10-D IOL, you'll need almost 3.5 D of toric correction in the IOL. And that's just using the power of the lens as a variable. The IOL will also require more toricity if the cornea is steeper or if the lens is deeper in the eye. All of these variables come into play, so using a single correction factor for every case means you'll make substantial errors whenever the dimensions of the eye—the K-reading, lens power or IOL distance from the cornea—are not average."

Dr. Holladay notes that many calculators now take these factors into consideration, including the Holladay IOL Consultant, AMO's toric calculator and (soon) Alcon's next generation toric calculator and the Verion System. "However, many other calculators still use a constant," he says, "so it's important to be aware that if the eye you're dealing with is unusual in any way your calculator should take these factors into account. Otherwise, you're likely to encounter a refractive surprise.

"A second recent refinement in calculating toricity also comes from work done by Drs. Wang and Koch, and it relates to posterior-surface corneal astigmatism," he says. "When we do keratometry or topography we measure only the front surface of the cornea. Until recently, everyone assumed that if your anterior astigmatism was against-the-rule, any astigmatism on the back of the cornea would also be against-the-rule. In other words, if an

eye's steep meridian was vertical, people expected the steep meridian on the back of the cornea to be vertical as well. It turns out that isn't true.

"Using Scheimpflug technology, Drs. Wang and Koch have shown that 90 percent of the time, astigmatism on the posterior surface of the cornea is steeper vertically, irrespective of whether the front surface is with-the-rule, against-the-rule or oblique," he explains. "As a result, it's the net power of the cornea that matters in our IOL calculations, not the front surface power by itself.

"In practice, this means that if an eye has anterior against-the-rule astigmatism, the vertical posterior cornea is going to exaggerate that, so you should add 0.5 D to your toric IOL correction," he says. "If the anterior astigmatism is with-the-rule, you should subtract 0.5 D from what you measure with topography or keratometry. If the front surface astigmatism is oblique, say at 45 or 135 degrees, there's some controversy about what will work best, but most surgeons are basing their calculations on the measured amount, with no adjustment. So far, the data is showing that these corrections are indeed producing better outcomes."

Dr. Holladay notes that another approach, based on this same insight, is to simply pick the next lower or higher power toricity based on the angle of surface astigmatism. "In other words, if the patient has with with-the-rule astigmatism, go down one toricity power," he says. "So if you were going to use the T4 lens, you'd go down to the T3. Conversely, and if the eye has against-the-rule astigmatism, you'd move from the T4 up to the T5. This is called the Wang-Koch corneal astigmatism adjustment, and people using this simplified system are also getting improved results.

"It is possible to get an exact measurement so that you don't have to use a fudge factor, if you have the right technology," he adds. "We helped develop the Equivalent K-reading that's available in the Pentacam tomographer, which measures the back surface of the cornea and compensates for it, including any posterior astigmatism. Since the posterior astigmatism is with-the-rule in 90 percent of eyes, 10 percent of eyes will not be served well by the new adjustments *[described above]*. Using tomography would make sure the net astigmatism was correctly calculated, even in that 10 percent. But you have to have the technology to make that measurement, and even without it your outcomes should be improved in 90 percent of your cases simply by using the Wang-Koch adjustment."

"Ninety percent of the time, astigmatism on the posterior surface of the cornea is steeper vertically, whether the front surface is with-the-rule, against-the-rule or oblique."
— Jack Holladay, MD

Dr. Snyder adds a note of caution regarding measuring the posterior surface of the cornea. "The back surface of the cornea is not easily measureable," he points out. "A few devices in the marketplace do measure the posterior cornea, but whether they're accurate or not still has to be adequately determined. People consider these measurements the gold standard because they're all we have at the moment, but I suspect these measurements will get better in the future."

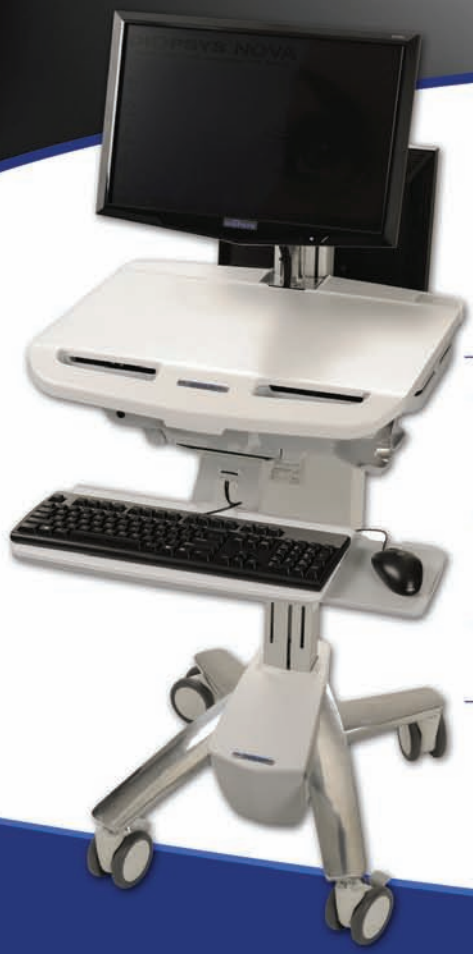
Intraoperative Aberrometry

Another way to refine cataract outcomes, of course, is to use intraoperative aberrometry to measure the refraction while the patient is aphakic on the operating table (and possibly after the lens has been implanted as well).

"There are two instruments today that provide online, real-time measurement of the refractive error of the eye when the patient is on the operating table: Wavetec's VerifEye and Clarity Medical Systems' Holos," says Dr. Holladay. "This technology allows you to take an aphakic measurement, which Wavetec has shown improves your ability to orient a toric IOL and let's you refine your spherical power so that more people are within a half diopter of the desired refraction than if you rely solely on preop measurements. This measurement accounts for everything—posterior as-tigmatism, anterior astigmatism, axial length, all of it."

Despite its advantages, not everyone is sold on this option yet, for a variety of reasons. "Doug Koch has done some fabulous work showing that the posterior surface of the cornea contributes meaningfully to the overall astigmatism of the eye," says Dr. Snyder. "Given the fact that our measurements of the posterior surface are still unproven in terms of accuracy, intraoperative aberrometry seems like a good way to surmount this concern.

"However, there are some important problems with this approach," he continues. "For example, the wound we create to remove the cataract not only alters the astigmatism a little, it also hydrates during the procedure, causing swelling. That swelling can have a significant effect on the measured astigmatism, and the amount of swelling can differ markedly from case to case. In a very short case, there will be less hydration; in a long case, there will be more. If the wound is a little too tight, there will be more hydration; if



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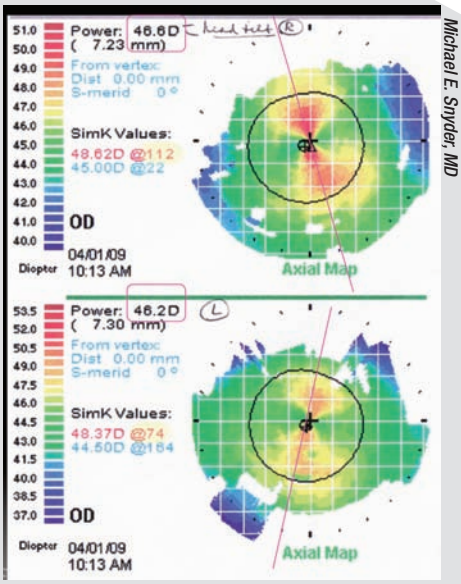
Locating the Measured Axis In the Eye During Surgery

Michael E. Snyder, MD, who practices at the Cincinnati Eye Institute and is a volunteer assistant professor at the University of Cincinnati School of Medicine, notes that a key part of measuring the astigmatic axis is being able to apply it accurately in the OR. "Unless you have some point of reference that reflects back to the positioning of the eyeball in the instrument that measured the astigmatism, you're introducing an opportunity for error," he points out. "Currently, I use the Lenstar to determine the axis; then, I take a picture of the eye using the Osher toric alignment system. This allows me to identify a perforating vessel or an iris crypt, something that I can use for alignment when the patient lies down. The problem is that the picture is not taken at the same moment the keratometry is captured. If the patient is tilting his head a little to the left or right in one of the instruments, that can introduce error.

"A few years ago I conducted an experiment to see how much this factor might affect an outcome," he continues. "I told my testing team that the next time a patient came in with a high degree of astigmatism on topography, take one reading and then have him tip his head ever so slightly to the right or left, still within the margin of what would ordinarily be acceptable when capturing the data. After a number of these had been done, we compared them. We found that the slight head tilt caused a meaningful difference in the axis reading, on the order of 10 to 15 degrees. Clearly, this will vary from individual to individual, and it could be influenced by seemingly unimportant factors; maybe the table is a little bit lower at one device than the other, or the patient's posture is a little different.

"That's why I'm looking forward to the next generation of the Lenstar," he adds. "It will capture the keratometry and topography and take a high-resolution photograph of the eye simultaneously, with the patient's head in one position. Then we will have points of reference for the globe torsion that were created at the same moment the keratometry was being measured."

—CK



Michael E. Snyder, MD

A very slight head tilt during the measurement can alter the results significantly.

the wound is a little too loose, there may be less. In addition, one person's corneal stroma may be more affected by hydration than another's. So even this technology isn't the gold standard that we want in measuring our keratometry for astigmatic correction.

"Of course, there is a perfect way to make the measurement," he notes. "We could get it right every time if we removed the cataract, left the patient aphakic and then brought him back one week later to do the wavefront aberrometry. That's really the only way to make sure that swelling from hydration doesn't affect the measurement, but the cost and inconvenience of that would be ridiculous.

"Eventually I believe we'll all be using this kind of technology, but there's a lot of refinement that needs to be done," he concludes. "There are real factors that can alter the measurement that we don't yet know how to fully compensate for."

Some surgeons also question whether the extra time and expense required to use this approach is worthwhile, in terms of the number of outcomes that are altered. Dr. O'Brien worked with intraoperative aberrometry for a short time and was not impressed enough to pursue it. "It didn't seem to make a huge difference," he says. "On a day with 20 cases, there were only one or two cases where it made a significant difference—but it added a lot of time to each surgery. The OR staff couldn't understand why we spent 10 minutes on it in every case when it didn't change the outcome most of the time. And of course, you have to be careful to inflate the anterior chamber to just the right physiologic pressure and shape to ensure an accurate reading.

"Also, do we need this when our measurements on the front end continue to get more robust, more reliable, faster and more reproducible?" he continues. "Plus, intraoperative aberrometry is not reimbursable and the cost is significant. I think the average surgeon is wondering how he can afford a femtosecond laser for cataract surgery, two or three expensive preoperative imaging devices, plus an intraoperative device."

Dr. Holladay acknowledges that, regardless of its advantages, practical considerations are likely to keep intraoperative aberrometry from replacing the need for preop measurement any time soon. "The preop measurements allow the surgeon to go into surgery with a set of lenses that he's bracketed to make sure he has what the patient needs," he points out. "About 60 percent of the time intraoperative aberrometry causes the surgeon to change the choice of lens he was going to use, up or down 0.5 D, so he has to bring six lenses to cover all possible bases.

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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.

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.

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 Brief Summary of full Prescribing Information on adjacent page.

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TRAVATAN Z®
(travoprost ophthalmic solution) 0.004%

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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5/13 TRV13049JAD

Without a preoperative measurement, he'd have to have access to a complete inventory during surgery, which could be a logistical nightmare."

There are other issues as well. "About one-third of the revenue that the surgeon generates from cataract surgery is from obtaining preop biometry," Dr. Holladay points out. "No one is going to give that up, at least until there's a reimbursement for intraoperative aberrometry. At this point no one is trying to obtain that, because ironically, a surgeon can charge the patient more to use this technology right now than he'd get if it was covered by Medicare. For all of these reasons, intraoperative aberrometry won't replace preop measurements any time soon."

Optimizing Your Outcomes

These strategies can help you make the most of the current technology:

• ***Don't wait any longer to switch to laser biometry.*** "This technology has been around for many years, and it is superior," says Dr. Snyder. "Laser interferometry has become the gold standard in axial biometry. It provides the best measurement we can get, while making the fewest possible assumptions. In contrast, ultrasound measurement always depends on whether we're close enough to the posterior axis, whether there's a posterior staphaloma or the macula is sloped relative to the instrument. Even the density of the cataract can cause the sound waves to be transmitted differently, leading to an inaccurate calculation of the measurement. Not every eye can be measured with laser biometry, but most can, especially with the newer devices."

• ***Use a different personalized A-constant when readings are made by ultrasound vs. laser biometry.*** "Clinicians sometimes end up looking at records from another practice where the measurements were made using a different technology," says Dr. Snyder. "Also, some clinicians work in an institution where both ultrasound and laser biometry are in use. In that situation, you need to keep in mind that when using ultrasound, the primary spike gives the measurement to the front surface of the retina, the vitreo-retinal interface. In contrast, laser biometry measures to the retinal pigment epithelium. So, assuming the ultrasound measurement is otherwise perfect, the same measurement made using laser biometry will be longer by the thickness of the retina. Because the average thickness of the macula is only 0.25 mm, you might not think this would make a significant difference, but it can have a meaningful impact. Generally, every millimeter of axial length is equivalent to about 3 D of refractive change. So a quarter of a millimeter error could induce 0.75 D of refractive surprise. To compensate for that you need to have a different personalized A-constant for ultrasound than for laser interferometry."

• ***Pay attention to astigmatism.*** "I believe a discussion of astigmatism correction with every astigmatic patient has now become the standard of care," says Dr. Snyder. "Skipping this discussion is becoming a challenge for informed consent. I'm not suggesting that every surgeon has to make those corrections; you may feel that your patient population won't be able to pay for astigmatism correction, so you don't offer it. If you choose not to correct astigmatism, you can offer to refer to someone else who does. But you need to tell the patient that these technologies exist. Today, excuses won't cut it with an unhappy patient, and a brief, candid preoperative discussion can save a lot of aggravation."

• ***Even if you're not adjusting for astigmatism, collect the data.*** "As long as you're measuring astigmatism preoperatively, you can look at postoperative astigmatic outcomes that correlate with your particular approach so you can best advise your patients on their options and what to expect," says Dr. Snyder. "That in itself has value."

• ***If you can't acquire laser biometry data in a given eye, use immersion ultrasound, not contact ultrasound.*** "Immersion ultrasound does not compress the anterior chamber, so the measurements are more accurate and more reproducible than those obtained using contact ultrasound," says Dr. Snyder. "Of course, immersion may be impossible in some individuals because of orbital anatomy or lack of cooperation. In that case contact A-scan remains the old standby."

No Perfect Device—Yet

Dr. O'Brien notes that the increasing variety of technologies available to ophthalmologists has become a challenge for many clinicians. "Our group has an advantage, being at a large academic center where we can have several platforms," he says. "But a person in practice needs to make an informed decision. Everyone has placido technology, but everyone is also aware of its limitations.

"Now clinicians are asking, which of these new instruments should I opt for?" he continues. "Few practices can afford all of them. At the same time, as we move forward with femtosecond laser procedures and toric IOLs—not to mention multifocal toric IOLs—we want the most robust imaging we can get, at the most affordable price. It would be great if one device could do everything and put it all together for us. But anyone waiting to purchase the single perfect instrument will have to wait a little while longer." REVIEW

Dr. Snyder is a consultant for Haag Streit and Alcon. Dr. O'Brien has no financial interest in i-Optics or the Cassini instrument. Dr. Schallhorn is a consultant for AMO. Dr. Holladay is a consultant for AMO, Alcon, Oculus and Wavetec. He can be reached at docholladay@docholladay.com.

A New Take on Allergy Diagnostics & Treatment

Neel R. Desai, MD, and Robert J. Weinstock, MD, Largo, Fla.

New diagnostics may be a boon to both patient care and practice development.

Until recently, the treatment of ocular surface diseases, including allergic conjunctivitis, dry-eye syndrome and other ocular surface inflammatory diseases, lay frozen in the dark ages of ophthalmic care and science. Whole generations of ophthalmologists and eye-care professionals had been indoctrinated in to a mode of thinking about ocular surface diseases that amounted to treating such patients dismissively with little more than palliative care.

However, in just the last five to 10 years we have been witness to a veritable renaissance in not only the available diagnostic and treatment modalities but, perhaps more critically, the value practitioners place on attentively diagnosing and treating these diseases. We can, in part, credit the merger of the refractive and cataract worlds with placing these otherwise minor issues closer to the forefront of surgeons' considerations as they play a major role in achieving precision outcomes and maintaining high levels of patient satisfaction.

This paradigm shift represents a boon for, first and foremost, good medicine and patient care but also for practice growth and development. In this article, we wish to share with you our experiences with some of the newer diagnostic modalities, specifically ocular allergy testing, that have benefited our patients and, in turn, our practice.

The Shotgun Approach

If we are to be honest with ourselves, when faced with a red, irritated set of eyes, many practitioners might reflexively treat with a "shotgun" approach—often recommending artificial tears, a favored antibiotic-steroid drop, and/or antihistamine, without so much as a fleeting thought about true underlying etiology. Studies showing that up to 20 percent of patients with ocular surface disease complaints have undiagnosed and significant systemic diseases, underline our collective failure to systematically tease apart the potential separate but additive contributions of allergic processes, aqueous tear insufficiency, meibomian gland and lid margin disease, infectious processes, or other proinflammatory states from one another.[1] Does a patient with ocular irritation simply have dry eyes or does she also have ocular rosacea-driven lid margin disease, poor meibomian gland function, and hence tear-film instability? Does the patient with chronic redness and vague irritation have dry eyes alone, or an underlying

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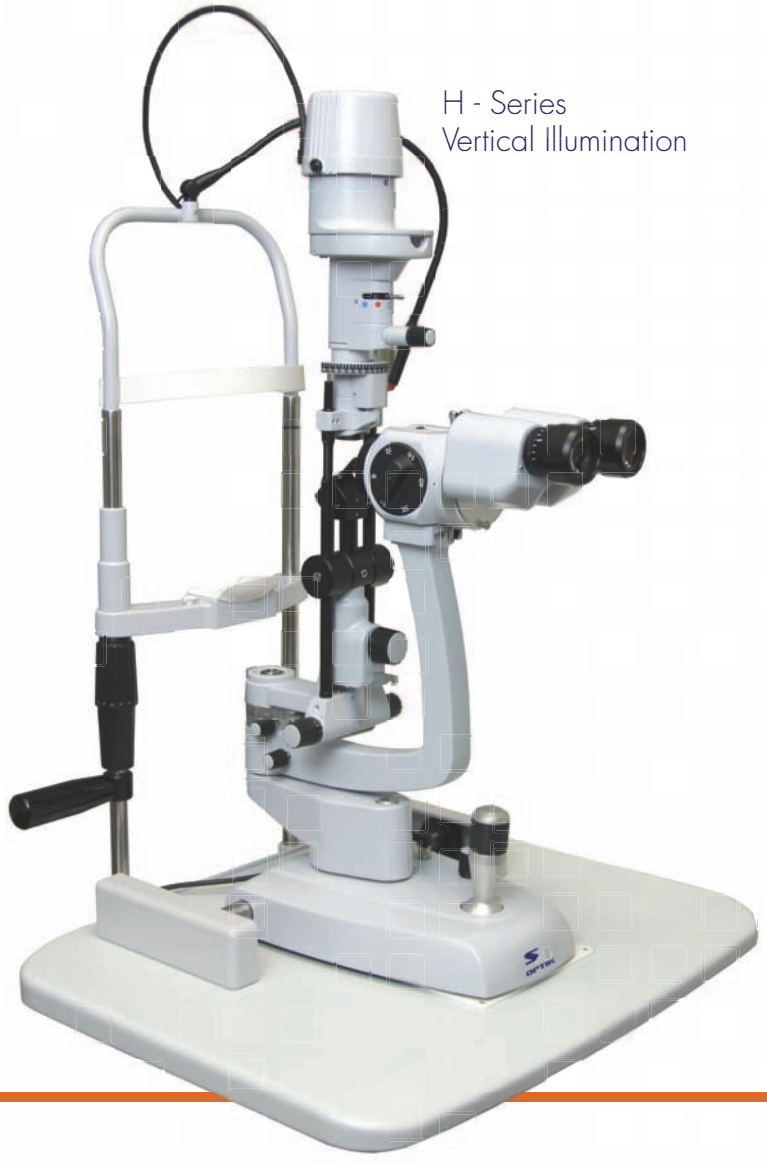

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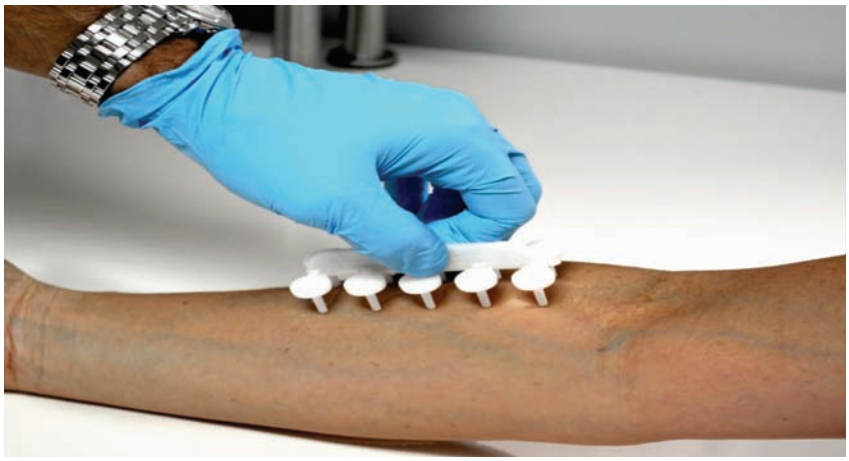

In about 10 minutes, this in-office test from Doctor's Allergy Formula can help isolate specific allergens that contribute to the patient's ocular allergy disease.

systemic inflammatory condition? Are ocular allergies playing a role in either of these very common clinical circumstances? How can we expect to adequately respond to each patient's unique mix of complaints if we don't make an effort to uncover the constellation of problems that contribute to the overall disease state? The answer to these questions is quite simply, "Seek and ye shall find."

The Scope of the Problem

There is no question as to the scope of the problem and the scale of the market in this arena. Population-based studies show that the rate of allergic disease is on the rise, encompassing patients with seasonal and perennial allergic conjunctivitis, vernal keratoconjunctivitis, atopic keratoconjunctivitis and giant papillary conjunctivitis.[2] Seasonal and perennial allergies, tied to the expression of specific IgE antibodies to environmental allergens, make up the most common form of ocular allergy and affect up to 15 to 20 percent of the population.[3] In this form of ocular allergy, allergens interact with IgE bound to sensitized mast cells, resulting in the acute hypersensitivity reaction characterized by mast-cell degranulation, increased levels of histamine, prostaglandins, leukotrienes and other pro-inflammatory molecules in the tear film. Mast-cell activation also triggers the expression of chemokines, adhesion molecules and other chemoattractive proteins that recruit and activate T-cells and macrophages in the conjunctival mucosa, characterizing the late-phase reaction.[4]

In our own practice, where close to 40 percent of patients report some form of ocular surface complaint and where many have been inadequately treated or dismissed by other eye-care professionals, we were long ago encouraged to create a true ocular surface disease clinic or service within our multispecialty practice. The attentive reception and methodical approach patients receive there has yielded happier, less-symptomatic patients for sure, but has also helped grow this segment of the practice exponentially and created a new gateway for new patients entering the practice—hence feeding the refractive, cataract, optometric, glaucoma, retina and oculoplastic services wherever needed.

How Testing Changes Treatment

Appropriate management of ocular surface disease hinges entirely on identifying the underlying etiology, contributing conditions (e.g., allergy), and enlisting other healthcare providers such as specialists in rheumatology or allergy and immunology. While the diagnosis of ocular surface diseases is largely a clinical challenge, diagnostic testing has proven immensely helpful in providing patients and practitioners a systematic rationale for treatment. Laboratory testing for underlying conditions contributing to dry eye and other ocular surface inflammatory diseases, now available as an easy in-office testing kit (Sjo Test, Nicox, Dallas), often uncovers previously undiagnosed rheumatologic and autoimmune disorders, that, if treated in conjunction with appropriate specialists, will yield greater relief for patients' ocular conditions while avoiding potentially devastating systemic manifestations.

Since the first step in treatment of ocular allergy is avoidance of the allergen, knowledge of specific offending allergens is critical to proper management.[5,6] When our practice first began to offer in-office allergy testing, we found that up to 80 percent of our practice's patients who reported allergic ocular symptoms such as redness, irritation, burning, itching and watering, had never been allergy tested. The vast majority of those who had been tested were tested more than five years earlier, and had no recollection of the specific allergens to which they were found allergic. Furthermore, most patients have never been prescribed treatment for ocular allergies, and instead resorted to over-the-counter remedies or relegated themselves to suffering. Such data demonstrates how this segment of the population has been grossly under-recognized and undertreated, while offering an incredible opportunity for the kind of practice growth beneficial to practices and patients alike.

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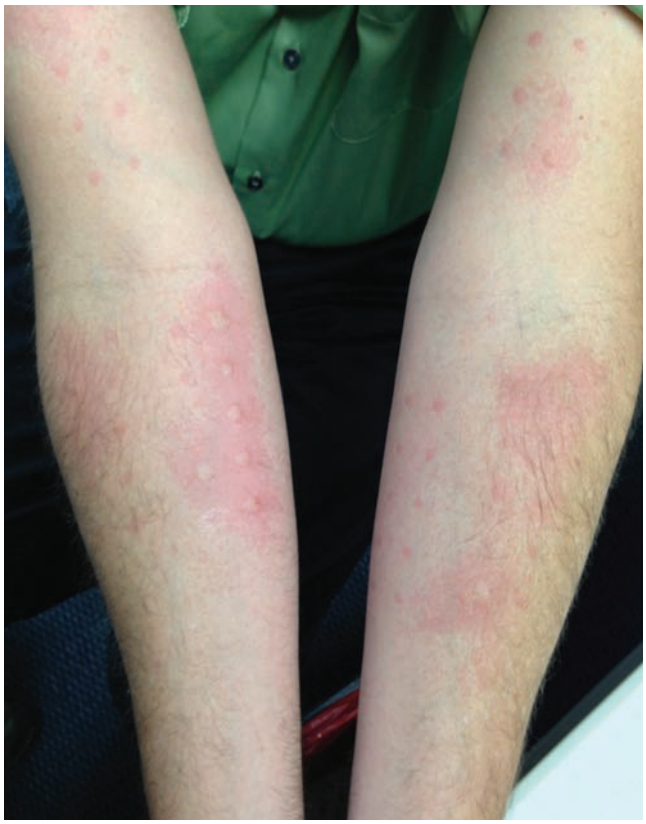

A first step in moving beyond the traditional shotgun approach to ocular allergy is determining whether the patient with chronic redness and vague irritation has dry eyes alone or an underlying systemic inflammatory condition.

In-office allergy testing, as described, has offered us greater confidence first, in knowing that allergies are playing a contributing role at all, and second, in directing pharmacological treatment. Pharmacological therapy represents the mainstay of treatment in ocular allergies when behavioral and environmental modifications alone are inadequate. Patients with multifactorial ocular surface disease who test positive for allergies can then be placed on appropriate pharmacologic therapy to, at minimum, resolve one of many contributing factors. Conversely, patients who test negative for all allergens or who do not show a minimal response to the histamine control are unlikely to benefit from treatment with topical or systemic antihistamines or mast cell stabilizers—the underlying etiology of the ocular surface complaints would warrant further evaluation. It bears noting that many topical antihistamines themselves can promote ocular surface drying and hence worsen symptoms. Therefore, it is critical that allergy testing be performed instead of a knee-jerk initiation of therapy.

In our practice, patients are referred into one of our weekly allergy testing clinics, wherein a trained technician administers the test and notes positive and negative responses. Such clinics run parallel to our regular clinic hours and allow for the most efficient use of time and resources. Patients are immediately provided written literature on the specific allergens to which they positively reacted, as well as instruction on avoidance. Patients follow up with us a few weeks later to review the testing results, recommend immunotherapies, make appropriate referrals and address other elements of their ocular surface disease, such as rosacea, blepharitis and posterior lid margin disease, and their respective therapies.

Topical antihistamines competitively and reversibly block histamine receptors and relieve itching and redness, but only for a short time. These medications do not affect other proinflammatory mediators, such as prostaglandins and leukotrienes, which remain uninhibited. Over-the-counter decongestants work to reduce redness via their vasoconstrictive mechanism of action. However, such medications may worsen the condition with chronic use; burning, stinging on instillation, rebound hyperemia and conjunctivitis medicomentosa are common with long-term use.[7] Mast-cell stabilizers inhibit degranulation of mast cells and thus blunt the release of histamine and other chemotactic factors but can do so only prophylactically. Hence, by themselves they do not reduce ocular surface inflammation or relieve symptoms. Azelastine is a selective second-generation H1 receptor antagonist, and also acts by inhibiting platelet activating factor (PAF) and blocking expression of intercellular adhesion molecule 1 (ICAM-1).[8] Epinastine has effect on both H1 and H2 receptors (the latter effect may be beneficial in reducing the eyelid swelling), and also has mast-cell stabilizing and anti-inflammatory effects.[9] NSAIDS and steroids can also help to inhibit the inflammatory cascade, but have limited use due to side effects with long-term

use. Immunotherapy with subcutaneous injections has been well-known to desensitize patients to specific antigens but has been used primarily to address allergic rhinitis rather than allergic conjunctivitis. However, sublingual (oral) immunotherapy (SLIT) is gaining momentum among allergists and may provide an opportunity for ophthalmologists to address the needs of our own subset of patients.[10]

Targeted & Methodical Approach

With approximately 24 million ocular allergy sufferers, many of whom demonstrate other concomitant ocular surface diseases, the reflexive "shotgun" approach to ocular surface disease leaves far too many patients inadequately diagnosed and treated. Practices that instead adapt to this growing population of patients and adopt burgeoning diagnostic and treatment modalities to home in on specific contributing factors such as ocular allergy, will be well-positioned to, at once, serve the needs of their patients and grow their practices.

Thus far, our patients are responding well to this new paradigm in ocular surface disease management that now includes in-office allergy testing. Many patients have expressed a sense of relief not only from any actual therapy, but from finally having a sense that their condition and symptoms are being compassionately acknowledged and methodically addressed. REVIEW

Drs. Desai and Weinstock practice at the Eye Institute of West Florida in Largo, Fla. They report no financial interest in any product mentioned in this article.

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First Steps in Creating A Pharma Start-up

William C. Stewart, MD, Jeanette A. Stewart, RN, and Lindsay A. Nelson, BS, Cheyenne, Wyo.

A primer for ophthalmologists on starting a new pharmaceutical company and bringing a new drug to market.

As a basic scientist or physician you may have conceived of a new idea for a product that might be a good basis for a dynamic pharmaceutical start-up. However, perhaps your initial euphoria about the idea may have quickly receded and you realized that the difficulties of actually creating such an enterprise seemed insurmountable.

Physicians and scientists typically are not trained to create pharmaceutical start-ups. As your routine responsibilities of teaching, patient care or research demand your time and resources, taking steps to initiate your new company may appear impossible. In addition, the effort required to resolve any university-related intellectual property and contract issues may impose further obstacles.

Join us in the next few pages as we discuss the foundational steps in beginning a start-up that can lead to an actual functioning pharmaceutical company. We hope the article eases your burdens as you implement your idea to help patients in the coming years. This article is intended only as a primer on starting a new pharmaceutical company and cannot replace more detailed information from Food and Drug Administration documents and appropriate consultants.[1] Additional information is also available in our prior global overview "The Start-up: From Dream to Reality") *(See Review of Ophthalmology, April 2013 issue, p. 62.)*

Is It the Right Idea?

• ***Can the medicine work?*** Even now you may have a spectacular new idea for a new medicine and are excited over its prospects for success. Perhaps this potential product will fulfill a personal dream related to professional, financial or humanitarian reward.

But be careful. Your excitement can lead to "product blindness." The facts are brutal: On aver-

Alphagan P 0.1%
(brimonidine tartrate ophthalmic solution) 0.1%

EXTEND YOUR REACH...

All the Way From Prescription to Patient

Make certain your ALPHAGAN® P 0.1% Rx is filled the way you intended

INDICATIONS AND USAGE

ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 0.1% or 0.15% is an alpha-adrenergic receptor agonist indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Neonates and Infants (under the age of 2 years): ALPHAGAN® P is contraindicated in neonates and infants (under the age of 2 years).

Hypersensitivity Reactions: ALPHAGAN® P is contraindicated in patients who have exhibited a hypersensitivity reaction to any component of this medication in the past.

WARNINGS AND PRECAUTIONS

Potentiation of Vascular Insufficiency: ALPHAGAN® P may potentiate syndromes associated with vascular insufficiency. ALPHAGAN® P should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans.

Severe Cardiovascular Disease: Although brimonidine tartrate ophthalmic solution had minimal effect on the blood pressure of patients in clinical studies, caution should be exercised in treating patients with severe cardiovascular disease.

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

DRUG INTERACTIONS

Antihypertensives/Cardiac Glycosides: Because ALPHAGAN® P may reduce blood pressure, caution in using drugs such as antihypertensives and/or cardiac glycosides with ALPHAGAN® P is advised.

CNS Depressants: Although specific drug interaction studies have not been conducted with ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 0.1% or 0.15%, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered.

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

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

ADVERSE REACTIONS

Adverse reactions occurring in approximately 10% to 20% of the subjects receiving brimonidine ophthalmic solution (0.1% to 0.2%) included: allergic conjunctivitis, conjunctival hyperemia, and eye pruritus. Adverse reactions occurring in approximately 5% to 9% included: burning sensation, conjunctival folliculosis, hypertension, ocular allergic reaction, oral dryness, and visual disturbance.

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

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Alphagan P 0.1%
(brimonidine tartrate ophthalmic solution) 0.1%

ALPHAGAN® P

ALLERGAN

(brimonidine tartrate ophthalmic solution)
0.1% and 0.15%

BRIEF SUMMARY

Please see **ALPHAGAN® P** package insert for full prescribing information.

INDICATIONS AND USAGE

ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 0.1% or 0.15% is an alpha adrenergic receptor agonist indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

CONTRAINDICATIONS

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ALPHAGAN® P is contraindicated in neonates and infants (under the age of 2 years).

Hypersensitivity Reactions
ALPHAGAN® P is contraindicated in patients who have exhibited a hypersensitivity reaction to any component of this medication in the past.

WARNINGS AND PRECAUTIONS

Potentiation of Vascular Insufficiency
ALPHAGAN® P may potentiate syndromes associated with vascular insufficiency.

ALPHAGAN® P should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans.

Severe Cardiovascular Disease
Although brimonidine tartrate ophthalmic solution had minimal effect on the blood pressure of patients in clinical studies, caution should be exercised in treating patients with severe cardiovascular disease.

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

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.

Adverse reactions occurring in approximately 10-20% of the subjects receiving brimonidine ophthalmic solution (0.1-0.2%) included: allergic conjunctivitis, conjunctival hyperemia, and eye pruritus. Adverse reactions occurring in approximately 5-9% included: burning sensation, conjunctival folliculosis, hypertension, ocular allergic reaction, oral dryness, and visual disturbance.

Adverse reactions occurring in approximately 1-4% of the subjects receiving brimonidine ophthalmic solution (0.1-0.2%) included: abnormal taste, allergic reaction, asthenia, blepharitis, blepharoconjunctivitis, blurred vision, bronchitis, cataract, conjunctival edema, conjunctival hemorrhage, conjunctivitis, cough, dizziness, dyspepsia, dyspnea, epiphora, eye discharge, eye dryness, eye irritation, eye pain, eyelid edema, eyelid erythema, fatigue, flu syndrome, follicular conjunctivitis, foreign body sensation, gastrointestinal disorder, headache, hypercholesterolemia, hypotension, infection (primarily colds and respiratory infections), insomnia, keratitis, lid disorder, pharyngitis, photophobia, rash, rhinitis, sinus infection, sinusitis, somnolence, stinging, superficial punctate keratopathy, tearing, visual field defect, vitreous detachment, vitreous disorder, vitreous floaters, and worsened visual acuity.

The following reactions were reported in less than 1% of subjects: corneal erosion, hordeolum, nasal dryness, and taste perversion.

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

DRUG INTERACTIONS

Antihypertensives/Cardiac Glycosides
Because **ALPHAGAN® P** may reduce blood pressure, caution in using drugs such as antihypertensives and/or cardiac glycosides with **ALPHAGAN® P** is advised.

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy
Pregnancy Category B: Teratogenicity studies have been performed in animals.

Brimonidine tartrate was not teratogenic when given orally during gestation days 6 through 15 in rats and days 6 through 18 in rabbits. The highest doses of brimonidine tartrate in rats (2.5 mg /kg/day) and rabbits (5.0 mg/kg/day) achieved AUC exposure values 360- and 20-fold higher, or 260- and 15-fold higher, respectively, than similar values estimated in humans treated with **ALPHAGAN® P** 0.1% or 0.15%, 1 drop in both eyes three times daily.

There are no adequate and well-controlled studies in pregnant women; however, in animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. Because animal reproduction studies are not always predictive of human response, **ALPHAGAN® P** should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether brimonidine tartrate is excreted in human milk, although in animal studies, brimonidine tartrate has been shown to be excreted in breast milk. Because of the potential for serious adverse reactions from **ALPHAGAN® P** in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
ALPHAGAN® P is contraindicated in children under the age of 2 years (see **CONTRAINDICATIONS**). During postmarketing surveillance, apnea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in infants receiving brimonidine. The safety and effectiveness of brimonidine tartrate have not been studied in children below the age of 2 years.

In a well-controlled clinical study conducted in pediatric glaucoma patients (ages 2 to 7 years) the most commonly observed adverse reactions with brimonidine tartrate ophthalmic solution 0.2% dosed three times daily were somnolence (50-83% in patients ages 2 to 6 years) and decreased alertness. In pediatric patients 7 years of age (>20 kg), somnolence appears to occur less frequently (25%). Approximately 16% of patients on brimonidine tartrate ophthalmic solution discontinued from the study due to somnolence.

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

Special Populations
ALPHAGAN® P has not been studied in patients with hepatic impairment.

ALPHAGAN® P has not been studied in patients with renal impairment. The effect of dialysis on brimonidine pharmacokinetics in patients with renal failure is not known.

OVERDOSAGE

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility
No compound-related carcinogenic effects were observed in either mice or rats following a 21-month and 24-month study, respectively. In these studies, dietary administration of brimonidine tartrate at doses up to 2.5 mg/kg/day in mice and 1 mg/kg/day in rats achieved 150 and 120 times or 90 and 80 times, respectively, the plasma C_{max} drug concentration in humans treated with one drop of **ALPHAGAN® P** 0.1% or 0.15% into both eyes 3 times per day, the recommended daily human dose.

Brimonidine tartrate was not mutagenic or clastogenic in a series of in vitro and in vivo studies including the Ames bacterial reversion test, chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, and three in vivo studies in CD-1 mice: a host-mediated assay, cytogenetic study, and dominant lethal assay.

Reproduction and fertility studies in rats with brimonidine tartrate demonstrated no adverse effect on male or female fertility at doses which achieve up to approximately 125 and 90 times the systemic exposure following the maximum recommended human ophthalmic dose of **ALPHAGAN® P** 0.1% or 0.15%, respectively.

PATIENT COUNSELING INFORMATION

Patients should be instructed that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions (see **WARNINGS AND PRECAUTIONS**). Always replace the cap after using. If solution changes color or becomes cloudy, do not use. Do not use the product after the expiration date marked on the bottle.

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

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

As with other similar medications, **ALPHAGAN® P** may cause fatigue and/or drowsiness in some patients. Patients who engage in hazardous activities should be cautioned of the potential for a decrease in mental alertness.

Rx Only

Revised: 11/2011

Based on package insert 71816US15C

APC57BC13

Alphagan® P 0.1%
(brimonidine tartrate ophthalmic solution) 0.1%

age, a new, undeveloped medication has only a very low chance of reaching commercialization.[2] Further, there are already more than 300 products currently being developed by both large and small pharmaceutical companies in ophthalmology alone. *(Internal data, PRN PharmaFarm)* Consequently, despite your enthusiasm you should make an honest assessment of your idea and its potential for success.

This assessment begins with a frank discussion with yourself regarding several vital questions, shown in Table 1. Ideally, the answers should be backed by data and not just opinion. Answering these questions is important so you can create a complete and compelling story about your new medicine's advantageous actions on a molecular level to treat the targeted disease.

If you cannot yet answer all the questions in Table 1, they preferably should be known before you seek institutional funding. Consultation initially, perhaps with close knowledgeable colleagues, may be needed to help answer these questions in areas beyond your own expertise. Importantly, before seeking other opinions, you should protect yourself legally. *(Please see confidentiality discussion below in "Legally Correct.")* After executing confidentiality commitments, you may more safely initiate discussions with colleagues.

However, despite your close colleagues' advice, you may need more assistance. Even at this early stage of development, brief initial discussions with industry-based consultants or contract research organizations (CROs) dedicated to assisting start-ups may help answer the more difficult questions. The type of consultants contacted would depend on the advice you need. *(Please see Table 2 for the list of consultant or contractor types we discuss in this regard.)* Often these individuals or companies will offer a complimentary initial discussion regarding a new idea, or work in part for equity.

Table 1. Initial Questions About the Function of a New Medicine

What is the mechanism of action?
What is the exact indication?
What unique problem does your medicine solve?
What is the molecular biological link to treat the targeted disease?
Can this medicine be delivered to the target tissue in sufficient levels to initiate its pharmacodynamic action?
What are the advantages over current therapies?
Are there any potential safety issues?

• ***Can you develop it?*** To a large degree, answering this requires an examination of some regulatory issues. First, identify the exact indication. Next, determine whether it has a known regulatory pathway, including a clear primary efficacy variable and if that pathway is feasible, too time consuming or expensive. Early consultation with a regulatory expert may be helpful.

Assuming your product is not a generic (505j application), another early step is to identify the type of new drug application, or NDA, that you will file to gain approval for the product. Most applications will require a 505b1 route, which is a full application for a new clinical entity, or NCE. There are occasions, however, when prior data exist for a new product, which allows for submission of an application known as a 505b2.[3] This type of application can save much time and money in your development process.

• ***Can you sell it?*** Once you determine your medicine can function as you intend, with a reasonable regulatory pathway, you must consider whether you can actually sell it. Again, this assessment requires critical, realistic thinking. Please see Table 3 for a summary of key questions to ask.

The initial question—potential market size—is the easy one; it's the number of people with the disease within the chosen treatment indication, to whom you can sell your product. This

Table 2. Potential Types of Consultants/Contractors to Assist a Pharma Start-up

Legal	Patent attorney
	Corporate attorney
	Start-up-experienced attorney
Administrative	Assistant
	Bookkeeper
	Accountant
	IT expert
Pharmaceutical	Overall development specialist
	Product manufacturing*
	Formulation manufacturing*
	Regulatory
	Clinical development*
	Preclinical development*
Market	Market assessment
	Reimbursement

*Consultant or CRO

data generally is accessible from an Internet search. This is the point where many inventors, and even chief executive officers, stop their analysis. Be careful though. Do not assume that doctors will readily prescribe a product only because it becomes commercially available. Unfortunately, this may not be the case.

Therefore, you must consider the next level of questions: What market penetration can your product realize within the existing patient population? And at what level of therapy will the product be used? Answering these two questions will help you project the rate at which your new product might be reasonably prescribed. Importantly, these questions should be answered by factual data, not just the opinion of a close colleague or you.

Also important is a SWOT analysis, which involves thinking though the Strengths, Weakness, Opportunities and Threats of every product. You should include an honest assessment of the current competition and why your new idea is better. Consider also future competition based on what is currently in development.

Next ask yourself: Who will pay? Will this be a self-paid product or is it for an indication and price level that will require private and government reimbursement? Consultants again are available to create initial assessments regarding this reimbursement.

Last, consider what you will do if your primary plans for your chosen treatment indication fail. What backup plans do you have as a secondary indication for commercialization?

Table 3. Market Assessment Questions

What is your potential market size?
What percent of the market can you capture?
At what stage of therapy will the medicine be used?
What is the SWOT analysis?
Who will pay for the medicine?
What are the backup plans should the primary plans fail?

You can perform inexpensive analyses by surveying ophthalmologists or optometrists to better understand if there is a perceived need for the new treatment. Further, cost effective patient surveys can be performed in physicians' offices, shopping malls or online as appropriate. Consider using an inexpensive survey website such as Survey Monkey (surveymonkey.com). The survey questions might assess: delivery route; dosing; willingness to pay out-of-pocket; perceived clinical need; place in therapy; and impact of potential safety issues. Additionally, speaking with members of the business development office at large pharma companies may provide you with a sense of potential future interest in your product.

Legally Correct

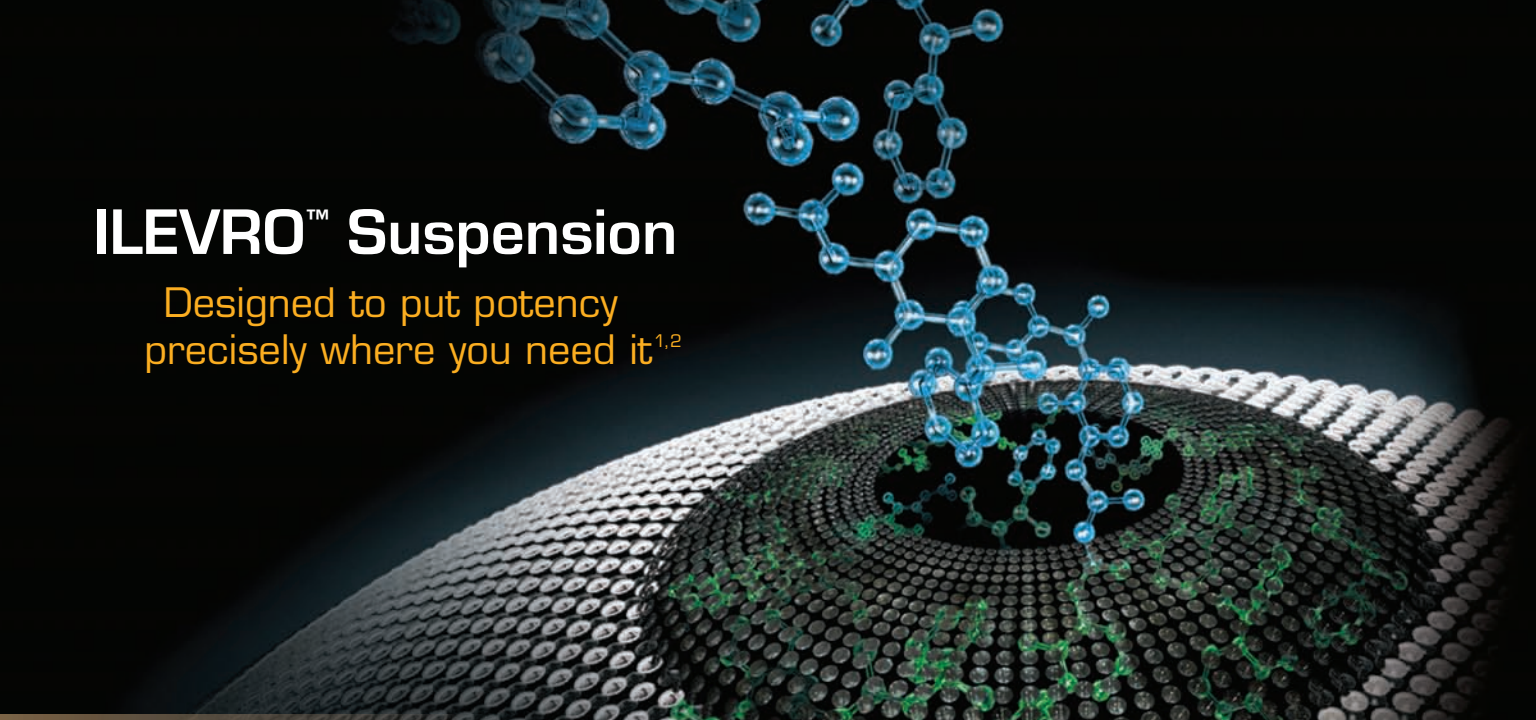
Protecting your valuable intellectual property and your own personal assets is important even at an early stage. Consider a few relatively simple steps.

• ***Patent protection.*** As soon as able, you should find a reliable pharma-experienced patent attorney to aid in developing an initial filing for your patent in the United States or other target country. The initial filing for a patent can be fairly inexpensive. The patent filing is not an issued patent itself, but will provide protection so another individual cannot file the same invention. This attorney also can initially analyze your start-up's freedom-to-operate within the scope of existing patents and public information (prior art) for the product, its formulation as well as its indication and how it will be delivered.[4]

• ***Confidentiality.*** Prior to discussing your medicine with anyone you should request a confidentiality agreement, or CDA. Templates for these documents can be found online and adapted to personal preferences. If any doubts exist about the quality of a CDA template, you should send it to a corporate attorney to review. Once a CDA has been signed, discussions about intellectual property can proceed. However, take care always to limit your IP discussions to those you trust, as even a well-written CDA may not assure complete confidentiality.

• ***Incorporation.*** Early in the development process you should incorporate to protect yourself legally and provide a basis to expand your company. We advise you to seek assistance from a corporate attorney. A C-corporation has the advantage of allowing for the distribution of multiple different stock types.[4] Incorporation is also important for contract development and provides a structure that allows funding of your company by investors.[4] It also helps protect your personal assets from financial liability if the company should go bankrupt.

• ***The university.*** If you are employed at a university your contract probably states that the institution receives some measure of patent rights for your discoveries. Consequently, early in the start-up process you should engage the university's technology licensing officer to determine their willingness to provide an exclusive license with favorable terms. Take care in developing the terms of this license. Creating an agreement with your university that will share improvement risks with the institution at a reasonable equity ownership and royalty rates will better enable you to attract investors and negotiate with a large pharma company for ultimate licensing. Again,



ILEVRO™ Suspension

Designed to put potency precisely where you need it[1,2]

ONCE-DAILY POST-OP

One drop should be applied once daily beginning 1 day prior to surgery through 14 days post-surgery, with an additional drop administered 30 to 120 minutes prior to surgery[3]

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[3]

INDICATIONS AND USAGE

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

Dosage and Administration

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.

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. Ke T-L, Graff G, Spellman JM, Yanni JM. Nepafenac, a unique nonsteroidal prodrug with potential utility in the treatment of trauma-induced ocular inflammation, II: In vitro bioactivation and permeation of external ocular barriers. *Inflammation*. 2000;24(4):371-384. **2.** Data on file. **3.** ILEVRO™ Suspension package insert.

ILEVRO™ (nepafenac ophthalmic suspension) 0.3%

Alcon®

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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 post-implantation 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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outside counsel with an attorney familiar with such deals is helpful.

Airtight Organization

• ***Administrative details.*** Keep detailed records from the very beginning. All aspects of your new venture are important to keep well-organized, but especially contracts, promises, legal communications and financial matters. There are a number of excellent, inexpensive organizational electronic tools available, many through the Microsoft Office suite of products. Numerous useful templates are built into the software, with additional preformatted document shells easily identified for download by a quick Internet search. Excel spreadsheets are one example of a useful tool for tracking and organizing development tasks. Alternatively, there are free products available on the Internet, but be sure to read privacy rules carefully before using them.

Online data storage not only provides secure storage and backup of documents, but also allows remote access for team members. Strongly consider implementing cloud services for your new start-up. Again be careful, however, to read and understand the security policies of the host.

Other experienced contractors, apart from an administrative assistant, can help you or your CEO establish essential procedures. For example, finding an IT expert to help establish your initial setup, troubleshoot technical issues and keep you abreast of IT advances, or a bookkeeper and accountant to set up your accounting, audit and tax-related procedures.

A well-organized development team is essential for your success. We recently published a study that evaluated success factors for ophthalmic pharma start-ups and found a greater chance statistically of a financial exit (sell or licensure) for companies doing so five years or sooner after incorporation than those further along in the development process. Although the study was small (n=25) it implies indirectly that an efficient, well-financed development plan might increase the chance for a financial exit.[5]

• ***Business plan.*** If you are still convinced that you have a viable product, the next step is to develop a comprehensive business plan. Although this seems like an arduous task, it will help assure you have formulated answers to basic, pertinent questions regarding your product. Further, it prepares you to articulate your company's story so you can better express it to others. Business plan templates are available on the Internet. The typical organization is shown in Table 4.

Funding & Founding Documents

Paramount to a successful start-up is funding your venture. Recently we evaluated ophthalmic start-up CEOs, and noted that funding their venture was most often the greatest hurdle they faced.[6]

You may decide to use personal funds to initially fund your company. Unless your wealth runs to nine digits, though, you almost assuredly will need outside investment to mature and complete development of your product. You, however, do have ownership equity, which can be used to induce others to help develop the new treatment.

Owner's equity can be a difficult subject because you may desire to keep your ownership of the company to protect the rewards of your invention. However, investors also have worked hard for their money and seek an equitable return for what they might view as a high-risk endeavor. Consequently, the investor and you can help each other, but it requires you to disperse your owner's equity, over time, in a judicious manner. In the end, you may own only a small percentage of the entity you founded. However, in a successful company, the remaining equity will have a higher valuation and should make your efforts financially worthwhile.

Funding a new start-up generally occurs in three rounds: A, B and C. The A round is often called the "friends and family" round, from whom you might receive initial funding for the venture to help found your company. Importantly, even at this early stage a clear and detailed budget is useful to assist you in telling your investors the exact product they are purchasing, to the stage the current investment round should take the company, and a description of the next steps to procure new financing.

Once you receive initial funding from interested early investors, your corporate attorney should put a founders' agreement in place. This document will specify the stock distributions, as well as the rights and restrictions upon the founders and the stock. This should be a detailed document delineating the

Table 4. Typical Business Plan Organization

Summary
Company description
New medicine description
Product need
Competition analysis
Funding request
Budget

relationship among the founders.[4] Try to resist the temptation to conduct the deal on a handshake. A detailed agreement will help determine the relationships between founders in future years and help keep disputes to a minimum.

In addition, your attorney should assist the founders and you in formulating a stock option plan among the founders to specify how the remaining equity (typically about 20 to 40 percent of the total potential shares) will be distributed to management, employees and contractors.[4] Typical ranges of percentage of ownership exist for each of these different company roles.[4] It is the options that allow a start-up to save salary and contractor payments and induce qualified personnel to assist in product development.[4] You will likely need an attorney experienced in pharma-related start-up deals to assist you with the above documents.

The A round funding also might include public or private grants (state/local development grants, as well as federal funds, are available from the Defense Advanced Research Projects Agency, the Department of Defense, and the Small Business Technology Transfer or the Small Business Innovation Research programs) or angel group funding. The amount of the grant may help fund initial expenses, usually ranging from $100,000 to $1 million. The A round funding is typically allocated to: IP creation and maintenance; consultant payments; lead product identification; preclinical efficacy; non-GLP (Good Laboratory Practice) pharmacology and toxicology studies as well as an initial regulatory plan; and the initial creation of the drug substance and simple formulation of the new medicine.

Rounds B and C typically involve larger private institutional investors (angel or capital venture groups, large pharma companies) who typically consider the A round as too risky for investment. The second, and maybe the third, rounds of funding should help move your product typically into GLP toxicology and pharmacology, formal regulatory contacts with the FDA, submission of an investigational new device application, as well as early clinical Phase I and II trials.

• ***Board of directors.*** Once you incorporate your company and other investors have agreed to participate in the venture, you should form a board of directors. BOD members should be chosen carefully, as they supervise the CEO and represent the shareholders.[4]

Board members should be affable, willing to contribute and work as a team and be able to advise the CEO or you as needed. Although individuals can be drawn from a mixture of professional backgrounds, prior ophthalmic pharma start-up experience is a positive. Including several high-profile individuals may help the reputation of your company.[4] In addition, some board members should possess enough financial means to support your company in urgent times and help bring new investors to the company. Further, having at least one member of the BOD, or a separate scientific advisory board, with preclinical and clinical ophthalmic expertise is helpful to advise the BOD regarding technical questions. The typical start-up BOD is small and members are usually compensated with at least a company stock options package.[4]

We hope this review has provided you with the first steps to organize your new ophthalmic start-up with an established funding, legal and organizational basis. Don't forget the importance, before beginning your company, of carefully analyzing your ability to commercialize your product based on its pharmacology, regulatory pathway and market need.

Persistent, careful attention to administrative and personal details will help you build a successful company and product that will ultimately be an advantage to ophthalmic physicians and their patients. REVIEW

Dr. and Mrs. Stewart are co-founders of PRN Pharmaceutical Research Network, LLC, an international ophthalmic clinical study management and consulting firm, as well as PRN PharmaFarm, LLC, which specializes in financing new ophthalmic start-up companies to assist towards product commercialization. Ms. Nelson is a research coordinator for both companies. *They received no financial support from any private or government funding source for this article.*

Contact Dr. Stewart at: PRN PharmaFarm, LLC, 109 E. 17th St., Ste. 3407, Cheyenne, WY 82001. Phone: (843) 606-0776; e-mail: info@prnorb.com.

1. FDA. Development & Approval Process (Drugs). Online at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm.
2. Invention Success Rates - Odds of Inventor Success. What percent of inventor ideas are successful? What percent of patents make money? What percent of inventions are commercialized? InventionStatistics.com. Online at http://www.inventionstatistics.com/Innovation_Risk_Taking_Inventors.html.
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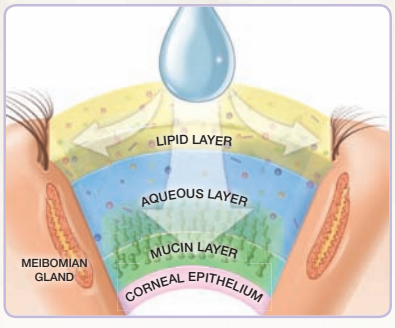

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References: 1. Akpek EK, Smith RA. Overview of age-related ocular conditions. *Am J Manag Care.* 2013;19 (5 suppl):S67-S75. **2.** Korb DR, Blackie CA, Meadows DL, Christensen M, Tudor M. Evaluation of extended tear stability by two emulsion based artificial tears. Poster presented at: 6th International Conference on the Tear Film and Ocular Surface: Basic Science and Clinical Relevance; September 22-25, 2010; Florence, Italy.

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Insights on Losing Sight

George L. Spaeth, MD, and Sonya Babar Shah, MD, Philadelphia

It is our privilege as eye doctors to help enhance health, preserve sight … and provide insight.

We are often asked, "How do you help people who are blind or who have far-advanced glaucoma?" This is an important matter that is often uncomfortable for both physicians and patients.

The key word in the opening sentence is "people." It is always possible to help the person. In every situation, including these in which a patient has far-advanced visual loss, we must focus on the person, not the visual acuity. How best to help is based on the answers to these questions:

- Who is the patient?
- What are the specific aspects regarding the patient's illness and visual problems?
- What are the patient's needs and wants?
- Which of these are attainable and/or the most important?

In the following cases, we'll look at four people who have or may experience significant vision loss, and some options that ophthalmologist might

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consider in helping them cope.

Case #1

A 90-year-old woman in excellent health owns a farm. She wants very much to continue to work the farm as long as she can.

Her vision is hand movements with accurate projection of light in the right eye and 20/40 in the left, with advanced field loss. She is phakic. The goal is to preserve as much vision as possible in the left eye, and to preserve as much field as possible in the right eye.

Because she is in good health without major medical problems, we expect her to live five to 10 more years. Her pressures must be low enough to prevent further deterioration. In the right eye this can be best accomplished with trabeculectomy and mitomycin-C with cataract extraction. "Wipeout" is not a concern. In the left eye, wipeout is a concern, but maximum lowering of pressure is also a goal. She should use drops along with laser trabeculoplasty and cataract extraction. If it cannot be lowered to a goal in the low teens, she and we must monitor her visual ability closely. If it is getting worse due to glaucoma, not another problem (dry eye, macular degeneration, posterior capsular opacification, etc.), then she should have a tube shunt procedure.

Case #2

A 75-year-old man has had a heart attack, smokes and is morbidly obese. He has bare light perception in his right eye with inaccurate projection. The pseudophakic left eye has advanced field loss that cuts close to fixation, resulting in 20/40 vision.

Here, the goal is to preserve his central acuity. Because of his obesity, it is hard for him to get around, but he can read. Surgery should be avoided if possible because of the high risk and likely minimal benefit. A combination of medications or laser trabeculoplasty should be tried. Treatment in the right eye should be minimal as it does not provide useful vision. We should aim for pressure low enough (<35 mmHg) to decrease the chance of retinal vein occlusion or bullous keratopathy.

To borrow from Milton, "To be blind is not miserable; not to be able to bear blindness, that is miserable."

Case #3

A 75-year-old runner is in excellent health. She has a slow heartbeat and low blood pressure, but far-advanced damage in both eyes. Her vision is 20/30 in each eye. The right eye has advanced field loss with about five degrees of field remaining, in the left eye it comes to within two degrees of fixation.

The goal here is to prevent any visual field loss whatsoever, as she will likely live 15 to 20 more years, as opposed to the patient in case #2. Thus, here the risks of filtering surgery would be warranted. This should be done in the right eye first to see how the patient responds to surgery.

Case #4

A 56-year-old man is in fair health, though is overweight and smokes cigarettes. His right eye has inaccurate light perception and a pressure of 28 mmHg on no treatment. The vision in the pseudophakic left eye is 20/40 due to mild macular degeneration and intraocular pressure is 32 mmHg with moderate field loss. No treatment is needed for the right eye in which there is no useful vision.

The patient has little understanding of his condition, but it is worth trying a course of topical medications. After several visits and discussions about his disease, he returns again, not having used his medications, with pressure of 30 mmHg in the right and 28 mmHg in the left. Given his demonstrated non-adherence, he must be scheduled for a tube shunt procedure in the left eye immediately. Trabeculectomy is likely too risky in a patient who is non-compliant. No treatment is needed for the right eye.

Some Considerations

Each individual is addressed differently. The question we should always be asking ourselves is, "How can I help this person?" It often relates to the level of vision. When the person has inaccurate light projection, the vision is likely not useful. It is usually not beneficial to treat such an eye.

Sometimes, lowering the pressure of an eye without useful vision may prevent bullous keratopathy or vein occlusion. However, medications should not cause any troublesome symptoms. Surgery should be a last resort, as the risk of sympathetic ophthalmia—no matter how small—is often too great to justify a presumed benefit of lowering pressure. Topical atropine and steroids may help, as would retrobulbar chlorpromazine. The definitive treatment is enucleation, which can be wonderfully liberating, allowing patients to get on with their lives.

These patients have lost their vision, but can maximize their quality of life. First, listen and learn who the patient is. What does she love? What is most important to them in their

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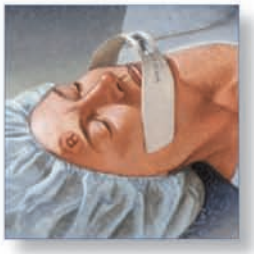

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lives? Will our treatment make them better, or feel worse?

People with little sight can function marvelously. Mildred Weisenfeld (founder of Fight for Sight), Helen Keller, Stevie Wonder, John Milton and Johann Bach all had no "useful" vision, but functioned well. The great Argentinean author, Burgos, commented that his ability to write well only developed after losing sight. To borrow from Milton, "To be blind is not miserable; not to be able to bear blindness, that is miserable." As physicians, our responsibility is to address the health of patients, not the data. We must focus on enhancing contentment and fostering a sense of purpose.

We should connect with our patients. We must never devalue any of the patient's concerns. When he or she feels worse, he or she *is* worse. We may not initially understand why. We must congratulate patients who are already coping well. In patients who have a poor quality of life, we must remind them that all is not lost, and direct them to resources that will enhance their lives.

Barry W. Rovner, MD, and coworkers have demonstrated that counseling patients with macular degeneration is more likely to result in improvement or preservation of a patient's quality of life than some treatments.[1] Many agencies give patients skills, knowledge, and access to a community that can enhance their independence and quality of life.[2] In Philadelphia, we are fortunate to have the Associated Services for the Blind (asb.org) just steps away from our institution.

When communicating with a patient who is discouraged, speak directly. Remember that your body language and the words you say will stay with the patient until the next visit. Our goal is to create an environment that engenders realistic hope, commitment, and action—one that encourages health. In doing so, it is likely the patient will leave with the tools to improve their quality of life. Our privilege as eye doctors is to help enhance health, preserve sight … and provide insight. REVIEW

Dr. Shah and Dr. Spaeth are in the Glaucoma Service at Wills Eye Hospital, where Dr. Spaeth is the Louis J. Esposito Research Professor. Contact Dr. Shah at (215) 928-3197 or sshah@willseye.org.

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A Recipe for Better Patient Compliance

How different drug formulations and dosing regimens may help ensure that patients take their medicine.

Mark B. Abelson, MD, CM, FRCSC, FARVO, and Linda Stein, MS, Andover, Mass.

When reviewing the progress of a patient who shows little sign of improvement, too often we hear the words, "Well, I may have forgotten to take a few doses ... " Poor patient compliance with drug dosing regimens can be a major impediment to effective treatments. And while the topical application of ophthalmic drugs is straightforward in principle, as clinicians we know that poor compliance is widespread.

So what's so hard about taking eye drops? Start with a drop that stings on application, combine with patients forgetting to take every dose, add in the difficulty of applying drops accurately (especially for older patients), mix with hit-or-miss renewal of costly prescriptions and then finish with an asymptomatic disorder. If we combine all this with low drug absorption and fast washout, it's a wonder that topicals work at all. But they do. In terms of both efficacy and safety, topical delivery of drugs, especially for front-of-the-eye indications, is superior to all other options of administration.[1] Of course, superior doesn't mean perfect, so there is plenty of room for improvement, from reinforcing medication instructions to engineering better medications.

Both physicians and patients underestimate the impact of non-compliance. For glaucoma patients, estimates of non-compliance range from 23 percent to 60 percent.[2-6] In this case, the cost of non-compliance is high, with progressive vision loss and eventual blindness as the result. In conditions such as dry eye or allergy, non-compliance can diminish patients' quality of life and productivity, and increase their frustration with continuing symptoms. When patients unknowingly fail to comply with dosing guidelines, their frustration with their condition as well as their "ineffective" treatments establishes a vicious cycle reducing the likelihood of successful treatment.

This month, we'll discuss several specific strategies to address the general issues of patient compliance and drug delivery optimization. First we'll provide a checklist for overcoming the patient-related issues of compliance, with the goal of optimizing the routine of reliable adherence to prescribing instructions. Then we'll consider advantages, limitations and regulatory hurdles associated with combination therapies. Finally, we'll describe approaches available now and in the near future that enhance efficacy by improving delivery formulations, making every drop count. Each of these strategies can contribute to an overall recipe for compliance success.

Personalize Treatments

Most medications require some degree of physician oversight, so any discussion of patient compliance issues starts with the doctor-patient relationship. Keep in mind that patients' compliance does not occur in a vacuum, and they are often juggling multiple medications, each with its own treatment regimen. While they may not volunteer such information, when asked, patients may admit to forgetting doses or having difficulty with proper administration of their eye drops.[7] It may be that a patient is not complying with her dosing regimen because of negative side effects. Encourage patients to discuss any possible side effects of their medications, since undesirable side effects can often underlie poor patient compliance. Sometimes, specific side effects that a

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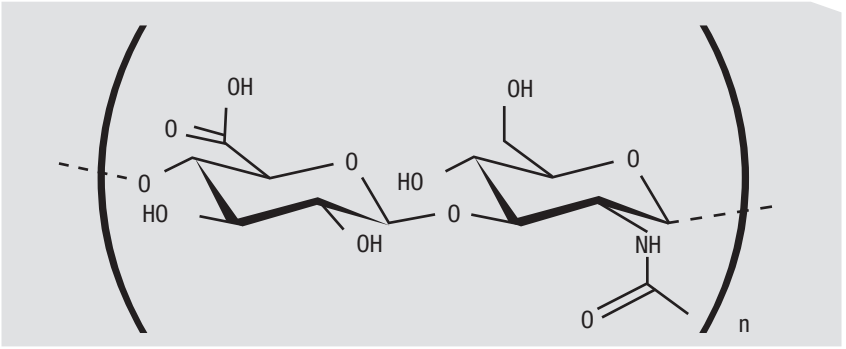
patient is experiencing are known to be associated with a particular drug or formula excipient, so the solution may be as simple as a change in medication.[8,9] Additional communication efforts can include patient education, such as training in proper eye-drop application, and sending reminders to patients to take their medication on-schedule and keep follow-up appointments. Other options include smartphone medication monitors, as well as enlisting family members to help patients remember to take all doses and correctly apply their eye drops.[5,10,11] Finally, remember that although ophthalmologists are nearly infallible, pharmacists are only human, so if there's a problem with any medication it's worth re-checking the prescription to insure accurate dispensing.

Complex drug dosing regimens have been cited as a significant barrier to patient compliance.[12,13] Simplifying dosing can be achieved either by prescribing treatments that require once- or twice-daily dosing rather than multiple daily doses, or by considering fixed-combination medications. Prescribing fewer daily doses (q.d. or b.i.d.) rather than more frequent, multiple daily doses can often improve patient compliance.[10,14] Once-daily medications are available for most indications, including glaucoma or allergic conjunctivitis, but when thinking about compliance it's the switch from t.i.d. to b.i.d. that is critical: This improvement converts a drop from something that must be carried throughout the day to one that can function effectively at the nightstand or the medicine cabinet.

Sometimes the treatment effects from one medication, including q.d. medications, can wane. In such cases it's best to first try switching from one monotherapy to another, before adding more, separate treatments.[15] If a patient requires multiple medications, he should be instructed to apply the two drugs at least five minutes apart,[16] since the second eye drop can wash out the first and reduce drug effectiveness.



The building block of hyaluronic acid, used in many tear-substitute formulas, is a modified disaccharide composed of glucuronic acid and n-acetyl glucosamine. The chemistries possible from this starting point are virtually limitless.

Combination Therapies

Not all patients respond to monotherapy, and some may require more than one medication. Fixed-dosage ophthalmic drug combinations of different pharmacological classes can be efficacious, reduce the side effects of each component and improve patient compliance. This isn't as simple as "mix and apply" however, and the Food and Drug Administration has established extensive guidelines for the approval of therapeutic drug combinations. Along with considerations of both pharmacodynamics and pharmacokinetics, development of combination products presents a unique mixture of opportunity and challenge.

Any fixed-dose combination of drugs should be composed of individual compounds with different mechanisms of action and, most often, similar pharmacokinetics. Having distinct MOAs allows for the best prospects for therapeutic synergy while minimizing possible shared adverse effects of the two agents. Combinations designed to lower intraocular pressure, for example, often include one agent that increases outflow with one that decreases aqueous humor production. Regulatory guidelines dictate that the combination must be superior to either of the individual components alone, however, so any combination product must reach this therapeutic hurdle.

Pharmacokinetics of combinations should also be similar, to avoid the potential for mismatches in steady-state levels of each component. An exception to this is when the individual agents act to treat distinct symptoms. For example, a combination product for ocular allergy may include a vasoconstrictor to relieve redness and an antihistamine for ocular itching. In this case, one agent provides immediate treatment (for redness) while the other acts both to reduce itch and to prevent subsequent itching, so a longer duration for the antihistamine component is actually beneficial.

The best examples of fixed-dose combination formulations are those used as IOP-lowering drugs in primary open-angle glaucoma or ocular hypertension. An example of a fixed-combination drug to lower IOP in glaucoma patients is a combination of timolol maleate (a beta blocker) and dorzolamide hydrochloride (a carbonic anhydrase inhibitor) taken twice daily. Another example is a fixed-combination of brinzolamide (a carbonic anhydrase inhibitor) and brimonidine tartrate (an alpha-2 adrenergic receptor agonist) taken three times daily.

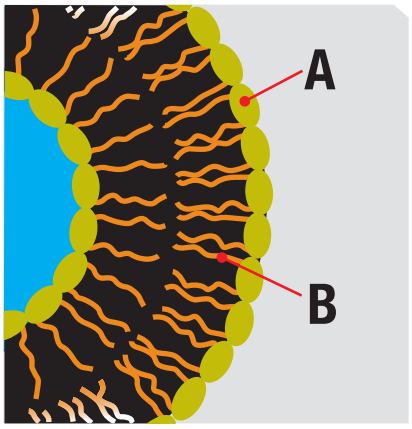
While some fixed-combination drugs require more than once- or twice-daily dosing, they may still simplify dosing regimens and thus can contribute to better patient compliance.

A survey of Swiss ophthalmologists was conducted for 98 of their patients who switched from taking timolol and dorzolamide separately to a fixed combination of these medications. A 4.6-percent reduction in average IOP occurred after the treatment switch; this enhanced efficacy was attributed to improved patient compliance. About 85 percent of patients chose to continue the fixed-combination treatment.[17]

Similarly, in a Japanese study, 162 patients with glaucoma or ocular hypertension who had been taking latanoprost and timolol maleate concomitantly switched to a fixed combination of these two drugs once daily. The IOP-lowering effect of the two drugs was maintained by the combined formulation. About 82 percent of patients reported that they preferred the fixed-combination therapy. Also, patients who reported that they "never" forgot to take their eye drops increased from 59 percent before the switch to 71 percent a month after the switch, and those who forgot to take their drops "over five times" decreased from about 9 percent before to about 2 percent after the switch.[18]

Avoiding the Corneal Barrier

The relatively impermeable cornea serves as a barrier, protecting the eye from deleterious foreign substances, but also limiting drug absorption. Conventional topical administration of eye-drop solutions encounters the challenge of limited corneal penetration, and many enhanced drug delivery systems seek to address this issue. Improving drug delivery may help reduce the effects of patient non-compliance. Drug delivery that increases ocular residence time has significant potential advantages, including increased drug effectiveness and reduced local and systemic side effects. Some of these methods may decrease dosing frequency, a key factor in patient compliance.



Liposomes consisting of hydrophilic segments (A) and hydrophobic segments (B) can increase a drug's residence time, absorption and transport.

Typically, less than 5 percent of an eye drop penetrates the cornea and is bioavailable, and less than 1 percent reaches the aqueous humor; the rest of the drug is lost through spillage, tear-fluid turnover, drainage and systemic absorption through the conjunctiva and nasolacrimal duct.[19]

Lipophilic drugs can permeate the outer corneal epithelium, which has an affinity for lipids, better than hydrophilic drugs, while the inner layer of the cornea, the stroma, is hydrophilic. Optimal ocular drug delivery involves a balance of lipophilic and hydrophilic properties to achieve good solubility and permeability through the cornea. In addition, some drug delivery methods (e.g., gels) provide more sustained topical drug delivery, which can reduce the amount of drug needed.

Methods used or being explored to improve topical drug delivery for the anterior of the eye include pro-drugs, excipients, gels, cyclodextrins, liposomes and nanoparticles. By enhancing the net delivery of active agent to the target tissue, each of these approaches has the potential to improve efficacy and thus alleviate the impact of poor patient compliance.

One strategy to improve the delivery of drugs involves compounds administered in an inactive or less active form that are converted to a more active form through metabolic processes *in vivo*. These compounds are called pro-drugs. Targeting pro-drugs to specific transporter or receptor tissues in the eye can increase drug absorption, with the pro-drug acting as a substrate for endogenous enzymes.[1,20] The increased drug absorption improves drug efficacy and can reduce side effects and dosing frequency by concentrating active drug at target sites. The prostaglandin latanoprost, commonly used for reducing IOP in glaucoma treatment, is an example of a lipophilic pro-drug that is topically administered in eye-drop form and then hydrolyzed in the body to a more biologically active form, latanoprost acid. Lipophilic ocular pro-drugs can increase the permeability, absorption and bioavailability of hydrophilic drugs. Conversely, hydrophilic pro-drugs used as substrates can improve the solubility of poorly soluble lipophilic drugs (e.g., cyclosporine A).[19,21]

Some excipients used in topical ocular formulations offer another way to improve drug delivery. These added ingredients include preservatives (e.g., BAK, ascorbic acid), surfactants and drug stabilizers (e.g., chelating agents such as EDTA). Beyond their action as preservatives or chemical stabilizers, some excipients may increase the viscosity, pre-corneal retention or permeability of ocular medications.[19]

An interesting example of this often reported in the literature is the ability of BAK to increase corneal permeability, although we think this case is more urban legend than scientific fact. A recent study of the effects of BAK in glaucoma patients showed

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that efficacy of the prostaglandin latanoprost was not dependent on the presence of BAK.[22] Other head-to-head comparisons have showed the same non-inferiority of preservative-free formulations. Most concerns regarding additives have involved side effects, such as ocular discomfort, tearing, dry-eye sensation, burning or itching.[17] Some patients, particularly those with ocular surface disease, may have trouble tolerating formulations with preservatives. In some cases these compounds induce a detergent effect in the eye (resulting in a loss of tear-film stability), damage the corneal and conjunctival epithelium and cause an immuno-allergic reaction.[16,17] It's clear that using excipients to improve drug absorption is a valid strategy, but not a quick fix for addressing problems of patient compliance.

Another group of drug excipients acts not simply by altering permeability, but also by increasing a drug's residence time on the ocular surface. Ophthalmic gel formulations increase the viscosity, muco-adhesion and pre-corneal residence time of eye-drop solutions. The gels provide sustained release, improve bioavailability and may reduce the number of daily doses required. For example, timolol solution is prescribed for twice-daily use, while timolol gel is a once-daily dose for IOP reduction.

Ophthalmic gels include hydrogels and *in situ* activated gels. Both types are composed of polymers that may also decrease systemic side effects associated with topical ophthalmic drugs.[23]

Often used in tear substitute formulations, hydrogels can increase ocular penetration of a drug, particularly water-soluble drugs, via longer corneal residence time. Hyaluronic acid is a biological hydrogel polymer that is naturally present in the aqueous humor and vitreous of the eye, and is commonly used in cataract surgery. Most hydrogels currently in use are synthetic bioadhesives.[23] A significant limitation of hydrogels is that they often result in blurred vision.[21]

This adverse effect is not seen with *in situ* activated gels, viscous liquids that change from a solution to a gel state after topical ocular administration based on temperature or other physiological conditions (e.g., pH). Gellum gum, a common gelling agent, is often used in ophthalmic formulations as an *in situ* activated gel. Combinations of a polymer and methylcellulose (or another non-toxic substance) are also used. The gel is considered non-toxic and is well tolerated by patients.

Commonly used in the food, pharmaceutical and chemical industries, cyclodextrins are modified polysaccharides that have a lipophilic center and a hydrophilic outer surface, making them great candidates for improving topical drug delivery. Cyclodextrin-drug complexes can increase the corneal solubility and bioavailability of poorly soluble lipophilic ocular drugs (e.g., steroids, carbonic anhydrase inhibitors), improve drug stability and reduce side effects.[19,23,24]

Cyclodextrins can also be cross-linked to form polymers for drug delivery. Some cyclodextrin-drug complexes have reduced corneal drug toxicity and irritation and this appears to be the primary benefit for hydrophilic drugs.[23] A study of a dexamethasone-cyclodextrin complex indicated a 2.6 higher area under the receiver operator curve result in the aqueous humor compared to a dexamethasone suspension.[19,25] Several cyclodextrin eye-drop products are currently available in Europe, and non-ophthalmic pharmaceutical uses are approved in the United States. The toxicity of cyclodextrin, however, has been raised as a possible issue.

Other potential delivery modalities include liposomes and nanoparticles. Liposomes are microscopic vesicles that typically contain an aqueous area surrounded by a lipid bilayer, and thus can accommodate both lipophilic and hydrophilic drugs. Encapsulating a topical ocular drug in liposomes and delivering it as an eye-drop solution may increase the drug's corneal residence time, absorption and transport, thus increasing drug effectiveness and reducing dosing frequency.[21,23] Liposomes are biocompatible and biodegradable.

Nanoparticles composed of bioadhesive polymers can potentially increase pre-corneal residence time, improve the uptake and transport of drugs with either poor permeability or poor solubility and prolong a drug's duration of action.[19,23,24] A drug is dissolved, entrapped, encapsulated, adsorbed or attached to the nanoparticle.

Personalizing treatment regimens and improving drug delivery represent two sides of the compliance issue. Encouraging our patients to be conscientious about their medication regimens is a simple, if sometimes daunting, route to optimizing treatment outcomes. By enhancing delivery strategies we can go a long way toward simplifying these regimes, significantly improving the odds of therapeutic success.

When it comes to solving the conundrum of patient compliance, this simple formula of equal parts patient participation and pharmaceutical fine-tuning should be a recipe for success. REVIEW

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Pediatric Glaucoma: A Review of the Basics

Despite similarities to glaucoma in adults, the clinical findings and surgical management of pediatric glaucoma vastly differ.

Wendy Huang, MD, New York City

Pediatric glaucoma is associated with a wide variety of pathology. Several classification systems have been developed to organize and categorize childhood glaucomas. The majority of systems are based on etiology and describe two main groups: primary and secondary glaucoma. Congenital and developmental glaucomas associated with syndromes and systemic abnormalities fall under the umbrella of primary glaucomas. Causative pathologies ranging from uveitis to congenital cataract surgery fall under secondary glaucoma.[1] The incidence of childhood glaucoma is estimated to be 2.29 per 100,000 patients younger than 20 years old based on a defined U.S. Population study in Olmstead County.[2] Primary congenital glaucoma is the most common form of childhood glaucoma, with a reported prevalence of 2.85 cases per 100,000 births.[3] As in adults, pediatric glaucoma is associated with elevated intraocular pressure and progressive optic nerve damage; however, the clinical findings and surgical management are vastly different.

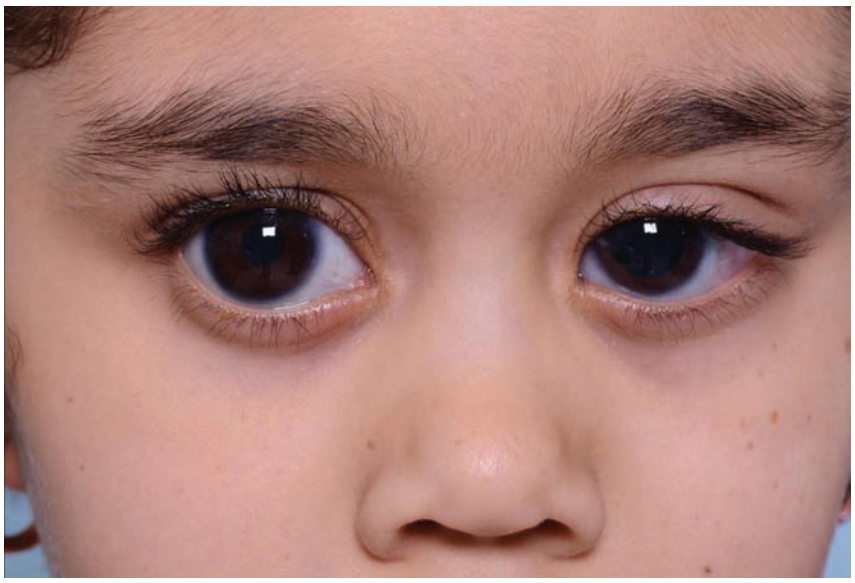

Figure 1. Buphthalmos of both eyes, right worse than left.

Clinical Findings

Manifestations of elevated IOP in children can vary depending on age of onset and rate of pressure elevation. Gradually increasing pressure can result in little to no corneal clouding. Presentation with buphthalmos and/or symptoms of tearing, blepharospasm and photophobia are more common *(See Figure 1)*. In contrast, those children with acute pressure elevations present with corneal clouding. This finding can also be seen at birth *(See Figure 2)*. Firm tactile pressure in these cases can be apparent and helpful in differentiating other causes of corneal opacification. The presence of a poor red reflex can elucidate subtle corneal clouding, although absence of a red reflex can be related to other pathology as well. Haab's striae, which represent breaks in Descemet's membrane, can be present in the absence of

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elevated pressure *(See Figure 3)*. This finding signifies a history of elevated IOP associated with rapid eye growth.

Obtaining IOP measurements in children is challenging. Current methods include rebound tonometry (iCare) and handheld applanation tonometry (Tono-Pen, AccuPen, Kowa and Perkins Tonometer). Rebound tonometry has the advantage of not requiring anesthetic drops; however, the child must be upright. Recent studies have suggested that although IOP by rebound tonometry correlates well with Goldmann Tonometry, there is a tendency to overestimate IOP, particularly in children with glaucoma.[4,5] The iCarePro can be used in all positions; however, the device is currently not available in the United States. Handheld applanation tonometry can also be performed in all positions.

An exam under anesthesia is essential in diagnosing childhood glaucoma. Pre-intubation IOP, refraction, axial length, corneal diameter, gonioscopy, and ultrasound biomicroscopy when visibility is poor, are key components of the exam. Progressive myopia, increasing axial length and changing corneal diameter in the face of borderline IOP and cupping are suggestive of fluctuating high pressures. Tracking these factors also aids in determining treatment response. In children more than 3 years of age, changes associated with buphthalmos become less apparent due to decreased scleral elasticity.[6] With general anesthesia, a more thorough exam investigating risk factors for glaucoma such as signs of past trauma, uveitis and syndrome manifestations can be assessed.

A large number of syndromes have associated glaucoma. The more common syndromes are: Sturge-Weber; Oculocerebrorenal (Lowe); Axenfeld-Rieger; aniridia; and Neurofibromatosis Type 1.

Sturge-Weber has a sporadic inheritance pattern and is characterized by nevus flammeus (port wine stain) of the face, angioma of the meninges and, rarely, involvement of the airway. Incidence of glaucoma has been reported to be as high as 71 percent.[7,8]

Children's Hospital of Los Angeles-The Vision Center

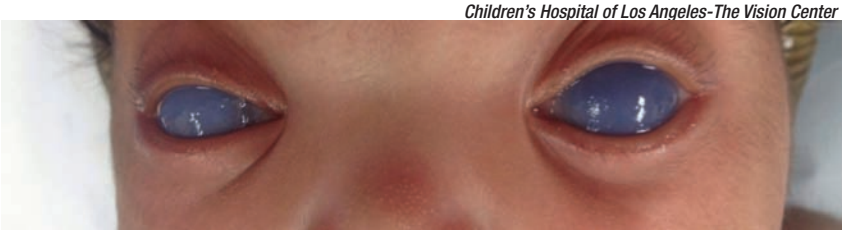

Figure 2. Corneal clouding found at birth with elevated intraocular pressure.

Oculocerebrorenal (Lowe) syndrome is X-linked recessive and presents with congenital cataracts, congenital glaucoma, mental retardation, renal tubular dysfunction (Fanconi's syndrome), aminoaciduria and hypotonia. Incidence of glaucoma has been reported to be 47 to 71 percent.[9]

Axenfeld-Rieger syndrome (ARS) is autosomal dominant but can occur sporadically.[10] It is associated with anterior segment abnormalities and is often categorized under anterior segment dysgenesis or goniodysgenesis syndromes. Approximately 50 percent of patients diagnosed with ARS will develop glaucoma. Onset typically occurs during late childhood but can present during infancy and into adulthood.[11] Physical manifestations include: redundant umbilical skin; telecanthus; broad nasal bridge; dental abnormalities (microdontia, oligodontia or hypodontia); and, in some cases, pituitary abnormalities with growth retardation.

Aniridia is characterized by hypoplastic iris tissue and is associated with foveal hypoplasia, cataracts, keratopathy secondary to limbal stem cell deficiency and, occasionally, optic nerve hypoplasia. The inheritance pattern is autosomal dominant, but can be inherited sporadically. In sporadic cases, patients should be worked up for Wilms' tumor-aniridia-genital anomalies-retardation (WAGR) syndrome. Prevalance of glaucoma is reported to be from 30 to 50 percent.[12]

Neurofibromatosis Type 1 has an autosomal-dominant inheritance. It carries a spectrum of findings including café-au-lait spots, freckling of the axial/inguinal area, sphenoid dysplasia, S-shaped plexiform neurofibromas of the lids, optic nerve gliomas, Lisch nodules and choroidal hamartomas. Eyes with an associated plexiform neurofibroma have a 50 percent risk of glaucoma.[13]

Treatment

• ***Medical.*** Medical therapy in pediatric glaucoma is often supplementary to surgical management. It is often used for preoperative treatment to facilitate clearing of corneal edema. In addition, it can play a role in treating patients who are too unstable to undergo anesthesia. Timolol is often used as a first-line agent and has been shown to effectively lower IOP in the pediatric population. There is an increased risk for bronchospasm, apnea and bradycardia. The use of betaxolol (b1 selective antagonist), timolol 0.25% gel, and timolol 0.1% can help to avoid these side effects. Overall, however, timolol drops are generally well-tolerated.[14] Latanoprost has been shown to have IOP-lowering effects, particularly in older children, but the non-response rate has been shown to be higher than in adults. Side effects are minimal, although darkening of the irides can occur, as in adults.[15] Topical carbonic anhydrase inhibitors are also effective in lowering IOP. They are generally well-tolerated with minimal side effects. Oral acetazolamide has been shown to be more effective in lowering IOP and can be used in children with glaucoma at doses of 5 mg/

kg/day to 15 mg/kg/day. Oral treatment carries a risk of systemic side effects, such as metabolic acidosis. Brimonidine has the most well-established side effect profile in children, causing bradycardia, hypotension, hypothermia, hypotonia and apnea in infants and severe lethargy in toddlers.[16] Because of these side effects, its use is limited in the pediatric population.

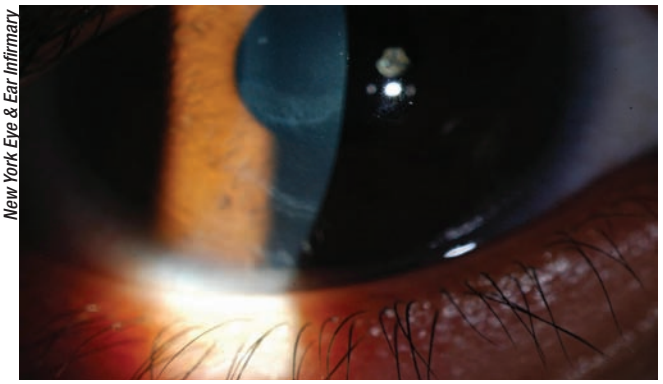

Figure 3. Haab's striae representing breaks in Descemet's.

• ***Surgical.*** Angle surgery is considered the mainstay of treatment for primary congenital glaucoma, with a reported 70 to 90 percent success rate after one to two procedures in patients treated after 3 months of age and before 1 to 2 years of age. This success rate significantly diminishes in patients presenting outside of this age range and those who fall in the spectrum of developmental glaucoma.[17]

Traditional goniotomy is often the first procedure of choice, but it requires a clear cornea to be performed safely. Endoscopic goniotomy has been described to avoid this issue.[18] Trabeculotomy *ab externo* does not require corneal clarity; however, it requires the technical challenge of finding Schlemm's canal. Traditional trabeculotomy treats 90 to 180 degrees. Success rates are comparable to goniotomy, but similarly decrease in the setting of developmental glaucoma and significant anatomic angle pathology. 360-degree trabeculotomy is possible using a 6-0 polypropylene suture that is threaded throughout the entire circumference of the angle. The suture is then pulled through the original sclerotomy site and treats the entire angle. It has success rates of up to 92 percent with one procedure.

Complications include misdirection into the suprachoroidal space, hyphema, cyclodialysis cleft and iris tear.[19,20] The use of an illuminated microcatheter (iTRACK 250A; iScience Interventional) has been introduced to avoid misdirection. The illuminated catheter can be easily located. In addition, when 360 degree passage cannot be achieved, a second sclerotomy site can be created over the illuminated tip, allowing for partial treatment of the angle.[21] Major complications for all angle surgeries include hyphema, hypotony and cataract.

Trabeculectomy has a 60 to 65 percent success rate when performed with antifibrotic agents. Success rates significantly decrease with aphakia. In addition, risk of bleb-related endophthalmitis in the pediatric population has been reported to be 7 to 14 percent.[22] This risk appears to increase over time.[23] Combination trabeculectomy-trabeculotomy has been described with a reported success rate of 72 percent as a primary procedure; however, it is unclear if there is a difference in success when comparing trabeculotomy alone vs. combined trabeculectomy/trabeculotomy.[24]

Aqueous shunt implantation has shown significantly greater success when compared to trabeculectomy.[25] Low endophthalmitis rates have been reported. It does appear, as in adults, that implants become less effective over time and require reoperation.[26] Implants available for use include: Ahmed valve (New World Medical); Baerveldt implant (Pharmacia); and Molteno implant (OP Inc). Ahmed valves and Baerveldt implants are the most commonly used and have both been reported to be effective.[26-28]

Cyclodestruction procedures are an option in difficult-to-treat cases. Cyclocryotherapy has been replaced by laser cyclophotocoagulation. A transscleral technique is most commonly used. Endoscopic cyclophotocoagulation has been reported to be effective as well.[29]

Prognosis

Reports of visual outcomes vary. Cases resulting in visual acuity sufficient to qualify for a motor vehicle driving license range from 29 to 46.6 percent of patients. Vision at the time of diagnosis, type of glaucoma and amblyopia appear to be the largest factors in visual outcomes. Children with primary congenital glaucoma have the best prognosis. In the setting of well-controlled intraocular pressure, amblyopia is a key factor in vision loss. As in pediatric patients with congenital cataracts, unilateral cases often have poorer visual outcomes secondary to amblyopia.[30,31]

Counseling patients and their families with regard to potential future vision loss can be challenging. Connecting them to resources for the visually impaired early is of utmost importance. The following are a few organizations with resources for the visually impaired and blind: Lighthouse International (lighthouse.org); Helen Keller Services for the Blind (helenkeller.org); American Foundation for the Blind (afb.org); National Federation for the Blind (nfb.org); and Family Connect (familyconnect.org/parentsitehome.aspx). REVIEW

Dr. Huang is a pediatric ophthalmologist specializing in pediatric glaucoma, amblyopia, eye muscle disor-

ders, pediatric cataracts, congenital blocked tear ducts and other pediatric eye conditions. She is a full-time faculty member of the New York Eye and Ear Infirmary of Mt. Sinai and an assistant professor of ophthalmology. She reports no financial interest in any of the products discussed.

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Electrophysiology Comes to the Clinic

How clinical electrophysiology can improve your diagnosis and management of posterior segment disease.

Ron P. Gallemore, MD, PhD, Michael Baker, OD, Calvin K. Chou, BS, and Spencer M. Onishi, BS, Los Angeles

Electrophysiologic testing for the evaluation of posterior segment disorders is often underutilized. There are practical limitations, including the setup itself, as well as patient convenience. Many feel that such testing is often academic, rarely impacting patient care. Here we review the main electrophysiologic tests and the indications for their use, as well as some of their limitations in the diagnosis and management of patients with retinal and optic nerve disorders.

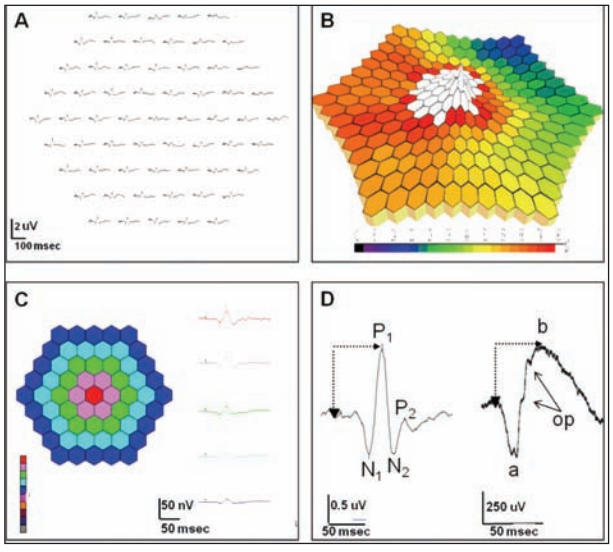

Figure 1. Multifocal ERG data illustrations recorded with the LKC EPIC-4000 system with CRT monitor (100 cd/m^2). A) Trace array. B) 3-D response density topography plot. C) Average response density plots in both 2-D (left) and tracing (right) illustrations. D) Individual mfERG waveform is composed of an initial negative deflection (N1) followed by a positive deflection (P1) and subsequent N2 and P2 components. Measurements include the N1-P1 amplitude and the P1 implicit time. Note similarities to the dark-adapted a- and b-waves of the full-field ERG (right).

The Setup

Commercial systems are now available that require minimal setup and staff training and allow more consistent, standardized measurements. The signals recorded vary between systems due to differences in filtering, amplification, averaging, stimuli and other aspects, so temporal changes should be made using the same system.[1] Here we review the main diagnostic tests, the techniques, and the signals recorded.

Multifocal ERG

The mfERG is an objective measure of cone-driven central retinal function.[2] A hexagonally patterned array stimulates different areas in a pseudo-random pattern.[2] The recorded signals are mathematically processed utilizing "binary m-sequences" to generate a topographic map of retinal function.[2,3] Areas of retinal dysfunction are identified by spatially comparing variations in the topographic array of signals.

Data is displayed *(See Figure 1)* as a trace array, 3-D density plot, and regional average data in a 2-D plot or waveform tracing. It is important to look at all of these ways of displaying the data, as it can enhance your interpretation of the results.

Trace arrays are composed of individual biphasic waveforms *(See Figure 1D, left)*, which have some resemblance to the standard full-field ERG (ff-ERG), with an initial negative wave

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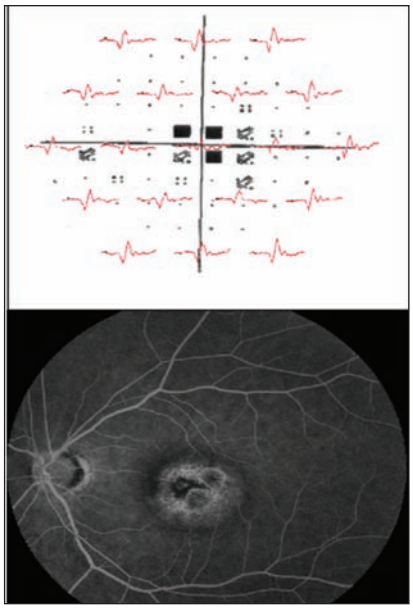


Figure 2. Top) mfERG/30-2 threshold field overlay in a patient with Stargardt's disease. Bottom) Late-phase fluorescein angiogram of the same patient.

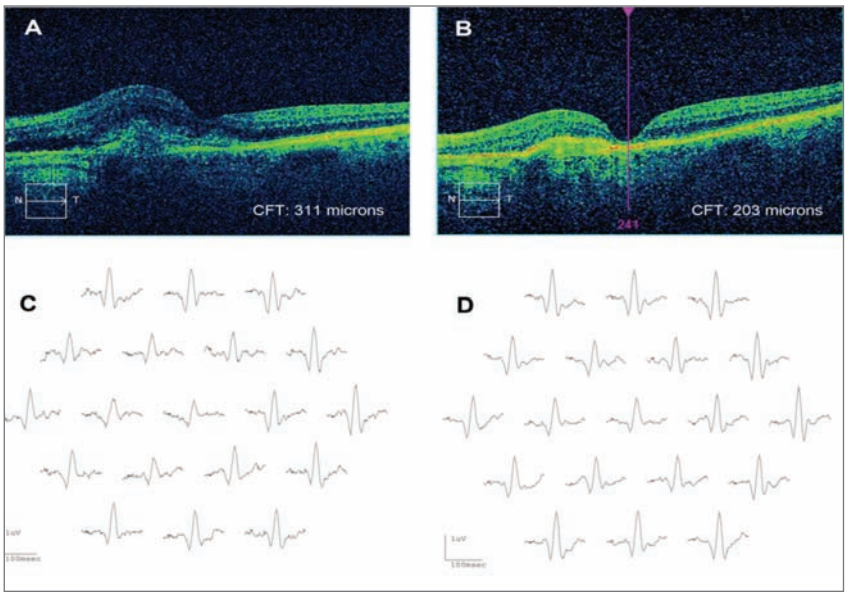


Figure 3. Improvement in mfERG signals in an 82-year-old Caucasian female being treated for age-related macular degeneration with anti-vascular endothelial growth factor therapy, OS. A) Optical coherence tomography showing subretinal fluid and pigment epithelial detachment. B) Post-treatment with anti-VEGF therapy, demonstrating resolution of the subretinal fluid. C) Central and nasal suppressions noted on the trace array prior to treatment. D) Increased retinal electrical activity noted with recovery of the central and nasal response densities, post-treatment.

(N1) followed by a positive deflection (P1), similar to the a- and b-waves of the ff-ERG *(See Figure 1D, right)*. While there is data to suggest that N1 represents the outer retinal activity associated with phototransduction (similar to the a-wave) and the P1 response contains signal activity from the inner retina (similar to the b-wave), the stimulus and mathematical signal processing as well as the spatial differences (full-field versus central) and lack of rod contribution make a direct correlation impossible. Hence, the mfERG cannot replace the information provided by the ff-ERG.

The mfERG can be recorded with varying numbers of traces, with or without signal averaging. Higher number arrays result in more precise data, but provide a lower signal-to-noise ratio, as well as longer testing time. The International Society for Clinical Electrophysiology of Vision (ISCEV) recommends 61 or 103 tracings.[4]

An mfERG abnormality (suppressed signal) usually correlates well with visual-field defects *(See Figure 2)*. Cataracts may influence mfERG recordings due to light scattering. Refractive error and axial length should also be accounted for when analyzing mfERG signals.[3]

Clinical applications of mfERG. Drug toxicity is a leading indication for the mfERG, which is more sensitive than the ff-ERG in detecting cases of toxicity caused by drugs affecting the macula. These include the antimalarial (anti-inflammatory) drugs chloroquine, hydroxychloroquine and quinine; anti-tuberculosis drugs including ethambutol; anti-epileptic drugs like vigabatrin; and antipsychotic medications including thiothixene. Other applications include detection of non-organic vision loss; dysfunction from inflammatory disease (especially birdshot chorioretinopathy); and dysfunction caused by vascular disease, including diabetes and retinal vein occlusion, presumably as the result of ischemia and sometimes out of proportion to the clinical findings.[5] Retinal degenerations can be monitored with the mfERG; residual cone function is detected in retinitis pigmentosa and it is suppressed in X-linked retinoschisis. We have found a robust initial mfERG to be a predictor for improved retinal function after anti-vascular endothelial growth factor therapy in wet age-related macular degeneration *(See Figure 3)*, though long-term sequential treatment with anti-VEGF drugs can be associated with an overall decrease in the mfERG even when vision appears relatively preserved.[6] This may be a useful measure in assessing long-term benefits of other drugs such as the anti-platelet-derived growth factor inhibitor, Fovista.

mfERG Tips: Improve the signal to noise ratio by dilating the pupil, increasing the stimulus intensity and reducing the trace array number. Make sure the patient maintains fixation so results are reproducible and 3-D plots are accurate.

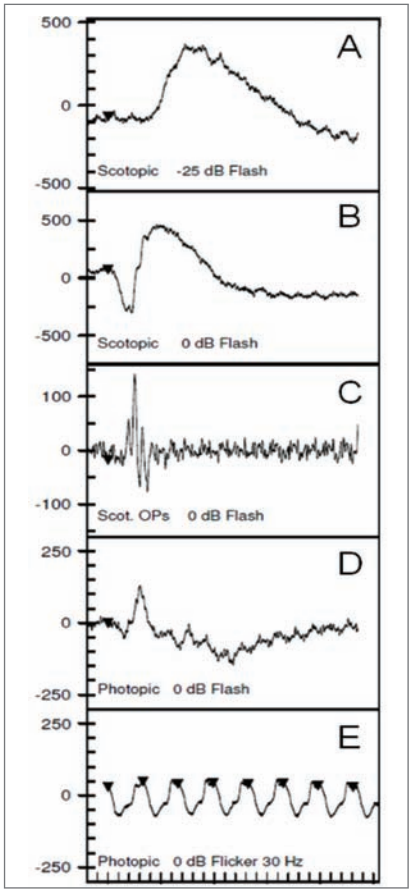


Figure 4. Normal ff-ERG tracings recorded from the right eye of a healthy 40-year-old female patient. This tracing shows normal scotopic and photopic responses. The ISCEV protocol includes five components designed to isolate rod and cone function: A) Dark-adapted 0.01 cd/m^{-2} ERG (rod response); B) Dark-adapted 3.0 cd/m^{-2} ERG (maximal combined rod-cone response); C) Dark-adapted 3.0 cd/m^{-2} oscillatory potentials; D) Light-adapted 3.0 cd/m^{-2} ERG (single flash cone response); and E) Light-adapted 3.0 cd/m2 flicker ERG (30-Hertz flicker). Dark-adapted recordings occur under background luminance of 0 cd/m^{-2} while light-adapted recordings occur under a Ganzfeld background illumination of 30 cd/m^{-2}.

Full-field ERG

The ff-ERG is a measurement of the summed mass electrical response of the retina under maximally dilated photopic and scotopic conditions. The ISCEV protocol includes five components designed to isolate rod and cone function as shown in Figure 4. Dark-adapt for 20 minutes before the scotopic ERG is recorded and light-adapt with a Ganzfeld background illumination of 30 cd/m^2 for 10 minutes before recording photopic signals. A bright flash elicits a biphasic response, the negative a-wave followed by the positive b-wave *(See Figure 3B)*.

The two primary measures are the wave amplitude and implicit times (onset of flash to peak or trough of wave). The a- and b-waves originate primarily in the outer and inner retina, respectively. An abnormal ff-ERG result occurs when approximately 20 percent of the retina is compromised.[7] The signal is recorded with alternate current rather than direct current amplification, allowing only fast ERG signals to be detected (a-waves and b-waves rather than slower c-waves, fast os-

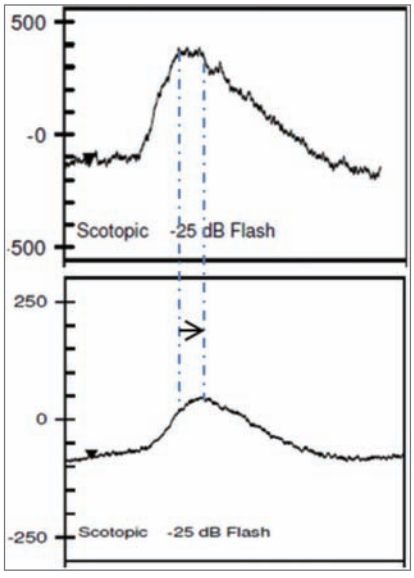


Figure 5. Full-field ERG tracing of healthy normal female patient diagnosed with Usher's syndrome (bottom). Scotopic response amplitude is decreased and implicit time increased (arrow) compared with aged-matched control (top) recorded on the same system.

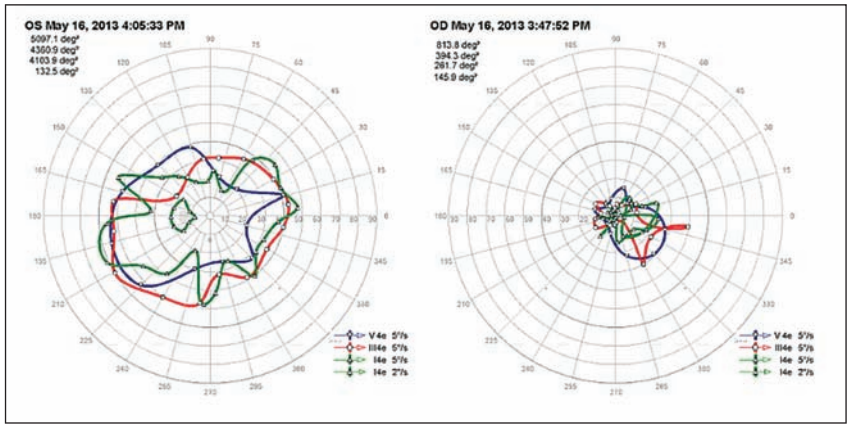
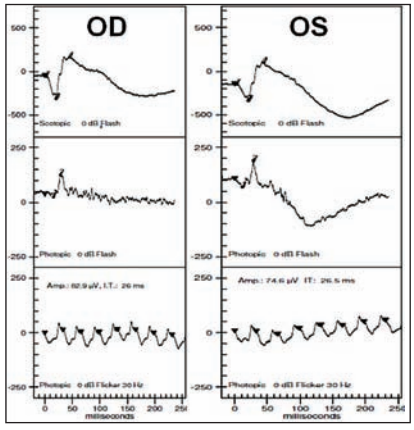


Figure 6. Full-field ERG of patient complaining of unexplained vision loss acute and stable five years after exposure to an ammonium-based cleaning solution. Goldman fields (top) are markedly constricted, OD>OS while all five ERG signals were of normal amplitude in each eye. MRI of brain and orbits, VEP, mfERG and EOG were all normal and repeat field testing was highly variable and never consistent (not shown).



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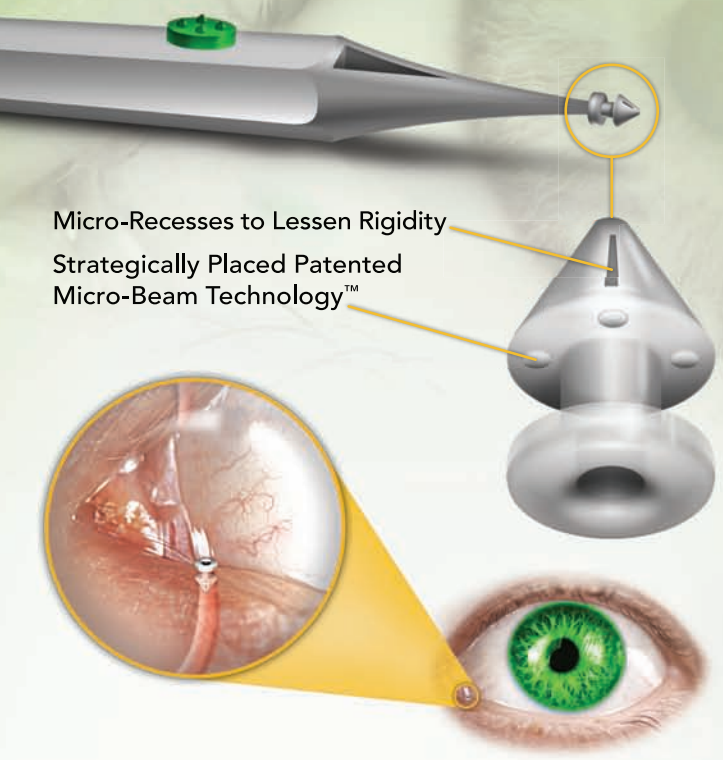

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cillation and light peak potentials).[8-9]

Clinical applications of ff-ERG. The most common use is detecting a hereditary degeneration and differentiating it from other causes. In RP the ff-ERG is often the definitive test and the scotopic a- and b-waves are generally extinguished early in autosomal recessive and X-linked RP.[10] A suppressed but intact b-wave may be seen in autosomal dominant RP and the increased implicit time may be helpful in making the diagnosis *(See Figure 5)*. Leber's congenital amaurosis presents with an RP-like picture of the retina and is also associated with markedly reduced ff-ERG signals. Congenital stationary night blindness is identified with the ff-ERG—usually a negative signal with a-wave greater than b-wave—and accounts for 10 to 20 percent of blindness in children.[11] Evaluation for unexplained vision loss with ff-ERG should be performed before initiating a costly workup. X-linked Juvenile Retinoschisis (XLRS) also manifests as a negative waveform ERG, and is the result of a mutation of the RS1 gene, causing microcystic changes in the macula.[12] Cone degeneration can be detected and distinguished from Stargardt's disease or other bull's-eye maculopathies using the ISCEV test protocol. The b-wave is useful for predicting rubeosis in central retinal vein occlusion. An implicit time greater than 50 msec and inter-eye difference of greater than 8 msec is highly predictive.[13,14] In such patients we initiate anti-VEGF therapy followed by panretinal photocoagulation laser treatment early in the course of the disease. The ff-ERG may also be particularly useful for identifying malingering associated with profound visual field loss *(See Figure 6)*. Chemical vitrectomy with ocriplasmin was reported to cause dyschromatopsia in less than 5 percent of patients, with an associated profound suppression of the ff-ERG. We have also noted ERG suppression in the absence of dyschromatopsia in cases where the drug has been effective in the treatment of macular hole *(See Figure 7)*. These effects appear reversible.

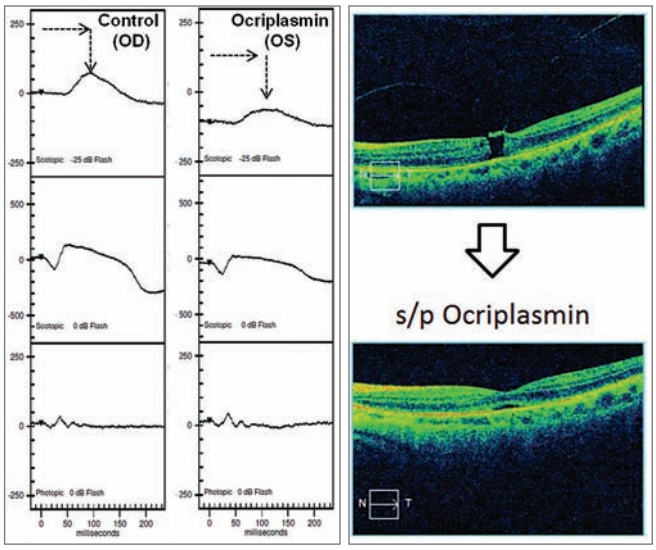


Figure 7. Left) A 63-year-old highly myopic Asian patient with cataracts showing decreased scotopic response but maintains normal photopic response three weeks status-post Ocriplasmin injection OS for a stage II macular hole. Decreased scotopic response indicates rod dysfunction. Patient has normal color vision, but decreased red cap sensitivity OS. Right) OCTs showing closing of macula hole three weeks s/p Ocriplasmin injection. Note small amount of subretinal fluid.

ff-ERG tips: Electrode contact is key for good signals. Minimize 60Hz line noise to optimize oscillatory potential recording. Be consistent with exact dark adaptation time.

Pattern ERG

The PERG is generated by an alternating checkerboard stimulus, which activates ganglion and amacrine cells, generating a small potential change recorded at the cornea.[15] It is used primarily to assess retinal damage secondary to glaucoma but may also be useful in the diagnosis and/or monitoring of ocular hypertension, optic neuritis, optic atrophy and amblyopia.

Electrooculography

The EOG is an indirect way to measure the slow electrical responses generated by the retinal pigment epithelium, which are selectively affected in some conditions. Under direct current of the ERG, a series of slower potentials can be measured following the fast a- and b-waves, but these are lost with standard alternate current ERG recordings. The EOG is used to measure these slower potentials (usually just the light peak and dark trough, but a fast oscil-

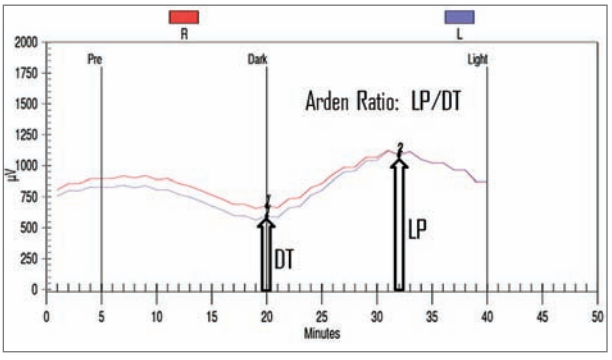


Figure 8. EOG recording of normal female patient. The Arden ratio (light/dark ratio) is the ratio between the light peak (LP) and dark trough (DT). In this case, the Arden ratio in the right eye is 2.21 (red line) and the left eye is 2.28 (blue line).

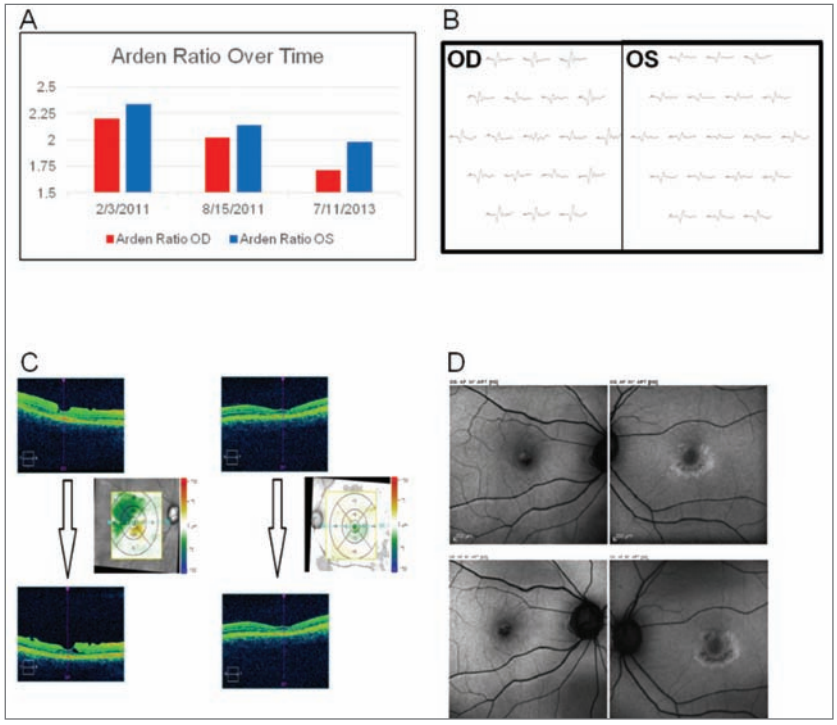


Figure 9. A) EOG Arden Ratio of patient diagnosed with plaquenil toxicity measured from time of plaquenil discontinuation (2/3/2011) and consecutively thereafter. Values begin in the normal range and subsequently decline over the next two years off plaquenil. Values of <1.7 are considered abnormal. B) In contrast, the mfERG is clearly suppressed at the onset OS>OD (19 trace array). C) OCT studies highlight the macular atrophy associated with progression of the bull's-eye, best seen on D) autoflourescence image documented at baseline (2/3/2011) and last follow-up (7/11/2013).

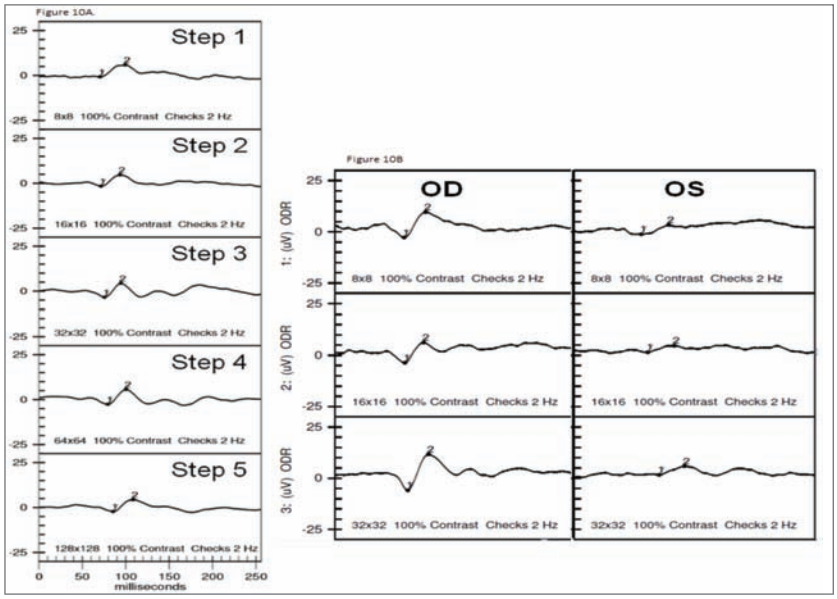


Figure 10. A) Pattern visually evoked potentials displaying normal latency and amplitude responses across stimuli ranging from Step 1 [100' arc (8x8)] to step 5 [6' arc (128x128)]. B) Pattern VEP affected by uncorrected refractive error. VA 20/20 OD (left), 20/200 OS (right).

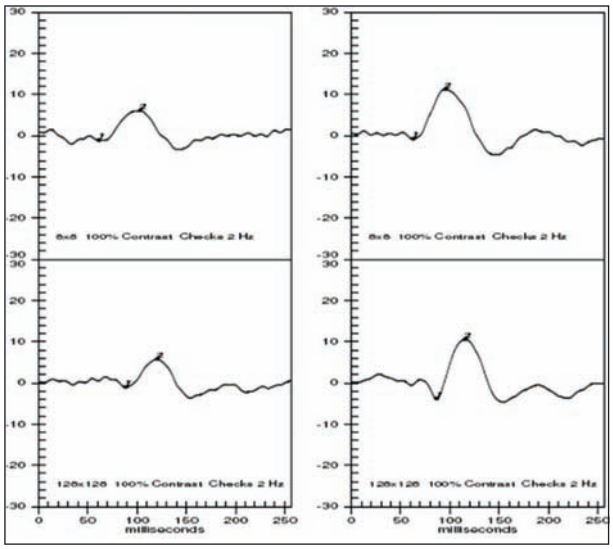
lation can also be identified).[16] Since the retinal pigment epithelium generates a resting potential across the eye, changes in that potential can be recorded by shifting the dipole—patients look side to side and the voltage is recorded during dark-adaptation followed by a light adaptation.[16] Figure 8 shows a typical EOG measurement. The response reaches its lowest trough eight to 12 minutes into the dark phase, and reaches its highest peak six to nine minutes into the light phase. The EOG amplitude is reported as the Arden Ratio: the greatest amplitude in light divided by the lowest amplitude in the dark. The size of the light peak and dark trough should approximately be 2:1 or greater, respectively. A light/dark ratio less than 1.7 is considered abnormal.

Clinical applications. The EOG has classically been used to detect hydroxycholoquine toxicity and Best disease.[16,17] In case of the former, we find other modalities may be more sensitive at early detection of toxicity, including a central 10-degree visual field with red target, autofluorescence *(See Figure 9)*, mfERG and optical coherence tomography, demonstrating foveal atrophy. Toxicity may be progressive after discontinuation of the medication and continued monitoring is in order. In addition to Best disease, other RPE dystrophies, including pattern dystrophies and the fundus flavimaculatus variant of Stargardt's, can be associated with a suppressed EOG with typically normal ff-ERG.[18]

Tip: Make sure saccades are consistent and do not overshoot and saturate the recording system. This can underestimate the Arden ratio.

Visually Evoked Potential

The VEP measures the function of the optic nerve and its connection



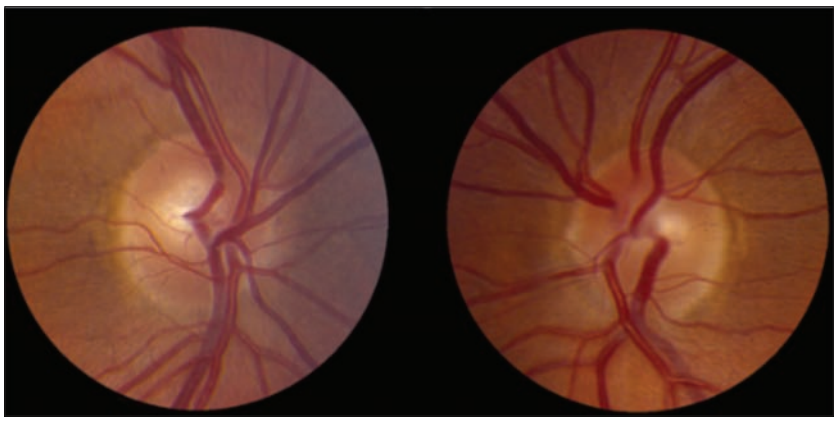


Figure 11. VEP in traumatic optic neuropathy. A patient suspected of malingering after hitting his head on a turnstile. VA 20/20 OU. A) VEP amplitudes reduced OD, eye with purported vision loss. B) Fundus images show subtle temporal cupping, pallor and disc excavation OD (left) with c/d of 0.3 compared with OS where nerve is crowded, c/d 0.15.

between the retina and brain. A VEP stimulus may be in the form of a pattern reversal (checkerboard) or pattern onset (flash). Pattern reversal is the preferred stimulus for most clinical purposes due to fewer variations in waveform and latency compared to the flash *(See Figure 10)*. Pattern reversal stimuli are the best choice in cooperative patients with visual acuity of 20/200 or better, particularly when testing for possible effects of optic neuritis. Smaller check sizes subtending 10 to 20 degrees (minutes) of arc are best for evaluating foveal vision. Larger check sizes subtending 40 to 50 degrees of arc are compared to age-related norms. Expected peak latency is about 100 msec using pattern reversal stimuli, and about 110 msec using flash stimuli for individuals below the age of 55. Beyond this age, VEPs change gradually, resulting in attenuation of amplitude and slowing of latency. A VEP finding that shows decreased latency/amplitude at all check sizes may indicate nerve damage.[19] VEP findings which show decreased latency/amplitude at only smaller check sizes may indicate refractive error opposed to nerve damage *(See Figure 10B)*. A common clinical referral is to determine whether a patient's visual problems are due to retinal or visual pathway dysfunction. Recording both an ERG and VEP will usually help determine the cause of visual dysfunction.

better utilized for evaluating parafoveal vision.[19] The higher-intensity Flash VEP is useful when poor optics, poor cooperation (nystagmus) or poor vision limit the use of pattern reversal VEP.

Interpretation of the VEP includes analysis of amplitude and latency of each waveform,

Clinical applications. The VEP is useful in assessing damage from glaucoma, retrobulbar optic neuritis, traumatic optic neuropathy *(See Figure 11)*, compressive optic neuropathy and damage from meningitis.[20] It is important to understand the limitations as noted above, but don't underestimate the potential in complex cases where optic nerve dysfunction is difficult to confirm or quantify with other tests.

Tips: Make sure the patient is properly refracted and note level of best-corrected vision. If vision is <20/200, a flash rather than the standard pattern VEP may be indicated. Make sure the patient is fixating on the target screen during the test.

Dark adaptometry/ Scotopic sensitivity

Dark adaptometry is used to measure absolute cone and rod sensitivity. Sensitivity of the retina is measured over time, producing a biphasic curve, with a rod-cone break occurring within 5 to 10 minutes. Dark adaptometry is useful in the diagnosis and management of retinal degenerations, high myopia, vitamin A deficiency and other night blinding conditions. The two major parameters that are measured are the dark adaptometry curve and the final dark-adapted threshold.[21] Fenretinide was found to slow the progression of geographic atrophy in Phase II studies. However, this drug also acted as a retinol-binding protein inhibitor, reducing dark adaptation kinetics and dark adaptometry was used as confirmation.[22]

In summary, a clinical electro-

physiology unit can be established in any retina practice and will provide useful information in the diagnosis and management of specific disorders. It may alter the course of patient care and improve clinical outcomes. Something to consider as you evolve your practice towards optimal state-of-the-art diagnosis and care for your patients. REVIEW

Dr. Gallemore is an assistant clinical professor at Jules Stein Eye Institute, UCLA School of Medicine, Los Angeles, and founder and director of the Retina Macula Institute and Research Center, Torrance, Calif.

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Optimizing Outcomes With Monovision

Making patients understand monovision and what to expect from it is half the battle, surgeons say.

Walter Bethke, Managing Editor

A discussion of LASIK with a patient over 40 becomes more extensive than the usual preop consultation because the surgeon has to address both the patient's distance vision and the current, or impending, loss of accommodation. Surgeons say that monovision LASIK can be helpful for some, but that choosing the right candidates and proper refractive targets can be tricky. Here, refractive experts detail their approach to monovision and how to ensure you get the best results in the right patient.

Patient Selection

Surgeons take different approaches to handling monovision in their practices, but all of them become more confident if a patient has already worn it in their contact lenses.

"First of all, I won't do monovision in anyone under 45," says Mobile, Ala., surgeon Richard Duffey. "In other words, you can't anticipate presbyopia, even though you know a patient is going to be presbyopic. The patient won't appreciate that you left one eye nearsighted, he only will know that he can't see well in the nearsighted eye. Having said that, if someone comes in already doing monovision in his contact lenses, and likes it, I'll do the same with LASIK. However, if a patient has never tried monovision, we seldom bring it up. If, however, someone comes in and neither eye is perfect for up close but he brings up monovision, I'll suggest that we do a contact lens trial first, with the non-dominant eye refracted for about -2.25 to see how he likes it. If he likes it, even if the trial is for a day, I'm willing to do monovision with the laser."

Asim Piracha, MD, associate professor at the University of Louisville's Department of Ophthalmology and Visual Sciences, will talk about it with patients over 40. "For plano presbyopes, I don't recommend much treatment," he says. "I tell them to stick with their readers. But if they hate their readers, I'll have them do a contact lens trial with monovision, wearing the lenses all day during all activities. I want to make sure they're comfortable with it.

"If the patient is a hyperopic presbyope who's a successful monovision contact lens wearer, I'll do monovision LASIK on him," Dr. Piracha continues. "However, if the hyperopic presbyope is over 45 and has never tried monovision, I lean toward refractive lens exchange with a multifocal intraocular lens over laser vision correction. This is because hyperopic patients are a little trickier with LASIK and, in general, their LASIK results aren't as good: I get 5 to 7 percent fewer 20/20 outcomes and a little bit higher enhancement rate. You also have the issue of the initial overcorrection from the hyperopic treatment that then regresses. I tell the patients it takes about two weeks for the distance vision to come around and about two months before it's stable. And if you do monovision in a hyperopic presbyope, they'll have good near vision day one but no distance vision, and will be at 20/50 or 20/60 in the distance eye. A lot will call back and say they can't see, but it's because they're still myopic from the hyperopic treatment, even though you discussed it with them."

Surgeons say the perfect candidate is a low myopic presbyope. "If both eyes are nearsighted, we'll do the dominant eye for distance and leave the non-dominant eye as it is—say it's -2 or -2.25—we'll leave it and see if they like it," says Dr. Duffey. Dr. Piracha

takes a similar approach for patients under -2 D in both eyes, checking it with a lens first. "I'll tell the patient to wear one contact lens only to correct for distance, especially if he's already a contact wearer," Dr. Piracha says. "If he functions well with the one lens, I'll just do LASIK on that eye. However, if he's over -2 D, I'll have him do a monovision trial and, if it's successful, I'll have to treat both eyes, correcting the non-dominant eye a little bit."

Dr. Duffey is wary of doing high corrections with monovision. "I won't take someone who is -7 D in both eyes and purposely shoot for plano in one and -2.25 D monovision in the other unless he's done monovision previously with contact lenses and liked it," he says. "Because if he doesn't like the monovision surgery, then I've got to go back and operate a second time on that first eye. Also, for the hyperopic presbyope, there's a limit to how much hyperopia you can treat. If someone is +3.5 D in both eyes, that's the limit of what I'll fix with hyperopic LASIK and therefore I don't have any room to make an eye -2 D because I'd have to correct +5.5 D in total."

Majid Moshirfar, MD, director of refractive surgery for the Moran Eye Center at the University of Utah, reminds patients—and surgeons—that monovision has its limitations. "It's not a panacea," he says. "Eventually, the patient's accommodation will reduce and, when it does, the monovision won't work the way it used to. The other thing is, if you do monovision on the non-dominant eye and correct the dominant eye for distance, you have to pray that the distance vision ends up 20/20 and great. If the distance eye ends up 20/25 or 20/30 the individual won't be happy because neither eye is good for distance. As a result, the patient will come to you for an enhancement. In my practice, most of the patients who come and ask for an enhancement are monovision patients in whom the dominant eye went down to 20/25 or 20/30 over three or four years. And the non-dominant eye is not helping the dominant eye."

Some surgeons will target a smaller amount of monovision in the non-dominant eye in order to facilitate intermediate visual tasks, such as computer work.

Setting the Targets

Surgeons will take many factors into account when deciding on the amount of anisometropia to create.

Though Dr. Moshirfar finds himself relying on monovision less in his practice than he did 15 years ago, he does have certain correction ranges for patients who are candidates. "For the 46 to 52 age range, I aim for -0.71 to -1 D," he explains. "For patients over age 52 I aim for -1.25 to -1.75. For people who need more, I won't go above -2 D because of the anisometropia that is created, and because patients with a high amount of monovision are more sensitive to any loss of distance clarity in the dominant eye." Dr. Piracha also does a conservative level of monovision. "I am aiming to give patients distance and intermediate vision, with the need for glasses for near work or small print. For patients in their 40s, I'll go for -1 D," he says. "If they're 50 or older, I'll do -1.25 D. Almost everyone will tolerate that amount."

"I tell patients that they may be able to get by with daily functions such as using the iPad, reading a restaurant menu or writing a check," Dr. Piracha continues. "But if they want to read small print such as stock quotes, they'll need readers. I'll also counsel them that, though not everyone needs glasses for driving at night, it might help to have a pair of glove box glasses if it's raining at night or they're in an unfamiliar environment, because you need good depth perception in those situations."

Dr. Duffey goes more for what would be considered the traditional level of monovision. "I like to set -2.25 D for most, unless they're already over the age of 60 and they know they'd like -2.5 D, in which case I'll set them closer to 2.5 D," Dr. Duffey says. "That way, whether they're 45 or 60 they'll have a decent level of monovision so they have really good near vision and there's not so much anisometropia that they have a hard time tolerating it. I have tried mini-monovision, but for the most part I'm not trying to do that. I want to get these patients closer to plano for distance and truly set them for monovision." REVIEW

Secondary AREDS2 Supplements Analysis

In a secondary analysis of the effects of lutein/zeaxanthin on the progression of age-related macular degeneration, the Age-Related Eye Disease Study 2 Research Group found that the total evidence on beneficial and adverse effects suggests lutein/zeaxanthin could be more appropriate than beta-carotene in AREDS-type supplements.

AREDS2 is a multicenter, double-masked, randomized trial of 4,203 participants, 50 to 85 years of age, who are at risk for developing late AMD; 66 percent of the patients had bilateral large drusen and 34 percent had large drusen and late AMD in one eye. In addition to taking the original or variation of the AREDS supplement (vitamin C, vitamin E, beta-carotene and zinc with copper), participants were randomly assigned to one of the following four groups: placebo; lutein/zeaxanthin 10 mg/2 mg; omega-3 long-chain polyunsaturated fatty 3 acids, 1 g; or the combination.

In an exploratory analysis of lutein/zeaxanthin vs. no lutein/zeaxanthin, the hazard ratio of the development of late AMD was 0.90 (95 percent CI, 0.82 to 0.99; p=0.04). Exploratory analyses of direct comparison of lutein/zeaxanthin vs. beta-carotene showed hazard ratios of 0.82 (CI, 0.69 to 0.96; p=0.02) for development of late AMD; 0.78 (CI, 0.64 to 0.94; p=0.01) for development of neovascular AMD; and 0.94 (CI, 0.70 to 1.26; p=0.67) for development of central geographic atrophy. In analyses restricted to eyes with bilateral large drusen at baseline, the direct comparison of lutein/zeaxanthin vs. beta-carotene showed hazard ratios of 0.76 (CI, 0.61 to 0.96; p=0.02) for progression to late AMD; 0.65 (CI, 0.49 to 0.85; p=0.002) for neovascular AMD; and 0.98 (CI, 0.69 to 1.39; p=0.91) for central geographic atrophy.

JAMA Ophthalmol 2014;132:142-149.

The Age-Related Eye Disease Study 2 (AREDS2) Research Group.

Temporary Tarsorrhaphy in Children Using Glue

A prospective case review of children undergoing temporary tarsorrhaphy with cyanoacrylate glue demonstrated that this technique allows a quick and efficient procedure with relatively easy reapplication in a clinic setting, avoiding the need for multiple general anesthetic procedures.

During a three-year period between January 2010 and January 2013 at a British tertiary specialist children's hospital, seven children underwent temporary tarsorrhaphy with cyanoacrylate glue instead of the conventional suturing technique. Indications were socket expansion (n=4), fornix deepening (n=2), prosthesis repositioning and prolapsed conjunctiva following enucleation (n=1). The age range was 3 weeks to 14 years (mean, 2.7 years). The glue tarsorrhaphy lasted between 0.5 and 13 weeks (mean, 4.5 weeks). There were no adverse outcomes, and the glue tarsorrhaphy was tolerated well in all cases, with relative ease of reapplication of glue in clinic.

Ophthal Plast Reconstr Surg 2014;30:60-63.

Trivedi D, McCalla M, Squires Z, Parulekar M.

Toric IOL Outcomes with Posterior Corneal Astigmatism

Doctors at Baylor College of Medicine evaluated the impact of posterior corneal astigmatism on toric intraocular lens outcomes and determined that corneal astigmatism was overestimated in with-the-rule eyes by all devices and underestimated in against-the-rule astigmatism in all devices except the Placido-dual Scheimpflug analyzer.

Corneal astigmatism was measured using five devices before and three weeks after cataract surgery. Toric IOL alignment was recorded at surgery and at the slit lamp three weeks postop. The actual corneal astigmatism was calculated based on refractive astigmatism three weeks postop and the effective toric power calculated with the Holladay 2 formula. The prediction error was calculated as the difference between the astigmatism measured by each device and the actual corneal astigmatism. Vector analysis was used in all calculations.

With the IOLMaster, Lenstar, Atlas, manual keratometer and Galilei (combined Placido-dual Scheimpflug analyzer), the mean prediction errors (D) were, respectively, 0.59 @ 89.7, 0.48 @ 91.2, 0.51 @ 78.7, 0.62 @ 97.2 and 0.57 @ 93.9 for WTR astigmatism (60 to 120 degrees) and 0.17 @ 86.2, 0.23 @ 77.7, 0.23 @ 91.4, 0.41 @ 58.4 and 0.12 @ 7.3 for ATR astigmatism (zero to 30 and 150 to 180 degrees). In the WTR eyes, there were significant WTR prediction errors (0.5 D to 0.6 D) by all devices. In ATR eyes, WTR prediction errors were 0.2 D to 0.3 D by all devices except the Placido-dual Scheimpflug analyzer (all $p<0.05$ with Bonferroni correction).

J Cataract Refract Surg 2013;39:1803-1809.
Koch D, Jenkins R, Weikert M, Yeu E, et al.

Adverse Effects and Short-term Results After SLT

A prospective study of 64 eyes of 64 patients not sufficiently treated with local anti-glaucoma therapy indicates that selective laser trabeculoplasty has a good ability to reduce intraocular pressure with a minor risk of adverse effects and no significant increase in macular thickness.

IOP, anterior chamber cells, anterior chamber flare and vitreous haze (according to the Standardization of Uveitis Nomenclature Working Group) were examined before SLT, as well as 24 hours, 14 days, six weeks and three months after SLT. Macular thickness measurements in nine Early Treatment Diabetic Retinopathy Study subfields, including central subfield (measured by Spectralis OCT), were also performed.

The average mean preoperative IOP measurement was 19.1 ±3.972 mmHg compared to 12.9 ±2.514 at 24 hours after SLT ($p<0.001$); 13.2 ±3.331 mmHg 14 days after SLT ($p<0.001$); 14.1 ±2.731 mmHg six weeks postop ($p<0.001$); and 13.9 ±2.922 mmHg three months post-SLT. The central subfield preoperatively was 278.14 ±74.355 µm compared with 277.14 ±71.461 ($p=0.177$); 277.14 ±71.461 ($p=0.354$); 287.34 ±74.363 ($p=0.414$); and 257.45 ±68.431 µm ($p=0.214$) at 24 hours; 14 days; six weeks; and three months after treatment, respectively. Anterior chamber cells, anterior chamber flare and vitreous haze were not noted at any time of examination.

J Glaucoma 2014;23:105-108.
Klamann M, Maier AK, Gonnermann J, Ruokonen P.

Femto Laser Can Effectively Reduce Phaco Time

German researchers have concluded that femtosecond laser-assisted cataract surgery allows a significant reduction in effective phacoemulsification time compared to manual phacoemulsification, which correlates positively with preoperative lens opacity.

In this intervention, 88 eyes (Group 1) underwent femtosecond laser-assisted surgery (corneal incisions, capsulotomy, lens fragmentation) using the LenSx platform (Alcon) and residual lens workup with pulsed ultrasound energy (Infiniti Vision System; Alcon). In 62 eyes (Group 2), complete cataract removal was performed with phacoemulsification only, using pulsed ultrasound energy with the same device (Infiniti). Pentacam nucleus staging (PNS) was evaluated using Pentacam HR (Oculus); endothelial cell density was measured using specular microscopy (NonCon Robo). The main outcome measures were mean preoperative PNS staging using an automatic ordinal scaling (PNS-O, grades 0 through 5) and a manually defined density grid derived from Scheimpflug imaging (PNS-P). Effective phacoemulsification time and endothelial cell loss were evaluated in both groups.

Preoperative PNS-O and PNS-P showed no significant difference between the groups ($p=0.267$). Effective phacoemulsification time was significantly lower in Group 1 for all PNS-O stages ($p<0.001$), and overall mean effective phacoemulsification time was significantly lower in Group 1 (1.58 ±1.02 seconds vs. 4.17 ±2.06; $p=0.0001$). With increasing preoperative PNS-P, effective phacoemulsification time increased in both groups; however, this gain was noticeably, but not significantly, lower in Group 2. Endothelial cell loss was significantly lower in Group 1 ($p=0.02$).

Am J Ophthalmlol 2014;157:426-432.
Mayer W, Klaproth O, Hengerer F, Kohnen T.

Thin-flap LASIK Safe in Thin Corneas

Researchers in a private center in Tokyo have concluded that LASIK in eyes with thin corneas shows similar long-term stability, safety and efficacy as LASIK in eyes with a central corneal thickness of 500 µm or greater.

Patients were divided into two groups based on CCT. The thin-cornea group (291 eyes of 146 patients) had a CCT of less than 500 µm with normal topography, while the control group (371 eyes of 193 patients) had a CCT of 500 µm or greater. Patients were evaluated to six years postop. Analysis was performed to determine whether there were differences between the groups at the last checkup three to four years postoperatively.

In the thin-cornea group, no significant differences were observed in LASIK outcomes when eyes were subdivided by the time of final checkup (three, four and greater than five years). There was a significant difference in visual and refractive outcomes between three months postoperatively and the last checkup in the thin-cornea group and the control group. No significant difference in visual, refractive or topographic outcomes were observed between the two groups at the last checkup.

J Cataract Refract Surg 2014;40:239-250.
Tomita M, Watabe M, Mita M, Waring G.


Branded vs. Generic: Proceed With Caution

Despite the best intentions of the FDA, generic versions of drugs are not always identical to their branded counterparts.

Malik Y. Kahook, MD, Denver

At the 2013 American Academy of Ophthalmology meeting I participated in a debate regarding the pros and cons of using generics vs. brand-name medications. I was asked to argue in favor of branded medications, but as in most debates, it's an oversimplification to blindly take one side or the other. The reality is more complicated. Generics have cost in their favor, but they sometimes do not provide the same treatment specifications or results as branded medications, despite the efforts of the Food and Drug Administration to ensure that they will.

Here, I'd like to talk about some of the ways in which generics may differ from the branded medications they replace, and what clinicians need to be on the lookout for.

The Issue of Bioequivalence

The hurdles required to get a new, "innovator" drug to market are substantially different from those for a generic follow-on drug. Of course, that's part of the reason a branded medication costs more. Where the initial innovator drug has to prove safety and efficacy through clinical trials, a generic is only required to show bioequivalence.

Although bioequivalence sounds like it might involve conducting biological studies, the FDA defines it as meaning that you must demonstrate that the ingredients of your generic version are an exact copy of the ingredients in the original drug, including both active ingredients and excipients. (If the active ingredients and excipients are not identical, the drug is not considered a generic; it has to go through regular FDA approval just like any new drug.) The premise is that this will cause the generic to have the same safety and efficacy as the branded drug.

Unfortunately, the idea that generics are equal to branded medications because the ingredients are the same is not necessarily true. Many factors that affect the efficacy of a topical medication are independent of the ingredients inside the bottle. For example:

• ***Bottle material matters.*** The ingredients of many branded medications are matched to the bottle material that's being used. This was certainly the case with latanoprost, where compatibility with the bottle material was a large part of the research and development process when bringing Xalatan to market. This is not something that's directly investigated by the FDA.

• ***Bottle shape and size affects use.*** Innovator drug trials not only test the drug but also the bottle in which it will be delivered to patients, so the impact of the bottle's shape and size has been taken into consideration. However, generic drug manufacturers are not required to copy bottle shape and size, and this can make a difference in how easily patients can use the drug.

For example, Xalatan comes in a flat, small bottle that takes a certain amount of effort and finesse to squeeze in order to instill a drop. In contrast, some of the generic bottles of latanoprost are round and more rigid, making the bottle harder for the patient to squeeze. *(See examples, facing page.)* Many of our patients are elderly and have physical limitations. If they're used to squeezing a particular bottle that's flat and slightly less rigid, and then they switch to a bottle that's

This article has no commercial sponsorship.

One issue that can cause confusion when switching from a branded drug to a generic, or from one generic to another, is difference in cap shape and color.

round and more rigid, the application process—and their adherence to the medication—might be different than when they were using the previous bottle. Furthermore, since bottle shape and size are chosen by each generic manufacturer, patients may sometimes get the drug in a flat bottle and other times get it in a round bottle. That has created a lot of confusion with our patients.

• ***Cap color doesn't always match.*** Ophthalmic drug bottle cap colors are intended to be coordinated based on the drug category. The FDA tries to ensure that the color is correct, but there have been cases in which a different-color cap slipped through. As a result, sometimes the generic drug bottle cap color (as well as shape and size) is different from the branded drug *(See example, above)*. This creates a lot of confusion when patients are trying to remember which of several drops they're supposed to take at which time.

Even if a patient has never used the branded drug with the correct cap color, an altered color is still a problem; the new cap color might actually be the same color as another medication the patient is taking. For example, prostaglandin analog bottles are supposed to have teal-colored caps. If your patient is using a generic version whose bottle has a white cap, she might confuse it with other classes of medication that are supposed to have a white cap.

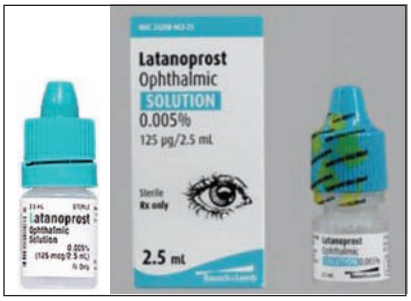
If you notice an example of incorrect cap color, the FDA has said it would like to hear about it so steps can be taken to correct the discrepancy.

• ***The drop size may be different.*** Topical drop bottles on the market right now provide a dose of 30 to 50 µl per drop. Unfortunately, there can be a lot of variability between branded and generic formulations simply because the tip might have a bigger or smaller hole. Obviously, this can affect how much of the drug is actually making it onto the eye; it might be less, it might be more.

Even more interesting, there was a generic timolol that came onto the market that didn't have a hole in the tip at all; the patient was required to pierce the tip to get medication out, similar to a tube of superglue. That created confusion with many patients; some didn't realize that they were supposed to do this, and tried to use the drops anyway. They thought they were putting a drop on, but they had never opened the bottle so nothing was coming out. Others thought the bottle was defective or empty. Plus, a self-made hole might end up being any size, affecting the dose, and the process of making the hole could easily compromise the sterility of the contents.

All of these considerations—bottle material, shape and size, cap color and diameter of the drop opening—are very important for both the physician and the patient. Unfortunately, these considerations may be overlooked, because the focus is on trying to prove bioequivalence.

• ***A patient's generic drug may look different from month to month.*** This is another unfortunate side effect of generic medications. It happens because there can be multiple manufacturers of a given generic, each with a different bottle. For example, there are six to eight



Another issue is differences in bottle shape and stiffness, which can make applying drops more difficult for an older patient. For example, Xalatan comes in a flat bottle; many generics of the drug come in round bottles that are more difficult to squeeze.

different manufacturers of generic latanoprost in the U.S. market right now. The one that a given pharmacy sells may change, because a chain such as CVS, Walgreens or Walmart will usually go with whichever manufacturer is giving the pharmacy group the best deal at a given time. As a result, a pharmacy might switch the generic it offers when a lower bid comes in from another generic manufacturer. So even if the patient is going to the same pharmacy, he may end up with different generic versions of a drug at different times. That can be confusing if the bottles look and/or behave differently. (There might even be a difference in tolerance and IOP control between the two.)

The Package Insert

Ironically, even if a generic drug turns out to have a problem, current rules prevent the manufacturers from alerting physicians or patients. There's a rule that requires generic drug manufacturers to include an exact copy of the package insert that's included with the innovator drug. While this rule was intended to reflect the idea that the drugs are bioequivalent, the unintended side effect has been to avoid placing the same diligence requirements and burden of ensuring safety on

the generic manufacturers that we require from branded manufacturers.

As a result, if the generic manufacturer introduces a medication onto the market and notices some side effects or adverse events that occur with the generic product, it's not allowed to change the package insert to alert physicians and patients that there may be a problem. In addition, this rule may actually reduce the motivation of generic manufacturers to conduct adequate monitoring of their products; after all, there's no threat of a lawsuit if a problem arises.

Fortunately, this issue has come to the attention of the FDA. In November 2013, the FDA proposed a rule that would permit generic drug manufacturers to update their labels if they receive information about potential safety concerns. If passed, this will go a long way toward ensuring safety for our patients.

Imported Generics

Another issue with generics is that many of them are manufactured outside of the United States, where quality control has sometimes been a real concern. Problems have ranged from mysterious impurities being found in the drugs, to imperfect ingredient matching, to outright fraudulent formulations that serve no beneficial purpose at all (which may in some cases result in grievous harm to patients).

According to the *New York Times*, India's pharmaceutical industry currently supplies 40 percent of the over-the-counter and generic prescription drugs consumed in the United States. Many of its factories are world-class and "virtually indistinguishable" from U.S. manufacturing facilities (according to the *Times*), producing high-quality, reliable medications. But at the same time, the World Health Organization has estimated that one in five drugs manufactured in India are fakes. (Similar problems have been reported with drugs manufactured in other countries, including China.)

The reality is that generics are not necessarily the same as the branded medications—even if they've satisfied the FDA's bioequivalence requirement. That means that when using generic drugs, the burden of ensuring safety and efficacy is on us and our patients.

Our group did a study a couple of years ago comparing latanoprost manufactured in India to Xalatan. We found that the stability of the active ingredients was not the same over time or when subjected to heat. Furthermore, we found contaminants in all of the imported bottles, including microscopic filaments resembling string, and what we dubbed "UFOs."

The point is that the oversight of manufacturing practices that happen overseas in non-United States-based companies, especially companies that don't have branded medications on the market, is just not the same.

Some physicians may assume that such imported drugs are only an issue when patients purchase drugs outside the United States via the Internet in order to save money, but the reality is that these imports are increasingly available here. Indian formulations of timolol and travoprost are currently available through U.S.-based distributors, and other drugs such as NSAIDs will be available soon. Obviously, many companies outside the United States are producing high-quality generics; the concern is that a few of them are not. That puts the burden on physicians and patients to make sure that a given generic is safe and effective. (At least the drugs that are available inside the United States have gone through the FDA bioequivalence process; the drugs that some patients purchase outside the country via the Internet may not have, making them even more suspect.)

In-clinic Strategies

Because of all of the variables we've been discussing, physicians should stay closely attuned to what's happening with patients when they switch from a branded to a generic, or switch from one generic to another. We have to be vigilant to be sure intraocular pressure control isn't wavering and that patients are not presenting with new signs and symptoms of intolerance to the medication.

Here are a few things you can do to protect your patients (and your practice):

- ***Ask patients to bring in their drops.*** I ask my patients to do this regardless of which medications they are using, and many of them do. That gives me the opportunity to record which generic manufacturer they're using and do my best to keep tabs on that, so that if a problem occurs or something changes, I can look for a possible connection.
- ***Have patients switching to a new generic return to the clinic sooner than you would otherwise have them return.*** This will allow you to make sure no untoward consequences are occurring. Stay alert for

changes in efficacy or new signs or symptoms.

• ***If you see any issues arising when a patient switches to a generic, alert the FDA.*** Remember that this situation puts the burden on the physician to make sure the generic drug is truly safe and effective.

• ***If a patient doesn't do as well with a generic, make the effort to get the insurer to cover the branded drug.*** I've been faced with patients who were tolerant of the branded medication but had difficulty tolerating a generic because of side effects such as redness or irritation. In those cases, we write to the insurance company and do everything we can to get the patient switched back to the branded formulation.

For example, a branded medication may have a specific preservative in it, while the generic formulation has an alternative preservative that the patient is sensitive to. Travatan Z is a branded medication made by Alcon that contains the preservative SofZia instead of benzalkonium chloride; the generic versions contain BAK because their bioequivalence was based on the older version of travoprost. If a pharmacy switches a patient who is allergic to BAK to the generic drug, it becomes an issue.

Unfortunately, seeing thousands of patients a year at our practice, it's really hard to make sure that we win the battle for every patient who ends up in this situation. However, we do make the effort.

The Burden Is on Us

Generics are here to stay, and they're becoming a major part of treatment for all diseases, not just in ophthalmology. They're typically safe and effective, and they can produce cost savings for both patients and the health care system in general. Make no mistake—I'm a big fan of cost-cutting. If we can find a safe way to cut costs while maintaining excellent care, I'm all for it. It's the second part of that equation that we have to keep an eye on.

I use generic medications myself every day, and the overwhelming majority of my patients are on generics now. They're almost all doing very well, with good IOP control and good tolerance to the medications. So I'm certainly not saying we should avoid using generics. However, the reality is that generics are not necessarily the same as the branded medications—even if they've satisfied the FDA's bioequivalence requirement. That means that when using generic drugs, the burden of ensuring safety and efficacy is on us and our patients. REVIEW

Dr. Kahook is The Slater Family Endowed Chair in Ophthalmology and vice chair of clinical and translational research at the University of Colorado School of Medicine in Denver. He is a consultant for and receives research support from Allergan and Alcon.

REVIEW Advertising Index

RPS In-Office Dry-Eye Test Gets CLIA Waiver

Rapid Pathogen Screening has received a Clinical Laboratory Improvement Amendments waiver from the Food and Drug Administration for InflammaDry—a rapid, disposable, in-office test to aid in the diagnosis of dry-eye disease.

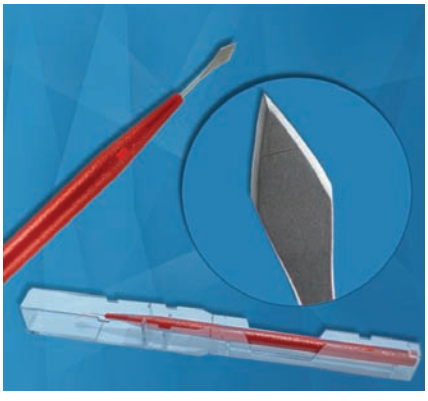
Obtaining the CLIA waiver, in addition to its FDA 510(k) clearance, enables the InflammaDry test to be used throughout the United States, an expansion from its current use internationally. CLIA-waived status is granted to tests that are simple to perform and have an insignificant risk of producing an erroneous result. The InflammaDry test can be administered by any medical office personnel in health-care facilities with a CLIA Certificate of Waiver.

The InflammaDry test detects elevated levels of matrix metalloproteinase 9, a clinically relevant inflammatory marker, in the tears of patients with dry-eye disease. InflammaDry is a single-use test that requires no additional equipment to administer or interpret results. Using only a small sample of human tears, the four-step process takes less than two minutes to complete and can be performed by a technician during a patient's initial workup. Results are available in 10 minutes, allowing a treatment plan to be established with the patient during his initial office visit. Providers are advised to bill CPT code 83516, immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semi-quantitative, multiple step method, for the InflammaDry test. Medicare payment for this code is currently $15.74. RPS anticipated that InflammaDry inventory would be available for sale in the United States in March 2014. For information, visit inflammadry.com or call (941) 556-1850.

Accutome Expands AccuSharp Series of Surgical Knives

Accutome has added to its AccuSharp Series of ophthalmic surgical knives with the new M-Series Angled Disposable Slit Knives.

The M-Series is made of the highest quality stainless steel and features a new "teardrop" bevel design for superior sharpness. The new knives provide surgeons with a 2.0-mm depth indicator to help generate proper wound architecture. For sharps safety, each blade locks into a protective plastic case. The M-Series comes in a variety of sizes compatible with the latest micro-incision cataract procedures.



Free samples are available by request. To learn more or request a sample, visit accutome.com; e-mail info@accutome.com; or call 1 (800) 979-2020.

Gulden Offers Orbital Sizers & Spheres

Gulden Ophthalmics has introduced enucleation and evisceration Eye Orbit Sizer Kits that help surgeons and/or the surgical support staff rapidly and easily determine the proper size for orbital implants or other ocular prostheses.

The Orbital Sizer Kits from Gulden save time and provide more accurate measurements and fitting of orbital implants. Each package contains five autoclavable re-useable sizers in 14, 16, 18, 20 and 22 mm sizes.

The sizers are constructed of stainless steel, providing excellent dimensional stability. The sizes are etched into the 3-inch long handles.

Gulden also offers its Venus line of sterile, surgery-ready eye spheres (same sizes as above) as well as a line of eye conformers. Eye spheres are permanent implants that occupy the cavity that results from the surgery;

This article has no commercial sponsorship.

eye conformers are temporary devices that maintain the shape of the eye and prevent closure or adhesion during the healing process.

For information, call (215) 884-8105; fax (215) 884-0418; e-mail: info@guldenophthalmics.com; or visit guldenophthalmics.com.

Ocusoft Adds Night Ointment

Ocusoft has introduced Retaine PM Nighttime Ointment for relief of severe dry eye.

Designed to keep eyes lubricated and comfortable during sleep, Retaine PM is a preservative-free, oil-based formula and is packaged in a large, economical 5-gram tube, 43 percent larger than traditional 3.5-gram tubes.

Retaine PM joins the line of Retaine brand eye-care products, including artificial tears and nutritional supplements, available through eye-care professionals. Introductory discount pricing is available to practitioners dispensing from their office; however, patients may also order online directly at ocusoft.com/retaine. For information, call 1 (800) 233-5469 or visit ocusoft.com.

Zeiss Introduces Progressive Choice Plus Sport Lenses

Zeiss has extended its line of Zeiss Progressive Choice lenses with the addition of Progressive Choice Plus Sport, a lens specifically designed for wrap frames.

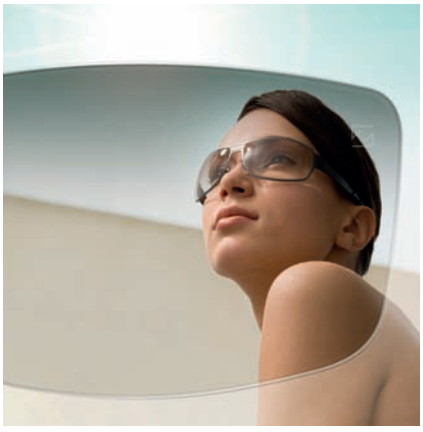
The Choice Plus Sport design combines advanced customization for the patient's full prescription with proprietary Zeiss prism compensation. This combination widens the area of clear vision by as much as 50 percent over standard lens designs in wrap frames, while dramatically reducing unwanted prism, the company says. It is available in two corridor lengths, with minimum fitting heights of 13 and 17 mm. Progressive Choice Plus Sport lenses are fully compatible with i.Scription by Zeiss, which addresses the effects of the patient's higher-order wavefront aberrations.

Progressive Choice Plus Sport lenses are available in 1.50 Hard Resin, 1.53 Trivex and 1.59 polycarbonate, with polarized options in all materials.

From Topcon: Imagenet 5 Digital Imaging System

Topcon Medical Systems has released the DICOM-compliant Imagenet 5 Digital Imaging System. Imagenet 5 is fully featured software for ophthalmic imaging capable of acquiring, displaying, enhancing, analyzing and saving digital images obtained with a variety of Topcon photographic devices, such as mydriatic and non-mydriatic retinal cameras and photo slit lamps. Imagenet 5 features a robust SQL expanded database and has numerous image-management functions that facilitate image acquisition, enhancement, measurement and comparison.

The digital acquisition procedures of Imagenet 5 cover color fundus imaging, red-free photography, fluorescein angiography, fundus auto fluorescence, indocyanine green angiography and photo slit-lamp imaging.



The Modality Work list utilization gives Imagenet 5 the capability of querying and displaying the work list provided by the EMR/EHR for the operator to select the scheduled patients for each procedure. Imagenet 5 easily integrates with Topcon's Synergy Ophthalmic Data Management System for complete connectivity. Imagenet 5 allows for review and image manipulation and can export images in various standard image formats as well as DICOM format. It has printing capabilities and runs on the Windows 7 operating system. For information, visit topconmedical.com.

Konan Expands Testing System With iPad-Enabled Amsler Grid

Konan's Chart2020 has been expanded with a Blind Spot Amsler test. It is now available on the Chart2020 DUO app at the Apple iTunes store. The Amsler test for iPad is a newly released add-in feature of Konan's Chart2020 DUO, available for a limited time at an introductory price from the iTunes Store. The Amsler test features the Blind Spot Amsler strategy, which provides a basis for easily controlling test distances, important for repeated tests over time.

The Chart2020 Duo app provides a framework for near and intermediate distance tests, as well as the most advanced controller for distance visual acuity and ocular performance testing for the Chart2020 Windows application. Chart2020 is an advanced eye-testing software solution featuring guided and self-scoring Konan Wizards, a unique user experience with one button control using Smart Docks, and the Chart2020 Duo application for the iPad retina display. For information, visit konanmedical.com. REVIEW

MerchandiseOffered

EquipmentandSupplies

Equipment and Supplies

Products and Services

Professional Opportunities

Ophthalmology Opportunity

Geisinger Health System (GHS) is seeking a BC/BE Cornea/Refractive Surgery Ophthalmologist for Geisinger–Scenery Park, State College, Pa.

About the Position

- Opportunity to start up a new practice and develop new programs
- Work with a surgical retina physician and a local optometry practice
- Enjoy a strong referral base from Geisinger's community practice sites
- Candidate should possess exceptional surgical skills and a dedication to patient care

Geisinger Health System serves more than 3 million people in central and northeastern Pennsylvania and is nationally recognized for innovative practices and quality care. A mature electronic health record connects a comprehensive network of 5 hospitals, 43 community practice sites and more than 900 Geisinger primary and specialty care physicians.

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A recent history of conjunctivitis and a worsening proptosis leads to a recommendation of a thyroid disease workup.

Wen-Shi Shieh, MD

Presentation

A 62-year-old black female presented to the Wills Eye ER for a two-week history of worsening right eye proptosis. She was previously diagnosed with conjunctivitis by an outside ER due to irritation in the same eye. When symptoms persisted, evaluation by an optometrist suggested a thyroid disease workup. At presentation, the patient described mild pain and blurred vision of the right eye, but denied any double vision.

Medical History

Past medical history was significant for hypertension, controlled with Atenolol and Amlodipine. Review of systems was negative for weight changes, fevers, chills or night sweats, respiratory or gastrointestinal changes or atypical arthralgias. The patient also denied any changes in hair or skin characteristics, heat or cold intolerance, as well as changes in energy level. Additionally, there was no history of smoking or personal history of malignancy. Family history was non-contributory.

Examination

Vital signs were within normal limits. Examination demonstrated a corrected visual acuity of 20/150 in the right eye improving with pinhole to 20/70. The left eye visual acuity was 20/20. The right pupil was sluggish while the left was reactive; no afferent pupillary defect was detected and visual fields were full by confrontation. Color plates were 8/8 briskly in each eye. Extraocular muscle motility was severely restricted on the right with 90 percent deficits in all fields of gaze. Left eye motility also showed an abduction deficit of 90 percent as well as an adduction deficit of 50 percent. Prominent right eye proptosis was noted along with palpable subcutaneous nodularity. There was lower lid retraction as a result of 4+ chemosis and 3+ injection in the right eye *(See Figure 1)*. These findings were absent in the left eye. Intraocular pressure was 22 mmHg in both eyes. Slit-lamp examination showed only superficial punctate keratopathy on the right. Dilated fundus exam was unremarkable.

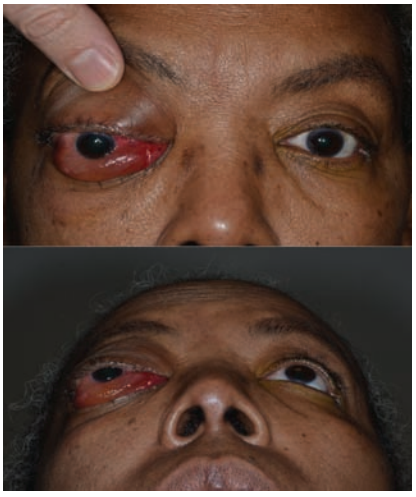

Figure 1. The patient at presentation with unilateral proptosis and chemosis of the right eye.

What is your differential diagnosis? What further workup would you pursue? Please turn to p. 104

Diagnosis, Workup and Treatment

Laboratory blood work was sent, including TSH, T3, free T4 and thyroid stimulating immunoglobulin, which all came back within normal limits. The patient underwent further imaging to characterize the orbit pathology. Computed tomography of the orbits without contrast *(See Figure 2)* was initially performed and showed extensive soft tissue infiltration throughout the right orbit, including near-complete involvement of the retrobulbar fat and obscuration of the optic nerve intraconally. Prop-tosis and mild tenting of the posterior right globe surface was noted. The right medial rectus muscle was markedly enlarged, including thickening of its tendinous insertion, while the remaining EOMs were normal in appearance. Additionally, there was abnormal enlargement of the left lateral rectus muscle. The orbital walls were intact. Given these findings, thyroid-related disease was considered less likely due to tendon involvement and the atypical pattern of EOMs affected.

Upon further questioning, it was ascertained that the patient had noticed mild nipple discharge from both breasts for a couple of months and never had a prior mammogram. A breast exam was subsequently performed which revealed an extensive right breast mass with overlying inflammatory skin changes and spread across the mediastinum toward the contralateral breast. Rapid progression of proptosis and possible early optic neuropathy warranted admission of the patient to expedite management and an orbitotomy with biopsy of the orbital lesion was performed. The final pathology report indicated morphologic and immunohistochemical findings consistent with breast carcinoma; furthermore, the specimen was estrogen receptor (ER) and progesterone receptor (PR) positive but human epidermal growth factor receptor (Her2) negative. Tumor markers were also sent and revealed normal CEA and CA-125; however, CA 15.3 was elevated at 100 (reference range <25).

During her inpatient course, she also had CT imaging of the chest, abdomen and pelvis, which revealed enlarged bilateral axillary and internal mammary lymph nodes and lucent lesions in the iliac bones. MRI of the orbits with gadolinium contrast demonstrated the aforementioned findings *(See Figure 3)* and MRI of the brain did not show any intracranial involvement. After discharge, oncology consultation was arranged in order to pursue further staging and management.

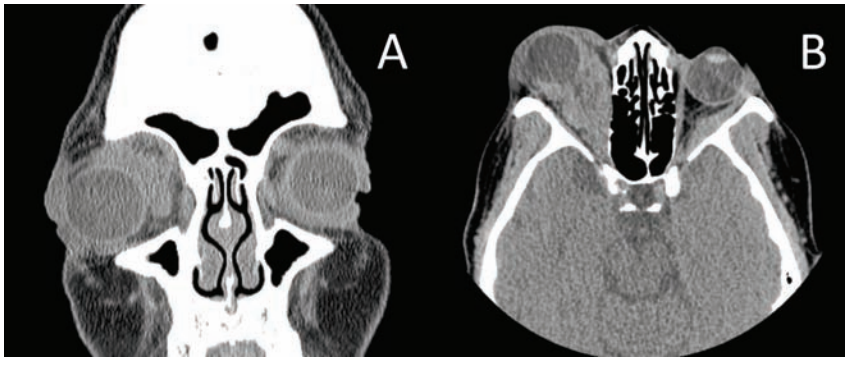

Figure 2. Computed tomography of the orbits without contrast. Coronal (A) and axial (B) views.

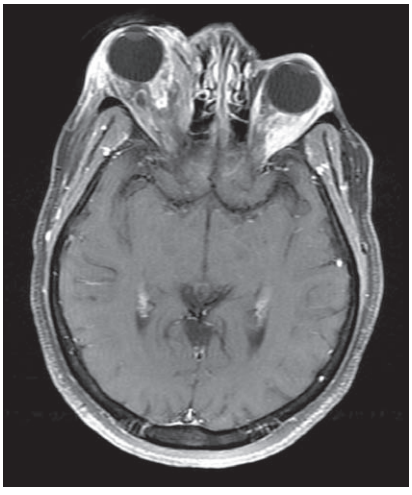
Figure 3. MRI orbits with gadolinium contrast. T1-weighted axial view demonstrating extensive infiltration of the right orbit.

Discussion

Breast carcinoma most frequently metastasizes to liver, bone, lungs, skin and brain.[1] Only a small percentage of cases are associated with disease spread to the orbit, with one study showing an overall rate of 0.2 percent.[2] However, breast carcinoma is considered to be the most prevalent primary tumor of all metastatic tumors to the orbit, with an estimated prevalence ranging from 28.5 to 58.8 percent of all orbital metastases.[3] In up to 25 percent of cases, orbital metastasis is the initial finding of a previously undetected primary malignancy.[4]

The presentation of orbital metastasis is mostly unilateral but can affect right and left sides equally. The anatomical distribution within the orbit predominantly involves the superior and lateral quadrants. Various ocular signs and symptoms are commonly reported, including proptosis,

eyelid swelling or mass, pain, ptosis, bulb divergence and blurred vision. Diplopia resulting from motility deficits is a prevalent symptom and occurs as a result of tissue-specific preference of breast cancer to extraocular muscles and surrounding orbital fat. Separately, enophthalmos is a less common but characteristic sign of orbital infiltration by the serous subtype of breast adenocarcinoma.[4,5]

In addition to metastasis, the differential diagnosis of an orbital process should include inflammatory lesions, benign tumors such as hemangiomas and lymphoproliferative disorders. Many cases of orbital metastasis can present with inflammatory signs and can be misdiagnosed as orbital pseudotumor, particularly in the absence of known primary cancer.[4,6] Other inflammatory conditions that may present in similar fashion and thus warrant consideration include sarcoidosis; Wegener's granulomatosis; thyroid orbitopathy; cellulitis; myositis; and scleritis. The distinguishing feature of orbital metastases is a rapid onset and progressive course with combined motor and sensory deficits, as well as no response to antibiotics or steroids.[7,8]

For evaluation of orbital masses, magnetic resonance imaging with gadolinium contrast is considered the imaging method of choice. MRI is advantageous over computerized tomography because of higher soft tissue contrast and lack of radiation exposure.[9] Orbital metastases appear on non-contrast CT as irregularly shaped lesions that are isodense to muscle and demonstrate slight enhancement with contrast. Orbital bony wall involvement is also a common finding. On MRI, metastatic disease is hypointense to fat on T1-weighted images and hyperintense to fat on T2-weighted images. This is characteristically distinct from orbital pseudotumor, which is isointense to fat on T2WI.[4]

Overall, orbital surgery geared toward removal of metastasis is not recommended because the procedure is not curative and may incur significant ocular morbidity.[10] Likewise, other radical surgeries or enucleation do not offer benefit in terms of survival and are only considered in cases complicated by intractable ocular pain or uncomfortable symptoms related to rapid tumor growth. At this time, the only surgical intervention recommended for breast carcinoma that has metastasized to the orbit is a tissue biopsy (either FNA or open biopsy) to establish the diagnosis.[11]

Findings of orbital extension from a primary breast carcinoma predict widespread disease to other organs.[1] The median survival time for patients with orbital metastasis of breast malignancy is reported to be 22 to 31 months.[4] Thus, the mainstay treatment is palliative radiotherapy, with clinical improvement of symptoms and vision in 60 to 80 percent. External-beam irradiation is the most common modality.[11,12] Two alternative modalities include stereotactic radiation therapy and stereotactic radiosurgery, both of which may allow better quality of life due to the application of high doses of radiation to a well-defined volume and shorter treatment courses. Pending performance status, chemotherapy and/or hormone therapy in patients harboring hormone-sensitive tumors may be indicated.[13,14]

As for post-chemotherapy or post-radical treatment surveillance, several serum-based products and tumor markers are utilized in the management of breast cancer patients. Of these biomarkers, CA 15.3 has been extensively evaluated in the literature. A 2012 study concluded that CA 15.3 is one of the most powerful tools for early detection of breast cancer recurrence, as well as a cost-reducing tool for chemotherapy monitoring.[15]

Our case demonstrates that when presented with an infiltrative orbital process, the differential diagnosis of breast cancer must be considered, especially in women. Despite the availability of sophisticated imaging modalities, obtaining a careful history and having a low threshold for diagnostic breast examination is recommended to aid diagnostic efforts. REVIEW

The author would like to thank Nicolas Biro, MD, of the Neuro-Ophthalmology Service for his time and assistance in preparing this case report.

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RESTASIS® (Cyclosporine Ophthalmic Emulsion) 0.05%

BRIEF SUMMARY—PLEASE SEE THE RESTASIS® PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

INDICATION AND USAGE

RESTASIS® ophthalmic emulsion is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

CONTRAINDICATIONS

RESTASIS® is contraindicated in patients with known or suspected hypersensitivity to any of the ingredients in the formulation.

WARNINGS AND PRECAUTIONS

Potential for Eye Injury and Contamination

To avoid the potential for eye injury and contamination, be careful not to touch the vial tip to your eye or other surfaces.

Use with Contact Lenses

RESTASIS® should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of **RESTASIS®** ophthalmic emulsion.

ADVERSE REACTIONS

Clinical Trials Experience

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

In clinical trials, the most common adverse reaction following the use of **RESTASIS®** was ocular burning (17%).

Other reactions reported in 1% to 5% of patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).

Post-marketing Experience

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

Reported reactions have included: hypersensitivity (including eye swelling, urticaria, rare cases of severe angioedema, face swelling, tongue swelling, pharyngeal edema, and dyspnea); and superficial injury of the eye (from the vial tip touching the eye during administration).

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C

Adverse effects were seen in reproduction studies in rats and rabbits only at dose levels toxic to dams. At toxic doses (rats at 30 mg/kg/day and rabbits at 100 mg/kg/day), cyclosporine oral solution, USP, was embryo- and fetotoxic as indicated by increased pre- and postnatal mortality and reduced fetal weight together with related skeletal retardations. These doses are 5,000 and 32,000 times greater (normalized to body surface area), respectively, than the daily human dose of one drop (approximately 28 mcL) of 0.05% **RESTASIS®** twice daily into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed. No evidence of embryofetal toxicity was observed in rats or rabbits receiving cyclosporine at oral doses up to 17 mg/kg/day or 30 mg/kg/day, respectively, during organogenesis. These doses in rats and rabbits are approximately 3,000 and 10,000 times greater (normalized to body surface area), respectively, than the daily human dose.

Offspring of rats receiving a 45 mg/kg/day oral dose of cyclosporine from Day 15 of pregnancy until Day 21 postpartum, a maternally toxic level, exhibited an increase in postnatal mortality; this dose is 7,000 times greater than the daily human topical dose (0.001 mg/kg/day) normalized to body surface area assuming that the entire dose is absorbed. No adverse events were observed at oral doses up to 15 mg/kg/day (2,000 times greater than the daily human dose).

There are no adequate and well-controlled studies of **RESTASIS®** in pregnant women. **RESTASIS®** should be administered to a pregnant woman only if clearly needed.

Nursing Mothers

Cyclosporine is known to be excreted in human milk following systemic administration, but excretion in human milk after topical treatment has not been investigated. Although blood concentrations are undetectable after topical administration of **RESTASIS®** ophthalmic emulsion, caution should be exercised when **RESTASIS®** is administered to a nursing woman.

Pediatric Use

The safety and efficacy of **RESTASIS®** ophthalmic emulsion have not been established in pediatric patients below the age of 16.

Geriatric Use

No overall difference in safety or effectiveness has been observed between elderly and younger patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Systemic carcinogenicity studies were carried out in male and female mice and rats. In the 78-week oral (diet) mouse study, at doses of 1, 4, and 16 mg/kg/day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value.

In the 24-month oral (diet) rat study, conducted at 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate in the low-dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related. The low doses in mice and rats are approximately 80 times greater (normalized to body surface area) than the daily human dose of one drop (approximately 28 mcL) of 0.05% **RESTASIS®** twice daily into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed.

Mutagenesis: Cyclosporine has not been found to be mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone-marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. A study analyzing sister chromatid exchange (SCE) induction by cyclosporine using human lymphocytes *in vitro* gave indication of a positive effect (i.e., induction of SCE).

Impairment of Fertility: No impairment in fertility was demonstrated in studies in male and female rats receiving oral doses of cyclosporine up to 15 mg/kg/day (approximately 2,000 times the human daily dose of 0.001 mg/kg/day normalized to body surface area) for 9 weeks (male) and 2 weeks (female) prior to mating.

PATIENT COUNSELING INFORMATION

Handling the Container

Advise patients to not allow the tip of the vial to touch the eye or any surface, as this may contaminate the emulsion. To avoid the potential for injury to the eye, advise patients to not touch the vial tip to their eye.

Use with Contact Lenses

RESTASIS® should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. Advise patients that if contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of **RESTASIS®** ophthalmic emulsion.

Administration

Advise patients that the emulsion from one individual single-use vial is to be used immediately after opening for administration to one or both eyes, and the remaining contents should be discarded immediately after administration.

Rx Only

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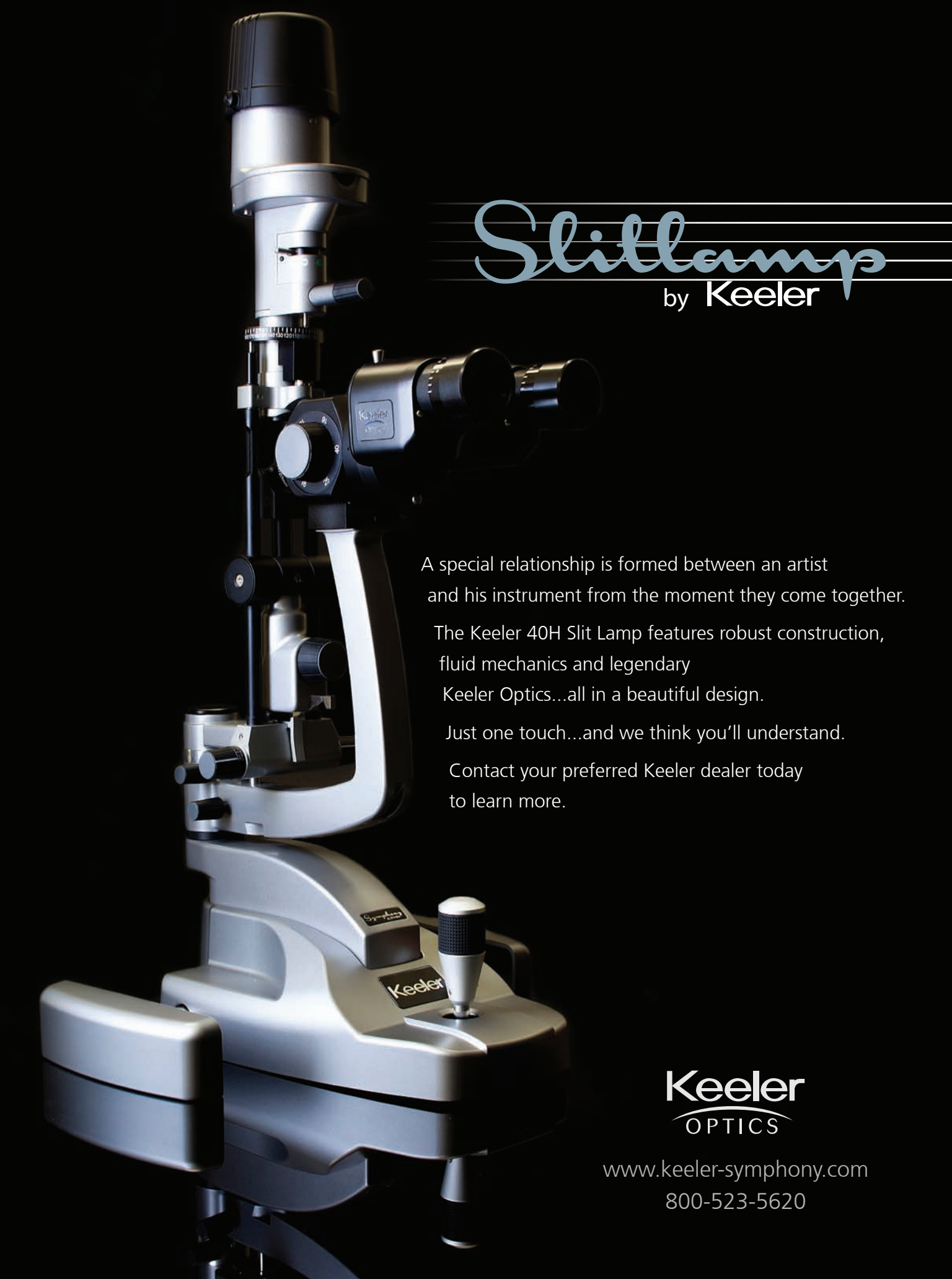
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Indication and Usage

RESTASIS® (cyclosporine ophthalmic emulsion) 0.05% is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

Important Safety Information

Contraindications

RESTASIS® is contraindicated in patients with known or suspected hypersensitivity to any of the ingredients in the formulation.

Warnings and Precautions

Potential for Eye Injury and Contamination: To avoid the potential for eye injury and contamination, individuals prescribed RESTASIS® should not touch the vial tip to their eye or other surfaces.

Use With Contact Lenses: RESTASIS® should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion.

Adverse Reactions

In clinical trials, the most common adverse reaction following the use of RESTASIS® was ocular burning (upon instillation)—17%. Other reactions reported in 1% to 5% of patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).

Please see Brief Summary of the full Prescribing Information on adjacent page.

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