REVIEW® of Ophthalmology
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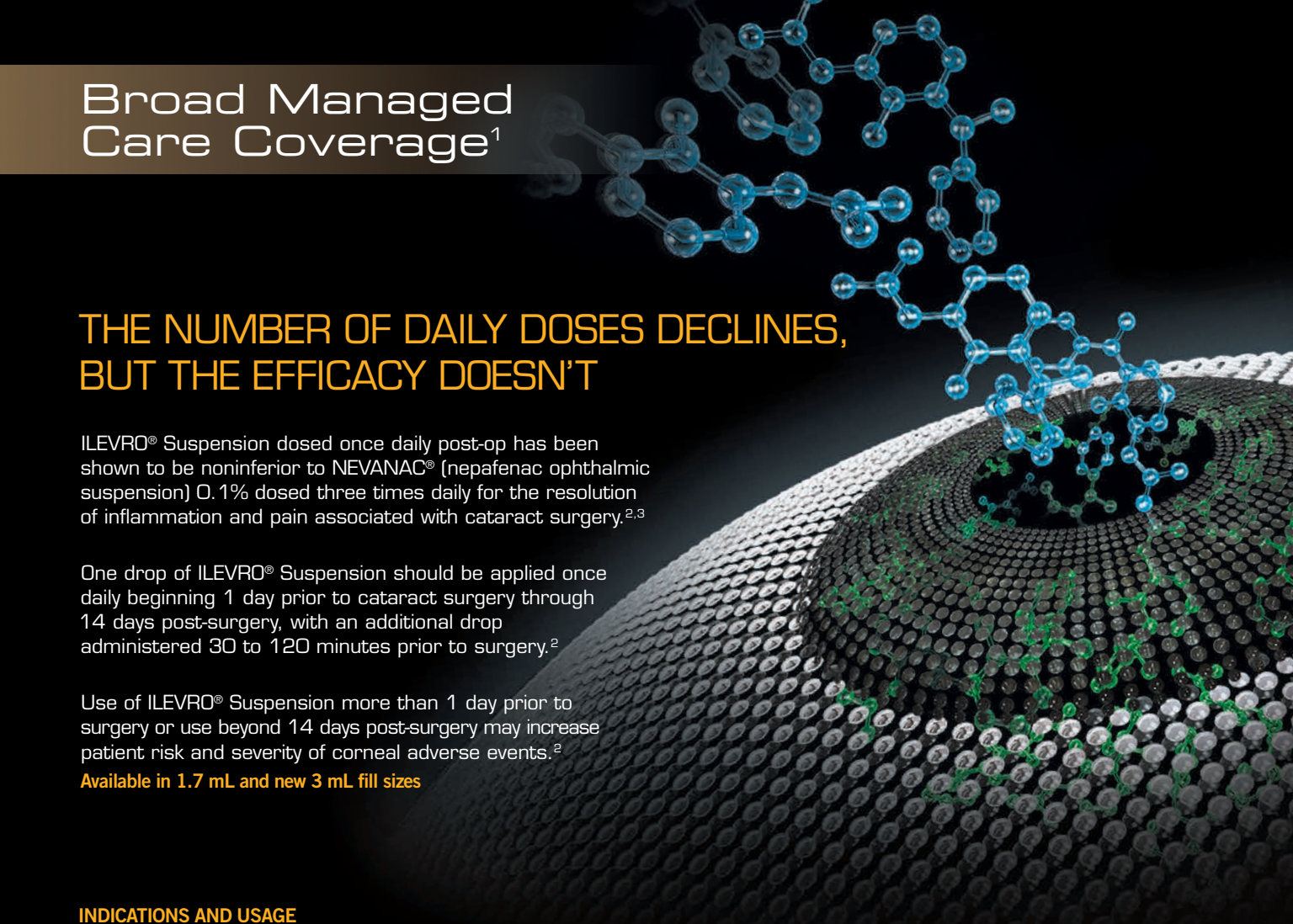
FEBRUARY 2016

REFRACTIVE SURGERY —ISSUE—

Broad Managed Care Coverage[1]



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

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

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

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

Available in 1.7 mL and new 3 mL fill sizes

INDICATIONS AND USAGE

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

IMPORTANT SAFETY INFORMATION

Contraindications

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

Warnings and Precautions

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

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

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

Adverse Reactions

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

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

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

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

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Pediatric Use
The safety and effectiveness of ILEVRO® Suspension in pediatric patients below the age of 10 years have not been established.

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Nepafenac has not been evaluated in long-term carcinogenicity studies. Increased chromosomal aberrations were observed in Chinese hamster ovary cells exposed *in vitro* to nepafenac suspension. Nepafenac was not mutagenic in the Ames assay or in the mouse lymphoma forward mutation assay. Oral doses up to 5,000 mg/kg did not result in an increase in the formation of micronucleated polychromatic erythrocytes *in vivo* in the mouse micronucleus assay in the bone marrow of mice. Nepafenac did not impair fertility when administered orally to male and female rats at 3 mg/kg.

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

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

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

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

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

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

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

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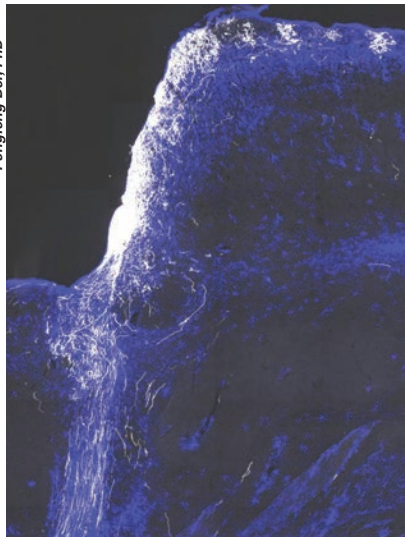
REVIEW NEWS
Volume XXIII • No. 2 • February 2016

Restoring Optic Nerve Cells; New Keratoconus Risk Factors

Research from Boston Children's Hospital suggests the possibility of restoring at least some visual function in people blinded by optic nerve damage from glaucoma, estimated to affect more than 4 million Americans, or from trauma.

As reported online January 14 by the journal *Cell*, the scientists restored vision in mice with optic nerve injury by using gene therapy to get the nerves to regenerate and—the crucial step—adding a channel-blocking drug to help the nerves conduct impulses from the eye to the brain. In the future, they believe, the same effect could be achieved with drugs alone.

In the study, previously blind mice turned their heads to follow patterns of moving bars after given the treatment, say co-senior investigators Zhigang He, PhD, and Michela Fagiolini, PhD, of the Department of Neurology and F.M. Kirby Neurobiology Center at Boston Children's. The technicians doing the tests did not know which mice had been treated.



Fengfeng Bei, PhD

The white areas in this image show extensive regeneration of nerve fibers (axons) in the central nervous system achieved by gene therapy after optic nerve injury. (The blue areas indicate scar tissue.)

"By making the bars thinner and thinner, we found that the animals could not only see, but they improved significantly in how well they could see," says Dr. Fagiolini.

While other teams, including one at Boston Children's, have restored partial vision in mice, they relied on genetic techniques that can only be done in a lab. Generally, their methods involved deleting or blocking tumor suppressor genes, which encourages regeneration but could also promote cancer. The new study is the first to restore vision with an approach that could realistically be used in the clinic, and that does not interfere with tumor suppressor genes.

The key advance in restoring vision was getting the regenerated nerve fibers (axons) to not only form working connections with brain cells, but also to carry impulses (action potentials) all the way from the eye to the brain. The challenge was that the fibers regrow without the insulating sheath known as myelin, which helps propagate nerve signals over long distances.

"We found that the regenerated axons are not myelinated and have very poor conduction—the travel speed is not high enough to support vision," says He. "We needed some way to overcome this issue."

Turning to the medical literature, they learned that a potassium channel blocker, 4-aminopyridine (4-AP), helps strengthen nerve signals when myelin is absent. The drug is marketed as AMPYRA for multiple sclerosis, which also involves a loss of myelin. When they added it, the signals were able to go the distance.

While the study used a gene therapy virus called AAV to deliver the growth factors that trigger regeneration (osteopontin, insulin-like growth factor 1 and ciliary neurotrophic factor), He and Fagiolini are testing whether injecting a "cocktail" of growth factor proteins directly into the eye could be equally effective.

"We're trying to better understand the mechanisms and how often the proteins would have to be injected," says He. "The gene therapy virus we used is approved for clinical study in eye disease, but a medication would be even better."

With regeneration kick-started, 4-AP or a similar drug could then be given systemically to maintain nerve conduction. Because 4-AP has potential side effects including seizures if given chronically, He and Fagiolini have begun testing derivatives (not yet FDA-approved) that are potentially safer for long-term use.

The researchers are further testing the mice to better understand the extent of visual recovery and wheth-

er their approach might get myelin to regrow over time.

"The drugs might need to be paired with visual training to facilitate recovery," says Dr. Fagiolini. "But now we have a paradigm to push forward."

Study Sheds New Light on Keratoconus

A largest-ever clinical study of keratoconus reveals previously unknown risk factors associated with the condition. The new study shows that men, African Americans and Latinos, and people with asthma, sleep apnea or Down syndrome, have much higher odds of developing keratoconus. But females, Asian-Americans and people with diabetes appear to have a lower risk, the analysis shows.

The findings, made by researchers at the University of Michigan Health System's Kellogg Eye Center and the U-M Institute for Healthcare Policy and Innovation, are published online ahead of print in *Ophthalmology*.

The research was sparked by questions whether changes to the eye with keratoconus affect other parts of the body. Studying eye conditions' associations with other health conditions is easier now because of vast data troves.

"Eye health relates to total body health, and we as ophthalmologists need to be aware of more than just eyeballs when we see patients," says Maria Woodward, MD, an assistant professor of ophthalmology at the U-M Medical School and first author of the new study. The last decade has brought new treatment options, but many people don't receive a diagnosis early enough to take full advantage of them.

Patients with keratoconus and their families, as well as physicians, should be aware of other potential health

Sena Biswas, PhD, and Matthew Chapin • Ora Inc., Andover, Mass.

Physician-Entrepreneur: From Concept to Development. A Case Study

We have previously emphasized early development of the target product profile, with examples of financing with non-dilutive capital through strategic partnerships. In this installment, we will review another innovative project from a physician-entrepreneur. We will explore the progression of a product's development, starting with the initial germination of the idea based on clinical observations; the journey of developing prototypes; initial clinical testing; attempts to secure funding; and current strategy for funding further development to value inflection.

The Premise

Donald Schwartz, MD, (Long Beach Eye Care Associates, a clinical professor at the Keck School of Medicine, University of Southern California) had been a practicing ophthalmologist for nearly 25 years and had been part of the evolution of cataract surgery from surgical lens removal techniques to phacoemulsification. Dr. Schwartz was intrigued by the idea that as the use of phacoemulsification became more widespread, ophthalmologists would routinely observe that glaucoma in glaucoma patients undergoing cataract surgery would improve as a result of the surgery. He hypothesized that the ultrasound was having an impact on the fluid buildup classically associated with glaucoma, and in July 2006, he decided he would explore the possibility of using ultrasound to help treat glaucoma.

We know that a large number of patients with glaucoma or ocular hypertension are under multiple drug therapies, up to two or three times a day, and are dealing with side effects such as eye redness and irritation. This makes compliance difficult for glaucoma patients, who are often elderly. Dr. Schwartz knew that many of his patients, experiencing only the side effects and inconvenience of the eye drops and no detectable impact of glaucoma, would only administer drops for the few days before their visit with him. These patients risked losing their vision over time, but there was little Dr. Schwartz or other ophthalmologists could do to help them. Dr. Schwartz was driven by the promise of a simple, non-invasive, office-based ultrasound procedure that would lessen or ideally eliminate the need for daily drug dosing for these patients.

Dr. Schwartz began spending a lot of time in the library and on the Internet researching the rationale for the observation that the ultrasound-based procedure for cataract surgery was having a positive impact on his glaucoma patients. He had no understanding of the specifics of ultrasound and only a nascent understanding of how this could interface with the physiology of glaucoma. He discovered that, in the

1980s, there had been a commercialized device that used high-intensity focused ultrasound to ablate the ciliary body—reducing secretion of fluid into the eye. However, that particular approach suffered from the lack of predictable impact on the ciliary body and ultimately failed at that time. Dr. Schwartz considered an alternative explanation—that the vibrations caused by low-frequency ultrasound could be clearing blockages in the trabecular meshwork, the natural fluid drainage system of the eye. He decided to investigate how this hypothesis could lead to a different approach of administering the ultrasound energy for a more consistent outcome.

First Steps

He spoke with a Swedish clinician who had researched the use of non-focused ultrasound on glaucoma patients. Based on these discussions and further research, Dr. Schwartz calculated the frequency of ultrasound that would be required to transmit energy to the eye below the level that would damage the ocular tissue. Using personal funds, he contracted for the manufacture of an ultrasound device that could deliver ultrasound waves at a frequency of 1 million Hz. He received the devices, but they were more complicated than he had anticipated. When he turned them on, he could not detect any output that would provide him with feedback during their use. He called the manufacturer, who assured him that the devices were functioning and he should simply test the devices using an oscilloscope. As a clinician, Dr. Schwartz had no access to oscilloscopes and gave up on this initial batch of devices.

False Starts

Dr. Schwartz went back to calculating specifications for a new set of devices and contracted with a new manufacturer, who agreed to make the devices for free in exchange for a royalty on sales. The new devices worked better; however, they still needed some minor adjustments. The manufacturer met with Dr. Schwartz and took the two prototypes, promising to make these adjustments. However, the next time Dr. Schwartz heard from the manufacturer, he learned that the manufacturer had decided that the glaucoma device was a long way from market, and so had disassembled the prototypes and sold them for parts.

Undeterred, Dr. Schwartz contracted with yet another manufacturer, using what he had learned from using the second set of devices, and soon he had new prototypes in hand. Continuing to use his own funds, Dr. Schwartz conducted experiments with the new prototypes, first on cow and pig eyes, and then on live pigs and rabbits. These experiments revealed promising impact on intraocular pressure with few or no side effects evident via histopathological analysis. Armed with this data, Dr. Schwartz applied to an institutional review board for a non-significant risk determination to conduct a human trial. Using his own funds, he tested the device in a series of clinical trials.

The first trial demonstrated that the device was safe and well-tolerated. The next two trials demonstrated that the device could lower intraocular pressure for a sustained period of time in combination with or in the absence of pharmacotherapy. Dr. Schwartz is currently conducting a fourth trial, with the device having been used on more 80 patients, with follow-up of several years. These clinical case follow-ups were very important in establishing initial proof of concept, prior to setting the stage for

larger, controlled and randomized trials that would require external funding.

Within the span of a few years, Dr. Schwartz had taken an idea, developed a working prototype, demonstrated proof of concept in human clinical trials, and filed patents. During this time Dr. Schwartz also tried to secure funding for the company he had founded, EyeSonix. He was surprised to find that despite the human testing, venture capitalists were not interested in funding the device, citing it as "too risky" and "too early" for funding. This is a common refrain heard from life-science entrepreneurs, especially regarding first-time entrepreneurs with no track record of success, nor operational or development experience.

Dr. Schwartz pursued angel financing as well, travelling across the country and even to Australia to find a funding source. After many meetings with a prominent angel network, EyeSonix had a prospect to secure financing. Ultimately, the group opted for a social media, tech startup that promised a quick return with no regulatory or clinical risks. This is another common challenge faced by life-science entrepreneurs: competing for funds with IT investments that have easy-to-understand value propositions and quicker timelines. Although sophisticated investors recognize that life-science investments provide a risk-adjusted return that is competitive with alternative investments, many angels—themselves entrepreneurs—naturally gravitate to invest in businesses they can understand.

To address the objection some had raised about the lack of experienced management, Dr. Schwartz hired a CEO and a chief technology officer, again bankrolling them with his own money. Ultimately, they parted ways.

Dr. Schwartz pursued non-mainstream avenues for funding, as well. Through a website that connects entrepreneurs with funding sources, Dr. Schwartz found another lead. A mysterious man named "Stefan" called Dr. Schwartz and advised him to bring many sources of identification and cash for a meeting with a high-net-worth individual in Lebanon. After researching the potential funder online, Dr. Schwartz discovered that the funder had political connections to controversial groups, and declined the meeting.

Connecting

In 2015, Dr. Schwartz approached Ora, a contract research organization and product development firm. The interaction between EyeSonix and Ora was instantly positive and quickly moved into a funding discussion. Ora recognized the potential product opportunity, and the further validation that a controlled, masked, randomized, clinical trial would provide both for fundraising and securing a commercialization partner for the product. Within a few months, Ora and EyeSonix agreed to terms for funding a proof-of-concept clinical trial at an independent clinical site. Dr. Schwartz believes that this funding will propel EyeSonix into launching a very valuable product, validating his years of hard work.

Reflecting back, Dr. Schwartz feels that EyeSonix has been a worthy endeavor, but one that took a lot more money and time than he had anticipated. He says perseverance and flexibility are what got him through. Going through multiple manufacturers, endless fundraising meetings and discussions with potential strategic partners was not what he had anticipated. His secret—a journal, in which he writes every few days. It has grown to more than 250 pages over the course of the development of EyeSonix. After every setback, Dr. Schwartz returns to the journal. Invariably he finds a reminder of a lead or a task that he had forgotten about, which generates renewed energy and a new path to pursue for the product.

"This has been the most exhilarating part of my career, one where I can make a major impact on eye disease," he notes. The desire to make a change and to make a difference is what drives Dr. Schwartz, and it's a common trait seen in entrepreneurs. Today, as Dr. Schwartz embarks on the next stage of his endeavor, he remains as passionate as ever, looking forward to the date that his product launches and fundamentally changes the way glaucoma is managed.

Mr. Chapin is senior vice president of the Corporate Development Group at Ora Inc. Dr. Biswas is a managing director of OraVision Ventures. Ora provides a comprehensive range of product development, clinical-regulatory and product consulting for developers, investors and buyers; preclinical and clinical trial services, regulatory submissions; integrated with asset, business partnering, and financing support in ophthalmology. They welcome comments or questions related to this or other development topics. Please send correspondence to mchapin@oraclinical.com.

problems uncovered in the study, the authors say.

The researchers made their findings by looking at data from health-insurance claims, half of them from more than 16,000 people with confirmed keratoconus and half from an equal number of people with similar characteristics but no keratoconus.

This allowed them to see which characteristics and medical conditions were most associated with keratoconus, and which weren't. The people in the study were mostly in their 30s and 40s.

The study helps confirm many suspicions about the condition raised by previous small studies, but casts doubt on others. For instance, men were already known to have a higher risk, which the study confirmed.

And people with Down syndrome had a much higher chance of having keratoconus—six times higher than others—a known risk but still a stark one. This reinforces the high importance of screening and treatment for the condition in members of the Down syndrome community, starting at a young age, Dr. Woodward says.

But the higher rates of keratoconus among people of African American and Latino origin—50 percent higher than whites—were previously unknown. And the finding of a 39-percent lower rate among people of Asian heritage contradicts previous research.

Meanwhile, there's been debate over a possible "protective" effect of diabetes. While diabetes causes other negative effects to the eye, the cornea may be strengthened as a by-product of those changes.

The new finding of a 20-percent lower odds of keratoconus among people with diabetes, and an even lower among those with complications from diabetes, appears to support this idea.

The researchers also looked at other chronic conditions thought to be associated with keratoconus, such as allergic rhinitis, mitral valve prolapse, collagen vascular disease, aortic aneurysm

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and depression, and found no higher odds of the condition.

But when it came to people who had been diagnosed with sleep apnea, which interrupts breathing during sleep, and can cause snoring, daytime sleepiness and a higher risk of heart disease and stroke, there were statistically significant higher odds of also having keratoconus. Similarly, people with asthma had higher odds of also having the eye condition.

The authors note that because they used insurance data, they can only see associations of conditions recorded on medical bills, and not cause and effect. And, their findings might not apply to people with no health insurance and therefore less access to medical care.

They also can't tell which of the people had other risk factors for keratoconus, such as eye rubbing, a family history of the condition, and other conditions not present in the database.

Study Confirms Myopia Surge

The largest study of childhood eye diseases ever undertaken in the United States confirms that the incidence of childhood myopia among American children has more than doubled over the last 50 years. The findings echo a troubling trend among adults and children in Asia, where 90 percent or more of the population have been diagnosed with myopia, up from 10 to 20 percent 60 years ago.

MEPEDS, the Multi-Ethnic Pediatric Eye Disease Study, conducted by researchers and clinicians from the USC Eye Institute at Keck Medicine at USC in collaboration with the National Institutes of Health, adds to a growing body of research into the incidence and potential causes of myopia in children and adults.

The possible culprit? Too much "screen time" and not enough sunlight, according to Rohit Varma, MD, MPH, and director of the USC Eye Institute.

"While research shows there is a genetic component, the rapid proliferation of myopia in the matter of a few decades among Asians suggests that close-up work and use of mobile devices and screens on a daily basis, combined with a lack of proper lighting or sunlight, may be the real culprit behind these dramatic increases," said Dr. Varma. "More research is needed to uncover how these environmental or behavioral factors may affect the development or progression of eye disease."

The USC study found that the incidence of childhood myopia in the U.S. is greatest in African-American children, followed by Asian-American children, Hispanic/Latino and Non-Hispanic white children. Future research may include re-examining the MEPEDS cohort to evaluate how widespread use of "screens" and other environmental or behavioral factors may be affecting the progression of childhood myopia and other eye diseases over time.

From 2003 through 2011, MEPEDS provided free eye exams at USC Eye Institute clinics to more than 9,000 Los Angeles-area children ages 6 months through 6 years. "In addition to being the largest pediatric eye study ever undertaken, it is the first of its kind to examine children as young as 6 months old," said Dr. Varma. "Typically, children do not undergo vision testing until they reach school age. By including younger children, we have the opportunity to identify eye diseases and their causes at the formative stages."

USC Eye Institute researchers and clinicians collected basic health information during a home visit with the child and parents, followed by a detailed eye examination under dilation. REVIEW

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Down, Boy.

Help Tame Postoperative Ocular Inflammation and Pain With LOTEMAX® GEL

Indication

LOTEMAX® GEL (loteprednol etabonate ophthalmic gel) 0.5% is indicated for the treatment of post-operative inflammation and pain following ocular surgery.

Important Safety Information about LOTEMAX® GEL

- LOTEMAX® GEL is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.
- Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. If this product is used for 10 days or longer, IOP should be monitored.
- Use of corticosteroids may result in posterior subcapsular cataract formation.
- Use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation and occurrence of perforations in those with diseases causing corneal and scleral thinning. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification, and where appropriate, fluorescein staining.
- Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infection. In acute purulent conditions, steroids may mask infection or enhance existing infection.
- Use of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and exacerbate the severity of many viral infections of the eye (including herpes simplex).
- Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use.
- Patients should not wear contact lenses when using LOTEMAX® GEL.
- The most common ocular adverse drug reactions reported were anterior chamber inflammation (5%), eye pain (2%) and foreign body sensation (2%).

Please see brief summary of Prescribing Information on adjacent page.

LOTEMAX® GEL
loteprednol etabonate
ophthalmic gel 0.5%

BAUSCH + LOMB

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to prescribe Lotemax Gel safely and effectively. See full prescribing information for Lotemax Gel.

Lotemax (loteprednol etabonate ophthalmic gel) 0.5%

Rx only
Initial Rx Approval: 1998

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

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

Apply one to two drops of LOTEMAX into the conjunctival sac of the affected eye four times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Intraocular Pressure (IOP) Increase

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

Cataracts

Use of corticosteroids may result in posterior subcapsular cataract formation.

Delayed Healing

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

Bacterial Infections

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

Viral Infections

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

Fungal Infections

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

Contact Lens Wear

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

ADVERSE REACTIONS

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C.

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

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

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

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment Of Fertility

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

PATIENT COUNSELING INFORMATION

Administration

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

Risk of Contamination

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

Contact Lens Wear

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

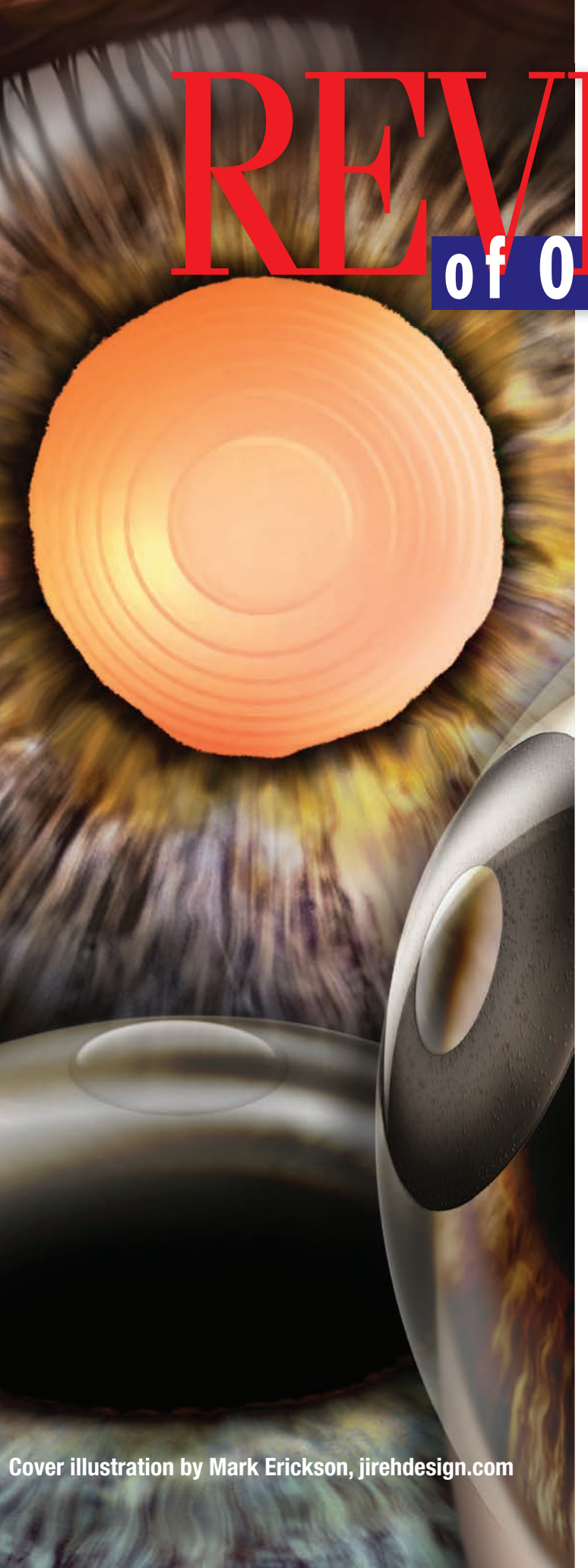
Risk of Secondary Infection

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

Bausch & Lomb Incorporated
Tampa, Florida 33637 USA

US Patent No. 5,800,807

US/LGX/15/0042
Based on 9269100-9269200 Revised: 9/2012



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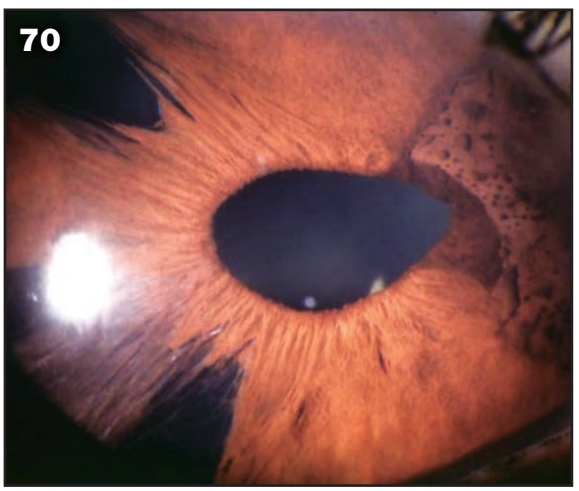

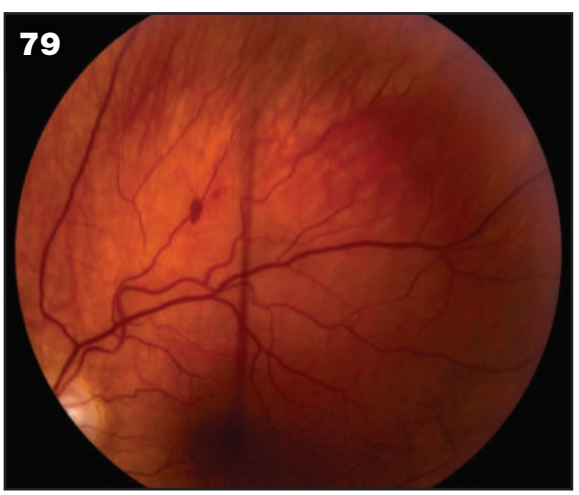

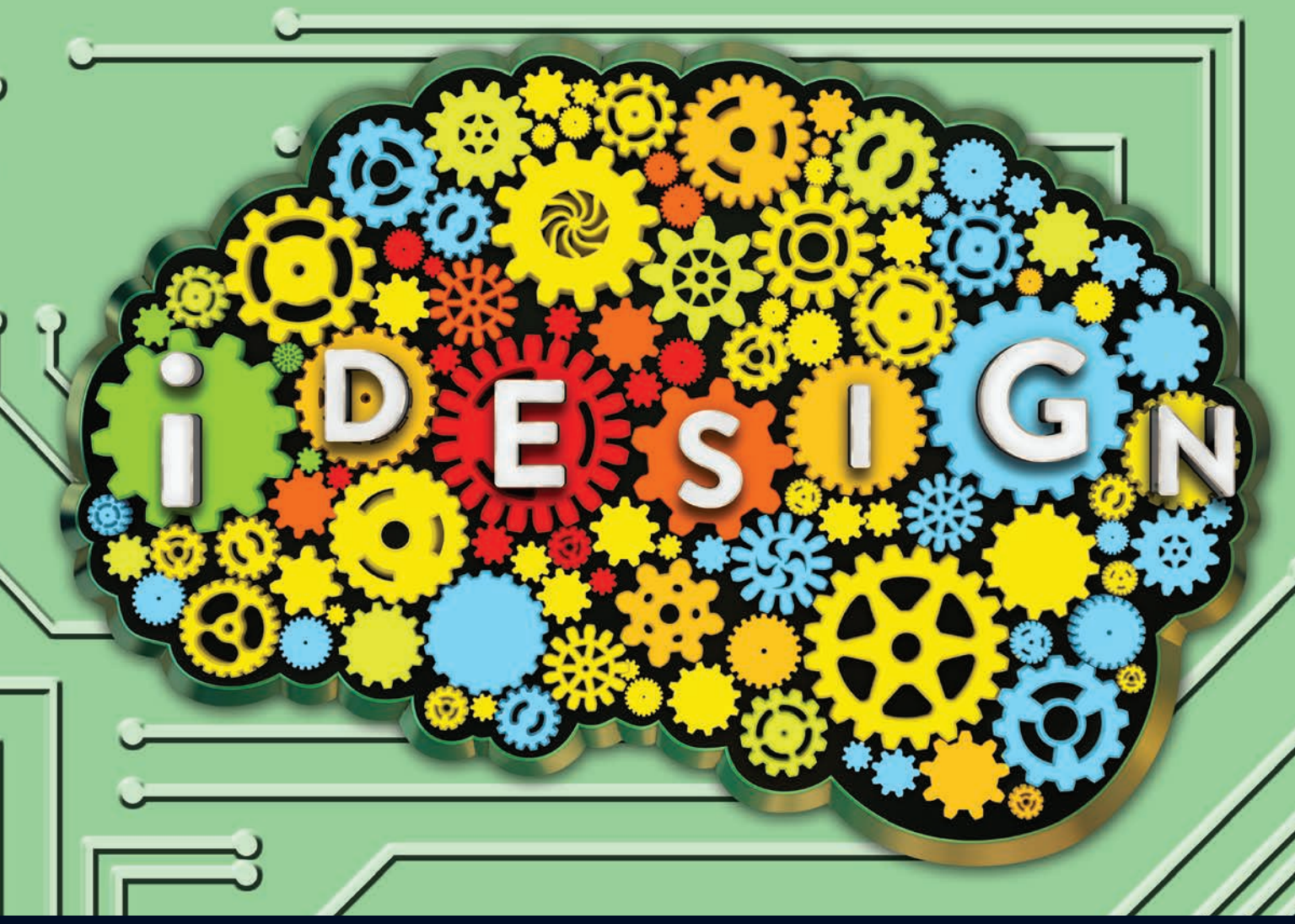

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*Compared to the ***WaveScan*** System

INDICATIONS: The ***STAR S4 IR***® Excimer Laser and ***iDESIGN Advanced WaveScan Studio*** System is indicated for wavefront-guided LASIK in patients with myopia as measured by ***iDESIGN*** System up to -11.00 D SE, with up to -5.00 D cylinder; with agreement between manifest refraction (adjusted for optical infinity) and ***iDESIGN*** System refraction of 1) SE: magnitude of the difference is < 0.625 D, and 2) cylinder: magnitude of the difference is ≤ 0.5 D; with patients 18 years plus, and with refractive stability (a change of ≤ 1.0 D in sphere or cylinder for a minimum of 12 months prior to surgery). **CONTRAINDICATIONS:** Laser refractive surgery is contraindicated in patients with: collagen vascular, autoimmune, or immunodeficiency diseases; pregnant or nursing women; keratoconus, abnormal corneal topography, epithelial basement membrane disease (EBMD) and degenerations of the structure of the cornea; symptoms of significant dry eyes; corneal thickness would cause anticipated treatment would violate the posterior 250 microns (μm) of corneal stroma; advanced glaucoma; and uncontrolled diabetes. If the patients have severely dry eyes, LASIK may increase the dryness, this may or may not go away. Severe eye dryness may delay healing of the flap or interfere with the surface of the eye after surgery, it may result in poor vision after LASIK. **CAUTION:** US federal law restricts this device to sale, distribution, and use by or on the order of a physician or other licensed eye care practitioner. For full indications and important safety information see adjacent page.

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New Thinking on IOL Calculations

Surgeons are developing new formulas, calculators and mathematical algorithms to help you select the right lens.

Walter Bethke, Managing Editor

For the past several years, surgeons have been hard at work devising new ways to make their intraocular lens calculations more accurate, and their labors are beginning to bear fruit. Here is a look at three new approaches to IOL calculation that are either available now or will be in the near future that might take your cataract surgery results to the next level.

• ***The UniversIOL Calculator.*** Samir Sayegh, MD, PhD, of Champaign, Ill., and his co-workers began developing this IOL calculator in response to what they saw as shortcomings in other calculators, especially with regard to toric lens calculation. The UniversIOL calculator is a web-based calculator that combines the major available lens formulas with a toric IOL calculator.

"The first thing we concentrated on was getting the sphere correct, and we provide a number of tools to do this," Dr. Sayegh explains. "We don't propose a new formula per se as some others might, but bring together all the high-quality third- and fourth-generation IOL formulas in one calculator. The user has the ability to use any one of these or a combination of them that would give him the best of all the formulas' calculations. The calculator also tells you how much the formulas differ from each other to give you a sense of how close you'll be to your target. The calculator also contains all the IOLs made so you can tell it which ones you work with. In other words, one IOL may get you close, but another might get you closer to your target. That's the idea of this kind of database approach to getting the spherical equivalent right."

Dr. Sayegh says the calculator will also perform a toric calculation at the same time as the sphere. "Previously, the standard approach for a surgeon using a toric lens would be to calculate the spherical power on a device such as the IOLMaster, and then go to an on-line toric calculator and re-enter the data to get a toric lens that corresponds to the sphere he or she had selected," says Dr. Sayegh. "This is time-consuming and risks entering incorrect data. Our calculator lets surgeons do the whole computation at once, though it also offers the standard approach of sequential data entry in case surgeons are more comfortable with that." He says that, since there may be some inaccuracies with the use of a constant toricity ratio used by some calculators, the UniversIOL also offers the option of using the more accurate variable toricity approach. Also, since the calculator has many variables, surgeons can lock in certain ones that they use frequently so they don't have to re-enter them each time.

Dr. Sayegh says that using the calculator's hybrid approach has achieved 95-percent accuracy in terms of eyes within 0.5 D of the predicted result, and nearly 1,000 eyes have been done using the calculator. Though the calculator will be released for general use in May 2016, Dr. Sayegh says high-volume practices can get early access by contacting him directly at sayegh@umich.edu. "Fairly high volume surgeons with high-quality measurements usually result in solid, standardized ways of doing the calculations that bring the best results," explains Dr. Sayegh. To see what the calculator looks like, visit 2020eyecenter.com/iol-calculator/.

• ***The Hoffer H-5 formula.*** In the March 2005 installment of Technology Update, Santa Monica surgeon Ken Hoffer told readers about his H formu-

An NSAID formulated to penetrate target ocular tissues

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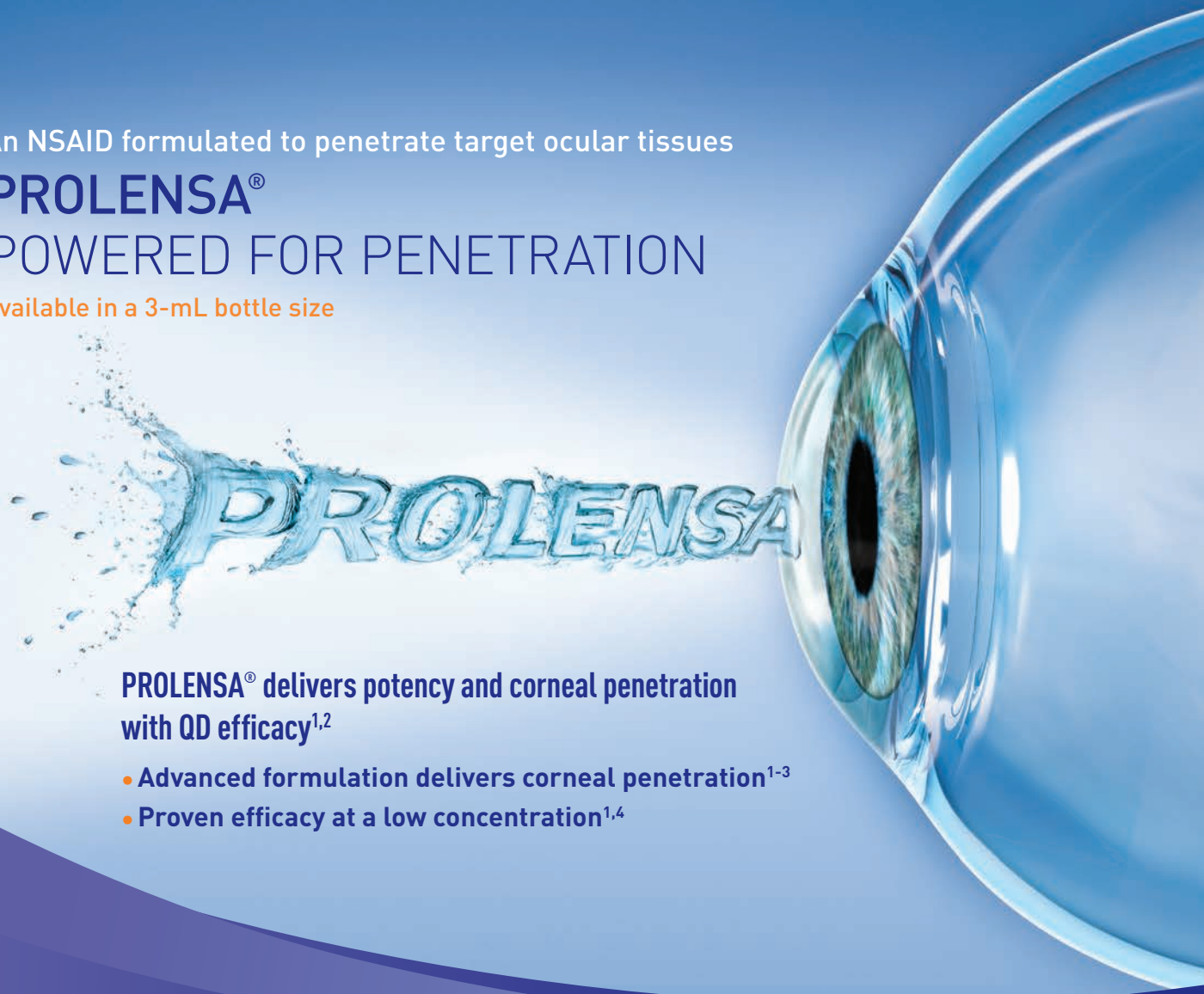

PROLENSA® delivers potency and corneal penetration with QD efficacy[1,2]

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- **Proven efficacy at a low concentration[1,4]**

INDICATIONS AND USAGE

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

IMPORTANT SAFETY INFORMATION ABOUT PROLENSA®

Warnings and Precautions

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

Adverse Reactions

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

Please see brief summary of Prescribing Information on adjacent page.

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

BAUSCH + LOMB

PROLENSA®
(bromfenac ophthalmic solution) 0.07%

Brief Summary

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Recommended Dosing

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

Use with Other Topical Ophthalmic Medications

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

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Sulfite Allergic Reactions

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

Slow or Delayed Healing

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

Potential for Cross-Sensitivity

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

Increased Bleeding Time

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

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

Keratitis and Corneal Reactions

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

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

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

Contact Lens Wear

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

ADVERSE REACTIONS

Clinical Trial Experience

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

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

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

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis and Impairment of Fertility

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

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

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

PATIENT COUNSELING INFORMATION

Slowed or Delayed Healing

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

Sterility of Dropper Tip

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

Concomitant Use of Contact Lenses

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

Concomitant Topical Ocular Therapy

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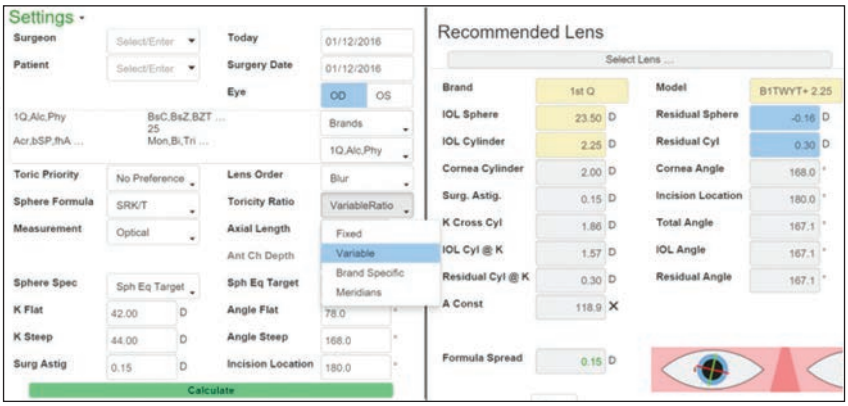
Samir Sayegh, MD, PhD



The UniversIOL calculator offers various methods to factor in the toricity when calculating a toric intraocular lens, including brand-specific values, fixed toricity and variable toricity, which some surgeons consider to be the most accurate way to calculate the value.

la, calling it a "work in progress," since it still had some shortcomings. Now, however, almost 11 years and thousands of surgery cases later, he reports that his work is complete in the form of his new H-5 formula. "In 2013 I came up with a formula improvement called the Hoffer H-5 formula," Dr. Hoffer explains. "It uses gender and race to change the average mean values in the Holladay-2 and Hoffer formulas. To create it, since it's based on gender and race, we decided to collect eyes especially from Europe, the Middle East, Asia and South America. That took quite a lot of time, especially getting everyone involved at the various clinical and university practices to fill out the spreadsheets with all the necessary data. In the end, we had 9,800 eyes. We realized, though, that when you're getting data from so many disparate offices and clinics from around the world, they were using different methods to collect it, so it wasn't always going to be perfect. So, we decided the best way to analyze the data was to look at what the prediction errors were. We focused on all the eyes that were within ±0.25 D of the predicted result. We figured data that yields a result within ±0.25 D has to be pretty accurate."

The next step for Dr. Hoffer and his co-workers was to take the eyes that made the cut, which wound up being 2,700 that were within the required ±0.25 D of prediction, and run the results compared to other popular IOL formulas. "Since it's based on the Holladay-2, but with the addition of gender and race—even though it changes some of the Holladay-2's parameters—we figured the Holladay-2 would be the formula against which to test it. Unfortunately, I was informed that a bulk input of the data into the Holladay IOL Consultant software wouldn't be possible. That meant I'd have to hire someone to sit for several months and input 9,800 eyes. Since that wasn't going to happen readily, we tested it against other popular formulas: the Hoffer Q; the Holladay-1 and the SRK/T. We couldn't test it against the Haigis because we weren't able to personalize the factors a_0, a_1 and a_2. I'm pleased to say that the results from the H-5 came out as a statistically significant improvement over the other formulas."

Dr. Hoffer says one of the reasons the formula is accurate is because it allows the surgeon to customize the IOL calculation for a particular patient. "For instance, if the patient is a Japanese woman, the formula goes to the "Asian, female" section on the input data, and it would then use the mean for an Asian female axial length, lens thickness, anterior chamber depth and K reading," explains Dr. Hoffer. "We replaced the means for average humans used in the Holladay-2 for actual means for particular genders and races."

As for when surgeons can use the formula themselves, Dr. Hoffer says he's not releasing the actual code because it's too complicated, and it would run the risk of someone programming it incorrectly. It will be available, however. "Zeiss has signed a license agreement to put the H-5 formula on the new IOLMaster 700 OCT device they are producing," says Dr. Hoffer. "They have the formula now. Topcon is also considering adding the formula to its devices."

Dr. Hoffer says he hopes the specific averages built into the formula will enable surgeons to get better results. "Ultimately, the goal is to develop a formula that's useful in all eyes," he says.

• ***Radial basis function approach***. On the leading edge of IOL calculation is this mathematical approach, from a team of surgeons and engineers led by Mesa, Ariz., biometry guru Warren Hill, MD. The RBF method uses artificial intelligence and pattern recognition to select an IOL for a patient.

Dr. Hill says that going outside the world of ophthalmology has allowed the problem of IOL power selection to be approached in a completely different way. "The goal of this project was nothing less than reinventing the way we think about it," Dr. Hill says. "Our core team investigators, the engineers at the company MathWorks and a dedicated group of physician beta testers in eight countries have successfully developed and validated a new way to select the power of an intraocular lens that is independent of vergence formulas, or a knowledge of the effective lens position." The details of this project were presented as the Charles D. Kelman Lecture at the 2015 annual meeting of the American Academy of Ophthalmology.

Dr. Hill says his team devised this approach by fitting a large and highly accurate LenStar database to a sophis-

ticated pattern recognition and data interpolation model called a radial basis function, which is based in artificial intelligence. "Radial basis function algorithms are used throughout the world in a wide range of technologies as diverse as facial recognition software, thumbprint security scanners, automobile engine calibration methods, electrocardiogram interpretation and financial forward forecasting software for the stock market," Dr. Hill says. "In creating the Hill-RBF algorithm for IOL power selection, the objective was to discover if the power of an intraocular lens could be predicted significantly better than by using vergence formulas. Following extensive modeling, we found that four variables—the desired spherical equivalent, axial length, central corneal power and anterior chamber depth—were all that was needed to accurately predict the necessary IOL power." Dr. Hill points out that current methods mostly limit possibilities to situations that are already understood. On the other hand, pattern recognition has the ability to learn tasks based solely on data, independent of what is previously known, so there is no calculation bias. "Short eyes, long eyes, unusual anterior segments simply represent patterns of data," he says.

Based on a review of over 260,000 cases submitted for optical biometry lens constant optimization over more than a decade, Dr. Hill says that the vast majority of ophthalmologists have a ±0.50 D accuracy ranging from 76 to 80 percent. Approximately 6 percent of physicians are at 84 percent ±0.5-D accuracy and less than 1 percent are at 92 percent or better. In a recent retrospective study of 3,212 cases by 13 surgeons in eight countries, Dr. Hill says the ±0.50 D weighted mean accuracy of the Hill-RBF method was 95 percent.

The next step involves prospective testing and making the Hill-RBF model available to ophthalmologists worldwide. "Haag-Streit will soon incorporate this into the LenStar EyeSuite," Dr. Hill says, "and, in an act of generosity, it has also agreed to make this technology available to ophthalmologists as an open-access, web-based calculator, much in the same way that Graham Barrett made his Barrett Universal II formula and the Barrett Toric Calculator available. By the time of the ASCRS meeting in May, there's a good chance it will be available as a LenStar upgrade." To learn more about the Hill-RBF lens selection method, you can visit rbfcalculator.com. REVIEW

Dr. Hill is a consultant to Haag-Streit. Dr. Sayegh has no financial interest in the products mentioned. Dr. Hoffer licenses the use of his formula.

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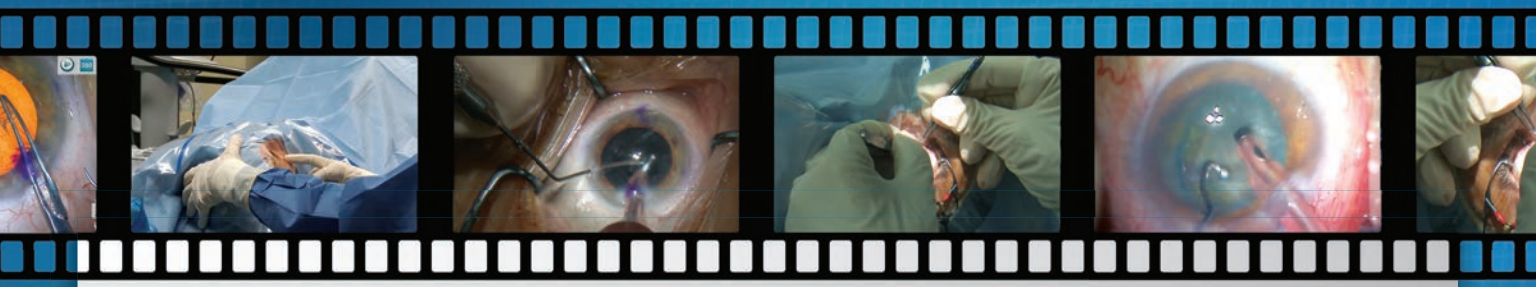

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1. Discuss strategies that can improve visualization in order to create a capsulorhexis.
2. Describe the steps in the impale and chop technique.
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Accreditation Statement
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What's New in 2016: Fees, Codes and More

There are no new ICD-10 codes at this time, but there are plenty of other changes to codes and reimbursements to know about.

Q Is the *2016 Medicare Physician Fee Schedule* favorable for ophthalmology?

A No. Several influences affect the *2016 MPFS*. The 2016 conversion factor published in November was $35.8279, which was a slight decrease from the 2015 conversion factor of $35.9335. It included a budget neutrality adjustment of -0.02 percent, an increase of 0.5 percent resulting from the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA) and a 0.77 percent target recapture amount (decrease) from the Achieving a Better Life Experience (ABLE) Act of 2014. Relative value unit changes occurred at the beginning of January *(see below left)*. The January fee schedule update reduced the conversion factor to $35.8043. The end result is an approximately 1 percent reimbursement reduction for ophthalmology services overall.

Table 1. 2016 Relative Value Unit Changes

CPT Code	Percent Change
Amniotic membrane placement (65778)	4
Cataract removal w/IOL (66984)	0
Probing NLD (68810)	-19
Trabeculectomy (66170 & 66172)	-19
Trabeculoplasty (65855)	-19
*Complex RD repair (67113)	-19
*RD repair (67108)	-19
Destruction retinopathy, cryo (67227)	-55
Treatment of retinopathy PRP (67228)	-66

* The November fee schedule publication indicated larger relative value unit reductions; however, the Centers for Medicare & Medicaid Services indicated revision of relative value units "shall be phased in over a 2-year period" for any decrease of 20 percent or more for services that had no changes to their global period. *Current Procedural Terminology* codes 67227 and 67228 were re-categorized as minor procedures in 2016 and now have a 10-day postop period, therefore, larger RVU reductions.

Q What type of relative value unit changes occurred on January 1, 2016?

A Several changes exist in the *Medicare Physician Fee Schedule*, published in January. See Table 1, left, for examples of some RVU changes and the percentage of change from 2015.

Q What is the target recapture?

A In the Protecting Access to Medicare Act of 2014, Congress set a target for adjustments to misvalued codes for calendar years 2017 to 2020. The target was 0.5 percent of the estimated expenditures under the *MPFS* for each of the four years. The ABLE act moved up the timeline and target to apply the adjustments for 2016 through 2018. It set the target to

1 percent for 2016. If the net reductions in misvalued codes in 2016 were not equal to or greater than 1 percent of the estimated expenditures under the fee schedule, a reduction equal to the percentage difference between 1 percent and the estimated net reduction in expenditures resulting from misvalued code reductions must be made to all *MPFS* services. The net reduction resulting from relative value unit adjustments is 0.23 percent for 2016. The target was missed by 0.77 percent, resulting in reductions to the *MPFS* in 2016.

Q What happened with ambulatory surgery center facility fees in 2016?

A For 2016, the wage adjustment for budget neutrality, in addition to the multifactor productivity adjusted update factor, increases the ASC conversion factor by 1.3 percent for those meeting the quality reporting requirements, resulting in small increases in facility reimbursement. Ambulatory surgical centers began the reporting of National Quality Forum Measures in October 2012. The reporting of these measures affects reimbursement. Nonparticipation or failure to meet the necessary requirements results in a 2-percent reduction to facility Medicare reimbursement.

Q Did hospital outpatient department rates increase similarly to ASC facility rates?

A No. Various adjustments to hospital reimbursements result in a hospital outpatient department rate decrease of -0.3 percent.

Q Were there any Category III code changes published in 2016?

A There were a number of changes. Code changes are released semiannually by the American Medical Association; a new Category III code implemented on July 1, 2015 appears in the *Current Procedural Terminology 2016* handbook:

- *0402T – Collagen cross-linking of cornea (including removal of the corneal epithelium and intraoperative pachymetry when performed) (Do not report 0402T in conjunction with 65435, 69990, 76514).*

One revised Category III code exists in 2016, with additional verbiage underlined below:

- *0308T – Insertion of ocular telescope prosthesis including removal of crystalline lens or intraocular lens prosthesis.*

Coverage and payment for Category III codes remains at the discretion of the Medicare Administrative Contractor.

Q What changes were published with Category I codes in *CPT* 2016?

A The *2016 CPT* coding manual contains a number of new codes, revisions, and deletions applicable to ophthalmology. Category I *CPT* code changes are as follows:

New code:

- *65785 – Implantation of intrastromal corneal ring segments, replaces 0099T.*

Revised codes:

- *65855 – Trabeculoplasty by laser surgery;*
- *67227 – Destruction of extensive or progressive retinopathy (e.g., diabetic retinopathy), cryotherapy, diathermy;*
- *67228 – Treatment of extensive or progressive retinopathy (e.g., diabetic retinopathy), photocoagulation.*

The "one or more sessions" verbiage was removed from these three procedures.

The following codes contain language changes reflected by underlines:

- *67101 – Repair of retinal detachment, 1 or more sessions; cryotherapy or diathermy, including drainage of subretinal fluid when performed;*
- *67105 – photocoagulation including drainage of subretinal fluid, when performed;*
- *67107 – Repair of retinal detachment; scleral buckling (such as lamellar scleral dissection, imbrication or encircling procedure), including, when performed, implant, cryotherapy, photocoagulation, and drainage of subretinal fluid;*
- *67108 – … with vitrectomy, any method, including, when performed, air or gas tamponade, focal endolaser photocoagulation, cryotherapy, drainage of subretinal fluid, scleral buckling, and/or removal of lens by same technique;*
- *67113 – Repair of complex retinal detachment … with vitrectomy and*

membrane peeling including, when performed, air, gas, or silicone oil, tamponade, cryotherapy, endolaser photocoagulation, drainage of subretinal fluid, scleral buckling, and/or removal of lens;

• *99174 – Instrument-based ocular screening (e.g., photoscreening, automated-refraction), bilateral; with remote analysis and report*.

These changes do not affect reimbursement.

Deleted in 2016:

• *67112 – by scleral buckling or vitrectomy on patient having previous ipsilateral retinal detachment repair(s) using scleral buckling or vitrectomy techniques*.

Q Were there any changes to diagnosis codes or issues with the implementation of ICD-10?

A No new ICD-10 codes were published in October 2015. Since implementation on October 1, 2015, the ICD-10 transition has been relatively smooth. Contractor policies continue to be updated with missing ICD-10 codes not brought forward from the ICD-9 covered lists. Claim denials due to this issue should be brought to the attention of the payer and appealed.

Q What types of regulatory issues were identified in the annual *Office of Inspector General's Work Plan* as areas of concern for ophthalmology in 2016?

A The annual publication of the *OIG Work Plan* included a series of initiatives that will continue in 2016 with a small number of new initiatives pertinent to ophthalmology. The continuing targets for scrutiny include:

• Payments for drugs;

Eligible professionals who did not successfully report PQRS in 2014 are penalized 2 percent … in 2016.

• Ambulatory surgical centers – payment system;

• Imaging services – payments for practice expense;

• Anesthesia services – payments for personally performed services.

New issues include:

• Anesthesia services – non-covered services;

• Physicians – referring/ordering Medicare services and supplies;

• Prolonged services – reasonableness of services;

• CMS management of the ICD-10 implementation;

• Ambulatory surgery centers – quality oversight; and

• Risk adjustment data – sufficiency of documentation supporting diagnoses.

Q Are there penalties and/or bonus dollars for participation in the Physician Quality Reporting System in 2016?

A The Patient Protection and Affordable Care Act made PQRS mandatory by 2015. Those eligible professionals who did not successfully report PQRS in 2014 are penalized 2 percent off of their *MPFS* reimbursements in 2016. Bonus payments ended with the 0.5-percent bonus paid to successful reporters in 2014.

Q Are there any major changes to PQRS reporting requirements in 2016?

A No. The requirements for successful reporting in 2016 are unchanged from 2015. Eligible professionals must include at least nine measures via claims and/or registry-based reporting covering at least three National Quality Strategy domains. In 2016, one measure must be from the cross-cutting measure set. Eligible professionals reporting fewer than nine measures are subject to the Measure Applicability Validation process to determine if additional measures apply. The MAV process may determine that the eligible professional successfully reported even though nine measures were not reported.

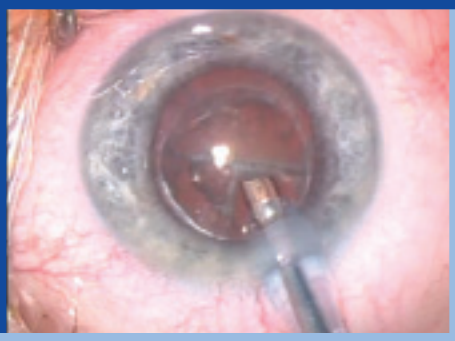
Q Are there continued penalties for those without electronic health records or those that fail to successfully report meaningful use?

A Yes. For those without EHR and those who did not qualify for a hardship exemption or complete their meaningful use attestation for 2014, a penalty of 2 percent of their *MPFS* applies for 2016.

Q What Medicare Part B changes affect beneficiaries in 2016 from a cost perspective?

A The Medicare Part B premiums remain $104.90 for most beneficiaries. The Part B deductible increases to $166. This is the first deductible increase since 2013. REVIEW

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



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Agenda session times have changed this year

Friday, February 12	Saturday, February 13	Sunday, February 14
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4:00 - 7:00PM Evening Sessions & Working Dinner	6:30 - 12:00PM Morning Session	6:30 - 12:00PM Morning Session
	4:00 - 7:00PM Evening Session	

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Does Your Patient Have A Dysfunctional Lens?

Walter Bethke, Managing Editor

Surgeons weigh the merits of a new characterization of pre-cataract.

Not many things in life go from perfect working order to unusable in an instant. Most go through a period of slow decline. Some surgeons are beginning to say that ophthalmologists need to think this way about the crystalline lens. Since the lens loses its function over time, they say the specialty needs a new term to describe this gradual decline: dysfunctional lens syndrome. Proponents of DLS argue the term is necessary in order to better educate patients about their eyes and to help surgeons determine where the elective procedure variously known as refractive lens exchange or clear lens extraction fits into the procedure spectrum. Other surgeons, however, don't think a new term is necessary, and that older patients either want refractive surgery to reduce their need for glasses or they have functional deficits and need cataract surgery.

In this article, surgeons discuss the concept of dysfunctional lens syndrome, how they talk about it with patients and some of the controversial aspects of using it as a diagnosis.

The DLS Concept

Surgeons who use the DLS diagnosis say it clarifies a process that was often hazy in the minds of physicians and their patients.

"What I noticed before we started discussing DLS," says Overland Park, Kan., surgeon Dan Durrie, "is that someone in his 40s, 50s, 60s or 70s would come to us with some vision changes and we'd say, 'Good news, you don't have a cataract.' Then he'd come back every couple of years, each time noticing that his vision had gotten somewhat worse, and each time we'd send him off with, 'You don't have a cataract.' And then, at some point, he'd come back and, miraculously, he would have a cataract that we could operate on because it had reached the point at which Medicare or insurance would cover it. In reality, the lens had been changing for 25 years.

"This way of communicating with patients about lens changes didn't help them understand that they had a progressive problem that starts out with their 'arms getting shorter' in their 40s and ultimately ends in a cataract," Dr. Durrie continues. "In their 40s, we'd tell them they had lost the zoom lens in their camera or were losing their accommodation and then, when they reached their 70s, we'd have a lot of discussion about cataract when they finally developed one, but there was this gap between age 43 to about 73—the average age people get cataract surgery—in which they didn't re-

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ally understand well what was going on with their lenses and what could be done about it."

George Waring IV, MD, FACS, director of refractive surgery and associate professor of ophthalmology at the Medical University of South Carolina, Storm Eye Institute, also uses the dysfunctional lens diagnosis in his practice. "Years ago, for patients in their mid 50s or early 60s who complained of wearing their distance glasses, bifocals and/or contact lenses, we'd do LASIK," he says. "And they'd be back in five years saying that their LASIK had worn off, but actually their lenses had aged. Because their lenses weren't truly clear, this had a bearing on visual quality. This lack of clarity, however, wasn't leading to symptoms that affected their daily activities or to an objective decrease in vision where the official diagnosis of cataract was warranted. So, instead of being enhanced with further LASIK, these patients would often go on to what was called clear lens extraction. However, we knew these weren't clear lenses, and that the lens was the etiology of the problem. So, we began to use advanced techniques to study and characterize the lens changes that in the past had been dismissed as 'precataracts.' "

In DLS, then, the patient is made to understand that, barring a corneal or retinal issue, the presbyopia he experiences in his 40s, the slight haziness that comes on in the 50s and 60s and the eventual Medicare-defined cataract are all facets of the same thing, a dysfunctional lens.

Rather than confusing patients who are told they have a lens syndrome but it's not covered by health insurance, Dr. Waring says the term DLS has actually helped. "The patient was coming in for LASIK and now you're telling him you're going to be removing his lens," says Dr. Waring. "DLS has greatly facilitated what used to be a challenging discussion prior to the characterization of this spectrum of the aging lens's changes. We now have advanced diagnostic and surgical instruments to evaluate and address changes in the crystalline lens. For example, femtosecond lasers are now available for lens surgery, like we have lasers for the cornea, and we can take patients on a digital tour of their eyes with advanced diagnostics to better educate them and to help in our clinical decision making. We can grade their visual quality and help them understand why it may make more sense for them to have laser surgery on their internal lens vs. their cornea—sparing them a second surgery in the process—and it's been very well-accepted by patients."

Presenting It to Patients

Surgeons who use the concept of DLS break it into three stages to help patients understand what's going on.

• ***Stage I.*** Dr. Durrie says he begins by pulling out an eye model, slit-lamp photo, and/or an Eyemaginations digital presentation or computer diagram to highlight the crystalline lens for the patient. "I tell that patient that, in our 40s, the crystalline lens that was clear and pliable in our 20s begins to lose its ability to focus up close—or up close and in the distance for the hyperope—due to the lens getting stiffer and the muscles around it not being able to bend it as well," Dr. Durrie says. "I say, 'This is stage I of what you're experiencing—dysfunctional lens syndrome. In stage I, the lens is still clear and colorless, but it's stiffer, due to the disulfide bonds building up inside the lens, part of the glutathione pathway, which cross-links the lens fibers.' I include the scientific detail at the end for inquisitive patients who want to know why it's happening. It comforts the patient knowing that we understand what's going on, and that it's normal and every person gets it if he or she lives long enough."

Acuity, though good in normal tests, can be bad enough with brightness acuity testing to warrant cataract surgery.

For patients in the first stage of DLS, besides glasses and contact lenses, there are three potential surgical options: monovision/blended vision; a presbyopic corneal inlay such as the Kamra (if the lens is clear); and, rarely at this stage, refractive lens exchange. "At this early stage, the last option would only be in someone such as a +2 or +4 D hyperope," explains Dr. Durrie. "These patients are usually in their 40s and their lenses are still clear but have become dysfunctional. So, sometimes, rather than discussing other surgical options, we suggest that maybe a high hyperope be educated about the option of refractive lens exchange."

• ***Stage II.*** Surgeons define this stage as occurring in the 50s and 60s, when the lens starts to turn yellow and slightly hazy. "This affects the patient by making his night vision not as good as it used to be," explains Dr. Durrie, "and he will also usually need more light to read. It's important to explain DLS in the patient's terms—i.e., what they see, not what we see."

The treatment options for stage II DLS are still in the elective category. "When they get into stage II, the corneal inlay option goes away," says Dr. Durrie. "Blended vision/monovision is still an option but is only a solution for stage II—you need to explain that eventually they'll need to have their lens replaced when DLS progresses. So, this leads to the more likely

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treatment discussion for individuals in their 50s and 60s: Is it maybe time to get the crystalline lens replaced with an intraocular lens by way of refractive lens exchange and, in doing so, prevent cataracts?"

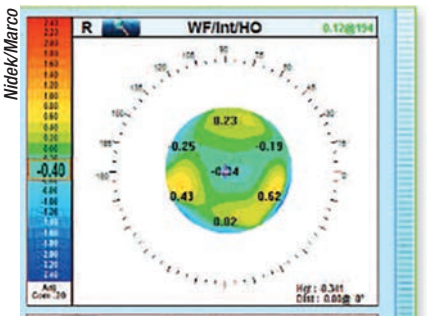
Asim Piracha, MD, of Jeffersonville, Ind., uses the DLS concept in his practice and says that, for these stage-II patients, a refractive lens exchange can benefit them more than LASIK. "Refractive lens exchange with a multifocal lens can give them four things," he says. "First, they'll get distance vision as with LASIK. Next, unlike LASIK, they'll possibly get good near vision with the multifocal IOL. Third, by taking care of the dysfunctional lens, the quality of their vision will improve. And, fourth, it's permanent—they'll never get a cataract and their vision will no longer keep changing due to the lens."

• ***Stage III.*** When the lens is defined as entering stage III, it simply means it has a cataract as defined by Medicare, which is usually acuity of 20/50 or worse with or without glare, or which involves visual impairment that severely hinders one's daily activities.

Diagnostic Instrumentation

Instrument companies are also getting involved in promoting the concept of DLS, with devices that make it easier to analyze the crystalline lens.

One device that's used by DLS proponents is the HD Analyzer (Visiometrics, Barcelona). "It was one of the first devices to popularize the idea of ocular scatter, or how much light is lost when rays travel through the optical system," says Dr. Durrie. "It provides an optical scatter index and a simulated visual acuity reading. When diagnosing DLS, if I have a patient with an ocular scatter index of 0.5 or less, that means he has outstanding optics. His tear film, cornea, lens and vitreous have no ocular scatter. We absolutely know his lens is still clear and, if he's in his 40s, has stage I. Patients with OSI between



The OPD-Scan III can show the physician the amount of aberrations caused by the lens vs. the amount caused by the cornea.

0.5 and 1 are still considered normal and not who we'd be looking at for lens procedures, but we might have to look at them more closely and ask why their optics aren't pristine. Once the OSI value gets above 1.0, there's ocular scatter present, but it can be coming from the ocular surface, corneal problems such as keratoconus, et cetera. At that point you have to conduct more discussions and diagnoses to determine where the distortion is coming from."

Another instrument some surgeons find useful is the iTrace (Tracey Technologies, Houston), which has a dysfunctional lens index function. The DLI will separate out the eye's aberrations, showing the clinician the amount coming from the cornea and the amount from the lens. "The iTrace also has an index number that it will give you," explains Dr. Piracha. "A 10 is a perfectly clear lens, and a zero is a dense cataract. Anything below 5.0 is significant for cataract and if the patient is at a 6.0 or 7.0, he's getting close." The Nidek/Marco OPD-Scan III can also tell the user how much of the aberration is internal (lens) vs. external (cornea). "You can also use the Oculus Pentacam to look at the lens and see how much of a density increase there is," says Dr. Durrie. "So it's not just one piece of equipment in DLS diagnosis, but it involves equipment some surgeons have in their offices already, or new equipment that the physician will add in order to have this DLS discussion with patients."

Dr. Waring says the diagnostics help refractive-surgery decision-making in general. "Where the advanced diagnostics have been extremely useful has been in guiding the refractive surgeon in the critical aspects of making the decision between a cornea- or lens-based procedure," he says. "So, in stage I, where the first dysfunctionality is experienced in terms of a loss of accommodation and where there's still a relatively clear lens as determined by diagnostics and the clinical exam, patients would benefit from a corneal procedure. In stage II, in which the lens has become less clear and the patients are only presenting to get out of glasses and do not subjectively or objectively qualify for an insurance-based cataract procedure, these patients may benefit more from a lens-based procedure relative to a corneal-based procedure. Either way, patients are reassured that this is a normal, age-related and ubiquitous process."

Controversies with DLS

There some surgeons who take issue with DLS, either with particular aspects of how it's treated, such as removing a clear lens, or simply with the idea that the profession needs a new term at all.

Boulder, Colo., surgeon Mark Packer says that, though he has no problem with refractive lens exchange as an elective procedure, he thinks the rationale behind DLS cedes too much power to payors in terms of making diagnoses. "The issue I have with the promotion of dysfunctional lens syndrome is that its proponents are basically trying to create a diagnostic category for patients with visual acuity that's too good for third-party payors to consider approving for cataract surgery," he says. "Fundamentally, I believe that we, as physicians, shouldn't allow Medicare or insurance companies to govern what we consider diagnostic catego-

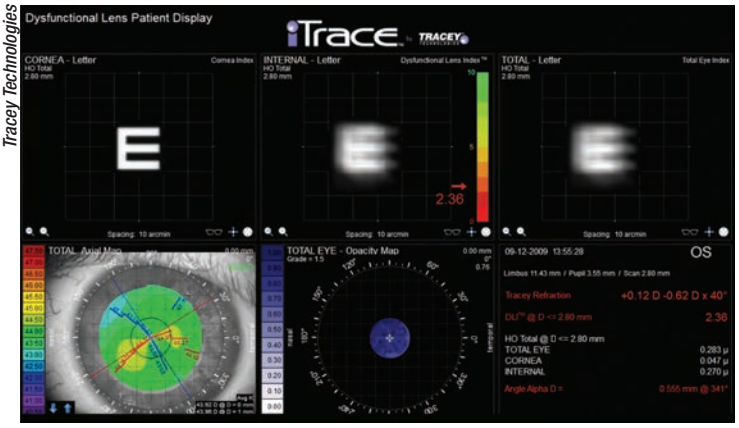
ries. That's the practice of medicine. I don't like the idea that we're making up diagnostic categories so they fit within the parameters that have been determined by payors. My primary motivation is: What does the patient want? What is the complaint? If it's a refractive complaint, it's very clear that it's out of pocket, and that's fine. But then there's the person who gets the best pair of glasses I can find and still can't drive well at night. That's different. I cringe at this formulation of a diagnostic category that's simply based on the premise: 'The patient's acuity is better than 20/40, so Medicare isn't going to pay, but we want somebody to pay, so let's call it dysfunctional lens syndrome and get more patients to pay for their own surgery.'

"I will say that the original idea behind dysfunctional lens syndrome was coming from a good place," Dr. Packer adds. "There are people with functional problems who don't meet the criteria for worse than 20/40 best-corrected vision necessary for cataract surgery to be reimbursed—so the question arose regarding what we were going to do for them. My answer would be, let's not call it something new, but instead let's call it what it is: It's either a cataract or it's serious optical aberrations, and there are already ICD codes for those. The treatment for those diagnoses is to replace the lens, giving the patient better vision. If someone has a functional problem and his best-corrected acuity is 20/20, that's what he has health insurance for; that's a medical problem and there are ways to document it."

Dr. Packer says that some patients who would be considered stage II in DLS would actually qualify for reimbursable cataract surgery, if the surgeon dug deeper and documented his findings, and he has done just that in his own practice. The only caveat is the patient would have to have come in with a functional complaint regarding his vision, not just the desire to see better without glasses.

"In contrast sensitivity testing, for example," explains Dr. Packer, "it's pretty well-accepted that a 0.3 log-unit decline from the normative value of whatever instrument you're using is significant. I usually go with the peak, which is usually 3 or 6 cycles/degree. The manufacturer can supply normative data of what the peak should be. The VF-14 questionnaire is another valid testing instrument. A score of 75 percent or below on the questionnaire indicates that the patient would benefit from cataract surgery. Basically, if you score above 75 percent, you're already seeing well and there's not a lot of room to improve, so postop satisfaction scores will drop. But at 75 percent and below, you'll see a high rate of

postop patient satisfaction from cataract surgery; in other words, people are saying, 'This solved my problem.' On the other hand, I've had patients say they were having a problem but score 95 percent on the VF-14—so there actually wasn't a problem."



Tracey Technologies

The dysfunctional lens syndrome functions on the iTrace show how internal aberrations (i.e., from a patient's crystalline lens) impact visual acuity by showing how much blur would occur with a standard letter E.

For a patient with a complaint, even if Snellen acuity in normal lighting conditions doesn't qualify him for cataract surgery, glare testing might. "Usually what's done is the physician uses glare testing to show that it drops the patient's acuity," says Dr. Packer. "If a patient reads the chart at 20/20, but when you put on the brightness acuity tester he only reads 20/50, everyone would agree that's significant. But what if it only drops to 20/30? In that case, you'd need some other documentation, such as contrast sensitivity with glare. That's a much more sensitive indicator than high-contrast acuity. A patient may also have a so-called wavefront cataract, meaning there's little in the way of lens opacity but there's a whopping amount of aberrations in his lens and he's got functional complaints stemming from it. For that, I'd say there's a diagnostic code, 'optical aberrations,' and the treatment for it is lens extraction, and then I'd document why I determined that. Maybe that's sort of a risky place to be for some surgeons, and some would rather say, 'I know you have functional complaints, but your insurance isn't going to pay for this, because they have particular visual acuity criteria.' My answer to that would be, yes they have that criteria, but there are clauses within those rules that say some things that give you a little bit of latitude that you can work with. Document the patient's functional complaint, such as not being able to drive despite the best pair of glasses, and then create a file documenting your findings. Perform the surgery and bill the third-party payor. If they don't pay or they audit you, you've got the function on the VF-14, the CS testing, your wavefront analysis and your quote from the patient of his impairment."

Dr. Waring, however, points out that DLS does make allowances for patients in stage III (insurance-based cataract) to get cataract surgery that's reimbursed by a third party. "The clear distinction is that DLS patients aren't coming in complaining of dysfunction that's affected their daily activities in the classic sense such as not being able to drive at night," he says. "All patients are screened for such problems as difficulty driving at night due to glare. They're also not qualifying for cataract surgery objectively in terms of decreased contrast sensitivity or BAT less than state standards—though it's important to note that the requirements for the diagnosis of cataract differ from state to state. If a patient in the cataract age range presents with a complaint about wearing glasses or bifocals and is requesting to get out of them, we'll screen him for cataracts and, if he'd benefit from a cataract extraction, we'd give him that as an option."

Dr. Piracha says that, though he agrees some patients have better than 20/50 acuity but still have visual issues, he has to stay within the laws of his state. "Even though I know the cataract's the problem, and can show the patient that the cataract's the problem, the other problem is that he's still 20/30, and according to insurance he's not bad enough yet to qualify for cataract surgery," says Dr. Piracha. "I'm very conscious of this because payors like to audit practices and not pay for procedures, and you don't want to get in trouble for fraud. I follow the CMS guidelines, which use best-corrected Snellen acuity, best-corrected near and glare testing at medium power on the BAT. Normally, if we have someone who's 20/30 or 20/40 with a lot of complaints and a beginning cataract, I'd say, 'We'll see you back in six months.' "

Surgeons who use the DLS diagnosis say another reason some colleagues may be waiting on DLS is because refractive lens exchange is a very involved procedure to undertake. "You have to have the tools to ensure the best results," says Dr. Durrie. "You need intraoperative aberrometry to pick the IOLs carefully, you need to be able to do excimer touch-ups. You have to be comfortable with all these things before suggesting the removal of a lens that doesn't have a cataract. I think many surgeons are still trying to decide on which side of the fence they're going to sit on DLS." REVIEW

Dr. Durrie is on the advisory boards of Visiometrics and AcuFocus. Dr. Waring is a consultant to AcuFocus. Drs. Piracha and Packer have no financial interest in the products discussed.

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

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

Indications and Usage

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

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

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

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

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

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

Preservative-Free

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

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

Istalol®
(timolol maleate ophthalmic solution) 0.5%

References: 1. Alm A, Stjernschantz J. Effects on Intraocular Pressure and Side Effects of 0.005% Latanoprost Applied Once Daily, Evening or Morning. *Ophthalmology*. 1995;102:1743-1752. **2.** Brubaker R. Flow of Aqueous Humor in Humans. *IOVS*. 1991;32:(13)3145-3166. **3.** Obstbaum S, Cioffi GA, Krieglstein GK, et al. Gold Standard Medical Therapy for Glaucoma: Defining the Criteria Identifying Measures for an Evidence-Based Analysis. *Clin Ther.* 2004;26(12)2102-2119. **4.** Istalol [package insert]. Bridgewater, NJ: Bausch & Lomb Incorporated; 2013. **5.** Timoptic in Ocudose [package insert]. Lawrenceville, NJ: Aton Pharma; 2009. **6.** Stewart W, Day DG, Sharpe ED. Efficacy and Safety of Timolol Solution Once Daily vs Timolol Gel Added to Latanoprost. *Am J Ophthalmol*. 1999;128(6)692-696.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

PRESERVATIVE-FREE STERILE OPHTHALMIC SOLUTION
in a Sterile Ophthalmic Unit Dose Dispenser

TIMOPTIC® 0.25% AND 0.5% (TIMOLOL MALEATE OPHTHALMIC SOLUTION)

in OCUDOSE® (DISPENSER)

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

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

WARNINGS

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

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

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

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

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

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

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

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

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

PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

OVERDOSAGE

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

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

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

DOSAGE AND ADMINISTRATION

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

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

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

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

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

Manuf. for:
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BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

Istalol® (timolol maleate ophthalmic solution) 0.5%

Initial U.S. Approval: 1978

STERILE

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

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

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

6.2 Postmarketing Experience

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

DRUG INTERACTIONS

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

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

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

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

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

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

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

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

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

OVERDOSAGE

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

NONCLINICAL TOXICOLOGY

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

PATIENT COUNSELING INFORMATION

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

Rx Only

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Topography-guided Ablation: A User's Guide

Christopher Kent, Senior Editor

This technology promises to improve many patients' vision, but surgeons need to start slowly.

At long last, American surgeons are getting access to topography-guided ablation—a technology that has been available outside the United States for several years—and many of the surgeons using it are getting great outcomes. Karl Stonecipher, MD, medical director of TLC Laser Eye Centers in Greensboro, N.C., and clinical associate professor of ophthalmology at the University of North Carolina, currently treats between 20 and 30 percent of the virgin eyes that come into his practice with this technology. He says that today, 100 percent of his topography-treated patients are 20/20 postop; 81 percent are 20/15; and 12 percent are 20/10. "These are some of the best outcomes I've seen," he says. "Also, we're getting these good results faster. My individual results show that I'm getting more patients who are 20/16 and 20/12 on postoperative day one. I think that's because we're uniquely treating the fingerprint on their eye."

Dr. Stonecipher points out that topography-guided treatment has been around for a long time. "It got through the FDA with flying colors," he notes. "In fact, it produced some of the best data we've ever seen. In the FDA trial the treatments reduced visual symptoms such as glare, halos and starburst. They improved BCVA; about 33 percent of patients actually saw better than they did before surgery."

Of course, as with any new technology, there is much to learn in order to avoid pitfalls and get great results. Here, Dr. Stonecipher and two other surgeons well-acquainted with topography-guided ablation discuss how this procedure differs from wavefront-guided and wavefront-optimized ablation; how to use this technology most effectively when treating virgin eyes; how to decide whether a given patient will benefit from this type of treatment; what you need to know if you attempt off-label usage; and offer a list of strategies to help ensure that your patients have the best possible outcomes.

The Topography Advantage

To make the best use of this technology it's important to understand the differences between wavefront-guided treatment, wavefront-optimized treatment and topography-guided treatment. "Wavefront-guided treatment treats the refractive error, the aberrations, the whole eye from tear film to retina," says Dr. Stonecipher. "Wavefront-guided takes in all of the imperfections of the optical system and puts them into the treatment profile. In contrast, wavefront-optimized

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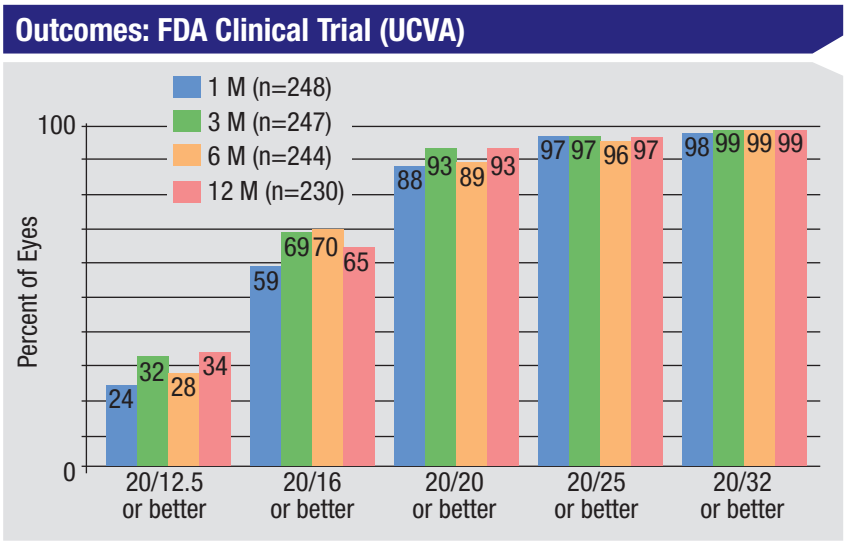


In an FDA clinical trial, topography-guided LASIK significantly reduced light sensitivity, nighttime driving difficulty, reading difficulty and glare. At 12 months, 40.4 percent gained one or more lines of BSCVA; 13.5 percent gained two or more lines of BSCVA.[7]

ablation treats sphere and cylinder with an algorithm that was developed to minimize the problems we were inducing with our original laser vision nomograms. Topography-guided ablation, on the other hand, treats the problems being caused by corneal irregularities. In the majority of cases, the cornea is the source of most of the refractive problems—with the notable exception of cataract."

Dan Z. Reinstein, MD, adjunct professor of ophthalmology at Columbia University Medical Center in New York City and medical director at the London Vision Clinic, notes several specific differences between topography-guided ablation and wavefront-guided ablation. "Topography-guided ablations are centered on the corneal vertex and encompass the whole cornea, whereas wavefront-guided ablations have to be centered on the pupil, as whole-eye wavefronts are measured and limited to the pupil aperture," he says. "Numerous studies have shown that refractive surgical corneal ablations are best centered on the corneal vertex in order to approximate the visual axis.[1,2] For example, in 2012 we published a case report of a decentration showing that a wavefront-guided ablation would actually have made the decentration worse; the topography-guided ablation that was performed achieved perfect topographic centration and alleviated the patient's visual symptoms.[3] In addition, topography-guided ablations have been shown to be more effective than wavefront-guided ablations for reducing higher-order aberrations."[4,5]

"One very important aspect of topography-guided treatments is that you're always making the cornea more regular, and that's never a bad thing," adds Arthur Cummings, FRCS, MD, a consultant ophthalmologist at Wellington Eye Clinic in Dublin, Ireland. "With wavefront-guided treatments, it's possible that you're creating aberrations on the cornea to offset aberrations that are inside the eye, and that's obviously not a good thing. You don't want to punish the cornea for the sins of the lens."

The "20-unhappy" Dilemma

One of the key issues for American surgeons finally getting access to this technology is that the Food and Drug Administration has only approved its use on some eyes with myopia and/or astigmatism. Outside the United States, many surgeons rarely use this technology on the type of eyes approved for treatment by the FDA; most surgeons see it as a way to remedy the post-surgical aberrations that lead to so-called "20-unhappy" patients. American surgeons are aware of this, and many are eager to have that option in their armamentarium.

"Topography-guided customized ablation treatment, or T-CAT, is indicated for myopia up to -9 D, with up to 3 D of cylinder," notes Dr. Stonecipher. "This technology reduces the induction of aberrations that a conventional treatment, even a wavefront-optimized platform, can produce. It's great for patients who haven't had previous surgery and have normal but asymmetric corneal topography. It's also effective for correcting decentration and enlarging optical zones in patients that have had previous refractive surgery, outside the United States. However, that's an off-label use of this technology in the United States and not recommended at this time."

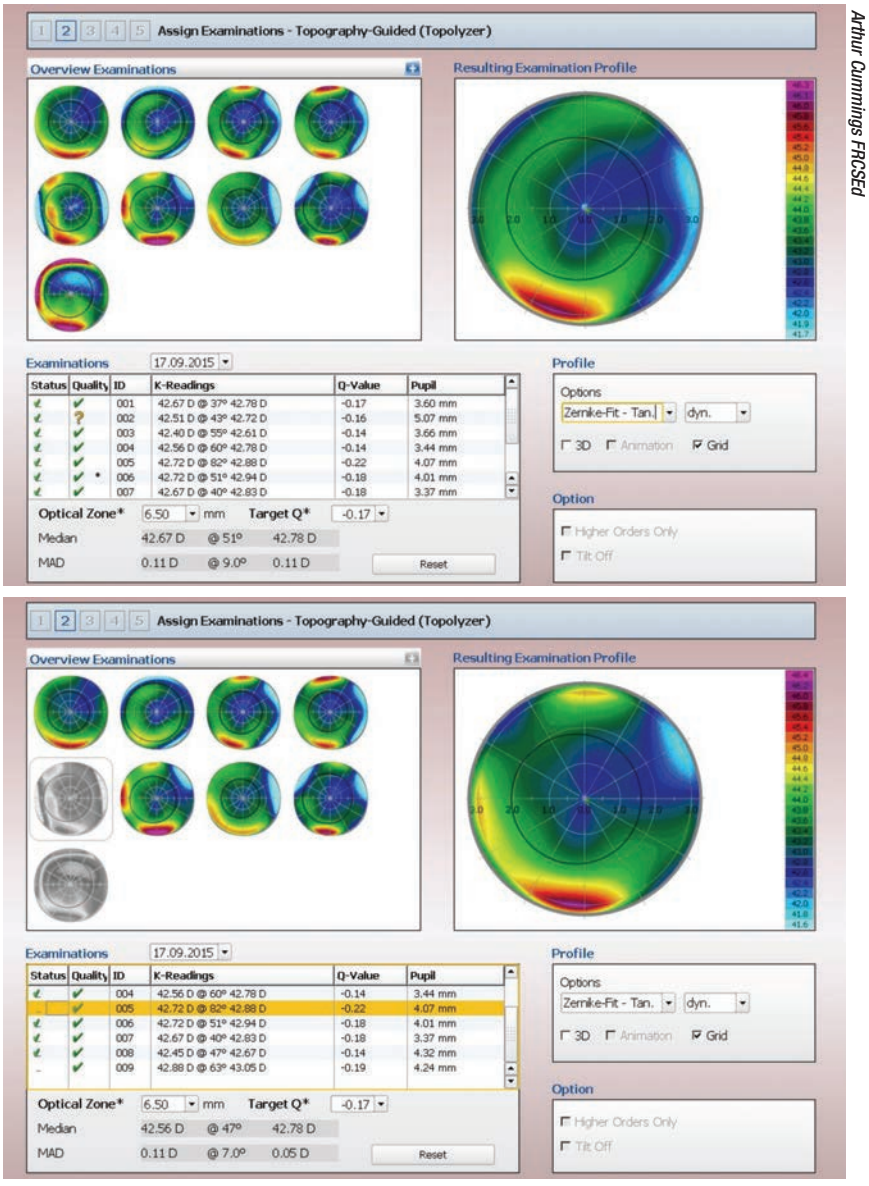
Dr. Cummings says that previously (in his practice located outside the United States) if a patient had no particular complaints, the surgeon would perform a wavefront-optimized procedure. "If the patient did have complaints, we'd try a wavefront-guided procedure, as long as we were able to obtain good data," he says. "If we couldn't get good data, we'd do a topography-guided treatment.

"Then, about 18 months ago, the FDA approval for topography-guided LASIK was granted, so Alcon asked a couple of users in Europe to see what they could do with this technology as a first-time treatment," he continues. "As a result, we started using it for that purpose more frequently. Our WaveLight EX500 laser is linked to an intranet called WaveNet, and we found that it hardly took any extra time to

plan a topography-guided treatment. So we started doing more and more topography-guided procedures, and the results were very good."

"The controversy," notes Dr. Stonecipher, "revolves around the fact that outside the United States topography-guided laser has always been the panacea for treating the patients who previously underwent RK, PRK or LASIK and ended up dissatisfied with their vision. A lot of American surgeons are talking about finally being able to treat those patients, to fix their corneas and finally make them happy. But for novice users, that is not the way to go. The reason is that normalizing the cornea can leave some patients with a spherical error of -1 or +1, or worse. If the previous refractive surgery left the patient with a very thin cornea, you won't be able to correct the error you've introduced.

"This is why it's very important for the surgeon just beginning to use this technology to start off with easy cases," he says. "Start off by treating the -1 and -2 D patients and see how the treatment affects the cornea. Using topography-guided treatments definitely requires changing your nomogram, because smoothing the cornea can induce myopia, hyperopia and even astigmatism."



Arthur Cummings FRCSEd

Although the Contoura software helps to analyze the reliability of the scans on which the ablation may be based (see boxes below scans), the surgeon ultimately decides which to eliminate. Here, the surgeon has chosen to eliminate scans #5 and #9, resulting in a visible change in the profile on which the ablation will be based (bottom screen).

Using the Technology

"This technology has changed the way I evaluate patients," notes Dr. Stonecipher. "Everyone coming in gets a CustomVue wavefront analysis, a Contoura topographic analysis and a Pentacam. We look at all of those to see whether the patient needs LASIK and if so, whether the eye has the anatomy to allow it. Then, we determine what type of platform and treatment the patient should get: wavefront-optimized, Contoura or wavefront-guided. Of course, we also have to make sure the patient doesn't have ocular surface disease or other issues that would affect the decision.

"There are several key steps to using this technology effectively," he continues. "First, you have to collect good data. If you can't get good images, you shouldn't use it. That's why topography-guided treatments are a challenge in people with unusual anatomy, ocular surface disease, long eyelashes or deep-set eyes. You don't want to treat noise. You also need a certain amount of applied area to treat.

"Second, you have to be able to judge which images you've collected are good and which aren't," he says. "Today, the software helps with this, but you still have to be able to make good judgment calls about which to include in the data pool and which to exclude. Do you have enough mires?

Does the eye have ocular surface disease? Are you covering enough area? Remember that this is a very large treatment—close to 9 mm, rather than 6 mm. You'll need to look at what's called the raw sagittal data to determine whether a map is good or bad, which is a new concept for laser vision correction. You'll also need to compare the pictures to see if one or two don't resemble the others, indicating exam variability. And of course you'll have to have a good ocular surface to get good diagnostics.

"Third, you want to isolate and look at the part of the ablation that's aimed at normalizing the cornea, rather than correcting spherical or astigmatic error," he says. "What is the pure amount of topographic change that you're going to cause, separate from the refractive error you're correcting? How will this affect your overall treatment, your nomogram? Will this topographic change make the patient more myopic or hyperopic, and if so, by how much?"

Dr. Cummings explains how to do this. "The instrument can show you exactly what parts of the topography it will be correcting, and the depth of tissue involved," he says. "If you plan a wavefront-optimized procedure and set it for -2 D, the screen should show a map with about 32 µm of ablation depth. If you then plan a topography-guided procedure on the same case, the ablation depth will likely be a little more than that [because of the additional topographic ablation]. Now, if you change the refractive component to zero or plano, there will still be something on the screen. We call this the higher-order ablation profile; the screen is showing you what it's going to do to regularize the cornea. The aberrations showing on the screen now are only 2, 3 or 4 µm deep, but removing them is exactly what will treat the topographic issues."

Dr. Cummings says that in a virgin eye, the wavefront-optimized ablation depth should be close to the topography-guided ablation depth. "When treating an eye that previously underwent refractive surgery, the topography-guided plan might indicate that it will ablate 45 µm instead of 32 µm," he says. "However, in a virgin eye the ablation depths should be pretty similar between the two treatment options. So, when you're just starting to do topography-guided procedures on virgin eyes, make sure that your wavefront-optimized ablation depth is close to the topography-guided ablation depth. That will help you avoid making any big mistakes."

Dr. Reinstein agrees. "If the ablation amounts are very close, you're in good shape," he says. "For example, if they disagree by 2 µm, you're talking about one-seventh of a diopter difference, which is clinically insignificant. In this situation, I would go with the topography-guided treatment; the refractive difference will be tiny, and the cornea will be less aberrated. If the difference between the two ablation depths is 5 or 6 µm or more, you're venturing into the territory where you might need to compensate for the refractive effect of the topography-guided procedure. If you're not ready to deal with that, you might want to opt for the traditional procedure until you understand the process better."

Getting the Details Right

Dr. Cummings explains how his practice uses this technology to treat primary procedure patients. "To do a primary procedure using Contoura, we first identify the patient as someone who has some corneal irregularity," he says. "Once we begin the process, the instrument takes eight Topolyzer maps and validates them as being either acceptable or not acceptable. [The Topolyzer integrates non-contact topography, keratometry and pupilometry.] There are two boxes on the Topolyzer scans. If they're both green, that's perfect. If one's green and the other is red, you can still use this scan by manually exporting it, but it's not going to be good enough for key things such as cyclorotational control. Fortunately, you don't need all eight scans. As long as you have a couple of scans that have two green boxes, the software will predict which one of those has the very best data, and that map will drive the cyclorotational control."

Dr. Reinstein agrees that the most important part of the treatment is obtaining a high-quality topography scan. He recommends doing the following:

- ***Check that the exam was properly focused.***
- ***Confirm that the mires are smooth and regular.*** "If they are irregular, use lubricating drops and repeat the exam," he says.
- ***Select the exam with the largest area of continuous data.*** "Pay particular attention to the superior region, as data acquisition can often be limited by the eyelid," he notes. "Remember that the ablation algorithm cannot differentiate between a true irregularity and an artifact in the data."
- ***Confirm that the scans have been well-centered—i.e., that the patient was looking at the fixation target.*** "Centration is the most important part of the ablation profile calculation," says Dr. Reinstein. "The profile should be calculated centered on the corneal vertex—i.e., the center of the mires on the topography scan—not on the entrance pupil center. And since the ablation profile has been generated centered on the corneal vertex, the ablation should be performed on the corneal vertex. Some systems have the corneal vertex location integrated into the ablation profile, but if not, then the surgeon should manually center the ablation on the coaxially sighted corneal light reflex."

"Cyclorotation is a very important factor in topography-guided ablations—much more so than in stan-

To Treat or Not to Treat?

One of the challenges of this technology is judging whether correcting the corneal surface will make a difference to the patient. "Right now, making this call is a little bit more art than science," says Karl Stonecipher, MD, medical director of TLC Laser Eye Centers in Greensboro, N.C. "If a patient's topography is totally normal and symmetric, the benefit of treating with Contoura is simple: You'll probably have a larger optical zone. This could matter in some patients. But in the clinical FDA trials, there wasn't a number that told you a given patient would do better with Contoura than he would with wavefront-optimized."

Dr. Stonecipher notes that this isn't this case when deciding whether to use wavefront-guided ablation. "A study I conducted with Guy Kezirian, MD," he says, "showed that if an eye has preoperative root-mean-square higher-order aberrations greater than 0.4 µm, patients got better results with wavefront-guided treatment than with wavefront-optimized.[6] But we don't have a study that tells us which patients will benefit from topography-guided ablation yet."

Dr. Stonecipher observes that this has resulted in a wide range of different surgeon choices about how many patients should receive a topographic treatment. "Some surgeons are treating every patient with Contoura, but many other surgeons are not," he says. "My advice is to start off slowly. Don't try to do 99 percent of your patients with this technology at the outset. There are many nuances to it. Remember that most problems surgeons encounter with this technology aren't the result of adulterating the cornea, but the result of causing an unintended spherical error. If patients pay extra to have this treatment, they won't be happy with an unexpected result—especially one you can't correct."

Arthur Cummings, FRCS, MD, a consultant ophthalmologist at Wellington Eye Clinic in Dublin, Ireland, notes that appropriate patients often identify themselves. "We've found that this technology is a good option when a patient volunteers that he doesn't see well at night, especially someone who drives at night," he says. "Another good candidate is any patient we can't correct to 20/20 or better. Also, sometimes you do a refraction and you see for yourself that there's a soft endpoint—the patient is not definite about what he's seeing because his vision is slightly fuzzy. "Basically, we now use this technology whenever we think there's something preventing the patient from having really acute vision."

Dr. Cummings adds that people are starting to come into his practice asking for the Contoura vision procedure. "Even in an asymptomatic patient you can do a procedure safely that's going to make his cornea more regular and give him better quality vision," he notes. "The most important thing is to do it right. Otherwise, you're going to end up with worse results than you would have gotten with a standard treatment."

—CK

dard ablations," adds Dr. Cummings. "Think of it this way: If you have a jigsaw puzzle on the table with one piece missing, and you have that piece in your hand and your registration is perfect, you can place that piece exactly where it belongs. The surface will be smooth and intact. But if your registration is slightly off in terms of rotation, the piece won't fit into the slot. You'll end up making the surface a lot less regular. So it's crucial to make sure your data is good, the patient is well-aligned and your eye trackers are functioning well."

Going Off-label

As noted, many American surgeons are anxious to try using this technology to treat 20-unhappy patients, even though this is not part of the FDA approval. The main reason caution is called for is that although topography-guided ablation is designed to improve the corneal surface, it can alter the refraction. "Because you're correcting aberrations when you change the cornea, whatever you do is going to have a refractive effect," explains Dr. Cummings. "The refractive change can be quite dramatic when an eye has serious corneal aberrations. If your patient had a procedure 10 years ago to treat a refractive error of -10 D using a broad-beam laser with a less-than-ideal ablation profile, maybe he ended up being -2 D, but he'll have a lot of spherical aberration. If you refract that patient in the dark, you may find he measures -5 D instead of -2 D.

"If you now do a topography-guided treatment that does nothing more than expand the optical zone, that patient is probably going to change from -2 D to -5 D," he continues. "That's why the key to doing topography-guided procedures on seriously aberrated eyes is to get to the point at which you can start predicting what that refractive effect is going to be. Once you can predict that, you can compensate for it. Then the cornea will become more regular and the refraction will be exactly what you intended. You'll start getting results like those in the FDA study, where night vision was significantly improved and glare was significantly reduced."

Dr. Cummings believes it won't take long for American surgeons to start attempting the use of topography-guided ablation to improve vision in patients with post-surgical aberrations. "This is why most surgeons want topography-guided ablation," he notes. "We couldn't wait for it to be available over here [in Ireland], because we had a number of patients with problems that wavefront couldn't correct. We saw their topographic errors, and all we could think was, 'Smoothing out

For allergic conjunctivitis[1]

THE POWER TO CALM THE ITCH

BEPREVE®—FIRST-LINE, YEAR-ROUND, WITH BROAD-SPECTRUM ALLERGEN COVERAGE

INDICATION AND USAGE

BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% is a histamine H_1 receptor antagonist indicated for the treatment of itching associated with allergic conjunctivitis.

IMPORTANT SAFETY INFORMATION

- BEPREVE® is contraindicated in patients with a history of hypersensitivity reactions to bepotastine or any of the other ingredients.
- BEPREVE® is for topical ophthalmic use only. To minimize risk of contamination, do not touch the dropper tip to the eyelids or to any surface. Keep the bottle closed when not in use.
- BEPREVE® should not be used to treat contact lens-related irritation. Remove contact lens prior to instillation of BEPREVE®. Lenses may be reinserted 10 minutes after BEPREVE® administration.
- The most common adverse reaction occurring in approximately 25% of patients was a mild taste following instillation. Other adverse reactions occurring in 2%-5% of patients were eye irritation, headache, and nasopharyngitis.

Made by the respected eye-care specialists at BAUSCH + LOMB

Please see the accompanying full Prescribing Information for BEPREVE® on the following page.

Reference: 1. BEPREVE [package insert]. Tampa, FL: Bausch & Lomb Incorporated; 2012.

BAUSCH + LOMB

For product-related questions and concerns, call **1-800-323-0000** or visit **www.bausch.com**.

BEPREVE®
(bepotastine besilate ophthalmic solution) 1.5%

BEPREVE® (bepotastine besilate ophthalmic solution) 1.5%

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% safely and effectively. See full prescribing information for BEPREVE®.

BEPREVE® (bepotastine besilate ophthalmic solution) 1.5%
Initial U.S. Approval: 2009

----------RECENT MAJOR CHANGES----------
Contraindications (4) 06/2012

----------INDICATIONS AND USAGE----------
BEPREVE® is a histamine H1 receptor antagonist indicated for the treatment of itching associated with allergic conjunctivitis. (1)

----------DOSAGE AND ADMINISTRATION----------
Instill one drop into the affected eye(s) twice a day (BID). (2)

----------DOSAGE FORMS AND STRENGTHS--------
Solution containing bepotastine besilate, 1.5%. (3)

----------CONTRAINDICATIONS----------
Hypersensitivity to any component of this product. (4)

----------WARNINGS AND PRECAUTIONS----------
- To minimize the risk of contamination, do not touch dropper tip to any surface. Keep bottle tightly closed when not in use. (5.1)
- BEPREVE should not be used to treat contact lens-related irritation. (5.2)
- Remove contact lenses prior to instillation of BEPREVE. (5.2)

----------ADVERSE REACTIONS----------
The most common adverse reaction occurring in approximately 25% of patients was a mild taste following instillation. Other adverse reactions which occurred in 2-5% of subjects were eye irritation, headache, and nasopharyngitis. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bausch & Lomb Incorporated. at 1-800-323-0000, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% is a histamine H_1 receptor antagonist indicated for the treatment of itching associated with signs and symptoms of allergic conjunctivitis.

2 DOSAGE AND ADMINISTRATION
Instill one drop of BEPREVE into the affected eye(s) twice a day (BID).

3 DOSAGE FORMS AND STRENGTHS
Topical ophthalmic solution containing bepotastine besilate 1.5%.

4 CONTRAINDICATIONS
Bepreve is contraindicated in patients with a history of hypersensitivity reactions to bepotastine or any of the other ingredients *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS
5.1 Contamination of Tip and Solution
To minimize contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use.

5.2 Contact Lens Use
Patients should be advised not to wear a contact lens if their eye is red. BEPREVE should not be used to treat contact lens-related irritation.

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

5.3 Topical Ophthalmic Use Only
BEPREVE is for topical ophthalmic use only.

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

The most common reported adverse reaction occurring in approximately 25% of subjects was a mild taste following instillation. Other adverse reactions occurring in 2-5% of subjects were eye irritation, headache, and nasopharyngitis.

6.2 Post Marketing Experience
Hypersensitivity reactions have been reported rarely during the post-marketing use of BEPREVE. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a casual relationship to drug exposure. The hypersensitivity reactions include itching, body rash, and swelling of lips, tongue and/or throat.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C: Teratogenicity studies have been performed in animals. Bepotastine besilate was not found to be teratogenic in rats during organogenesis and fetal development at oral doses up to 200 mg/kg/day (representing a systemic concentration approximately 3,300 times that anticipated for topical ocular use in humans), but did show some potential for causing skeletal abnormalities at 1,000 mg/kg/day. There were no teratogenic effects seen in rabbits at oral doses up to 500 mg/kg/day given during organogenesis and fetal development (>13,000 times the dose in humans on a mg/kg basis). Evidence of infertility was seen in rats given oral bepotastine besilate 1,000 mg/kg/day; however, no evidence of infertility was observed in rats given 200 mg/kg/day (approximately 3,300 times the topical ocular use in humans). The concentration of radio-labeled bepotastine besilate was similar in fetal liver and maternal blood plasma following a single 3 mg/kg oral dose. The concentration in other fetal tissues was one-third to one-tenth the concentration in maternal blood plasma.

An increase in stillborns and decreased growth and development were observed in pups born from rats given oral doses of 1,000 mg/kg/day during perinatal and lactation periods. There were no observed effects in rats treated with 100 mg/kg/day.

There are no adequate and well-controlled studies of bepotastine besilate in pregnant women. Because animal reproduction studies are not always predictive of human response, BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

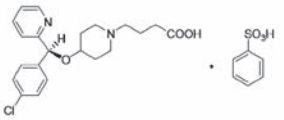
8.3 Nursing Mothers
Following a single 3 mg/kg oral dose of radiolabeled bepotastine besilate to nursing rats 11 days after delivery, the maximum concentration of radioactivity in milk was 0.40 mcg-eq/mL 1 hour after administration; at 48 hours after administration the concentration was below detection limits. The milk concentration was higher than the maternal blood plasma concentration at each time of measurement.

It is not known if bepotastine besilate is excreted in human milk. Caution should be exercised when BEPREVE (bepotastine besilate ophthalmic solution) 1.5% is administered to a nursing woman.

8.4 Pediatric Use
Safety and efficacy of BEPREVE (bepotastine besilate ophthalmic solution) 1.5% have not been established in pediatric patients under 2 years of age. Efficacy in pediatric patients under 10 years of age was extrapolated from clinical trials conducted in pediatric patients greater than 10 years of age and from adults.

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

11 DESCRIPTION
BEPREVE (bepotastine besilate ophthalmic solution) 1.5% is a sterile, topically administered drug for ophthalmic use. Each mL of BEPREVE contains 15 mg bepotastine besilate.
Bepotastine besilate is designated chemically as (+) -4-[[(S)-p-chloro-alpha -2-pyridylbenzyl]oxy]-1-piperidine butyric acid monobenzenesulfonate.
The chemical structure for bepotastine besilate is:



Bepotastine besilate is a white or pale yellowish crystalline powder. The molecular weight of bepotastine besilate is 547.06 daltons. BEPREVE® ophthalmic solution is supplied as a sterile, aqueous 1.5% solution, with a pH of 6.8.
The osmolality of BEPREVE (bepotastine besilate ophthalmic solution) 1.5% is approximately 290 mOsm/kg.
Each mL of BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% contains:
Active: Bepotastine besilate 15 mg (equivalent to 10.7 mg bepotastine)
Preservative: benzalkonium chloride 0.005%
Inactives: monobasic sodium phosphate dihydrate, sodium chloride, sodium hydroxide to adjust pH, and water for injection, USP.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Bepotastine is a topically active, direct H_1-receptor antagonist and an inhibitor of the release of histamine from mast cells.

12.3 Pharmacokinetics
Absorption: The extent of systemic exposure to bepotastine following topical ophthalmic administration of bepotastine besilate 1% and 1.5% ophthalmic solutions was evaluated in 12 healthy adults. Following one drop of 1% or 1.5% bepotastine besilate ophthalmic solution to both eyes four times daily (QID) for seven days, bepotastine plasma concentrations peaked at approximately one to two hours post-instillation. Maximum plasma concentration for the 1% and 1.5% strengths were 5.1 ± 2.5 ng/mL and 7.3 ± 1.9 ng/mL, respectively. Plasma concentration at 24 hours post-instillation were below the quantifiable limit (2 ng/mL) in 11/12 subjects in the two dose groups.

Distribution: The extent of protein binding of bepotastine is approximately 55% and independent of bepotastine concentration.

Metabolism: *In vitro* metabolism studies with human liver microsomes demonstrated that bepotastine is minimally metabolized by CYP450 isozymes.

In vitro studies demonstrated that bepotastine besilate does not inhibit the metabolism of various cytochrome P450 substrate via inhibition of CYP3A4, CYP2C9, and CYP2C19. The effect of bepotastine besilate on the metabolism of substrates of CYP1A2, CYP2C8, CYP2D6 was not studied. Bepotastine besilate has a low potential for drug interaction via inhibition of CYP3A4, CYP2C9, and CYP2C19.

Excretion: The main route of elimination of bepotastine besilate is urinary excretion (with approximately 75-90% excreted unchanged in urine).

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility
Long-term dietary studies in mice and rats were conducted to evaluate the carcinogenic potential of bepotastine besilate. Bepotastine besilate did not significantly induce neoplasms in mice receiving a nominal dose of up to 200 mg/kg/day for 21 months or rats receiving a nominal dose of up to 97 mg/kg/day for 24 months. These dose levels represent systemic exposures approximating 350 and 200 times that achieved with human topical ocular use. The no observable adverse effect levels for bepotastine besilate based on nominal dose levels in carcinogenicity tests were 18.7 to 19.9 mg/kg/day in mice and 9.6 to 9.8 mg/kg/day in rats (representing exposure margins of approximately 60 and 20 times the systemic exposure anticipated for topical ocular use in humans).

There was no evidence of genotoxicity in the Ames test, in CHO cells (chromosome aberrations), in mouse hepatocytes (unscheduled DNA synthesis), or in the mouse micronucleus test.

When oral bepotastine was administered to male and female rats at doses up to 1,000 mg/kg/day, there was a slight reduction in fertility index and surviving fetuses. Infertility was not seen in rats given 200 mg/kg/day oral bepotastine besilate (approximately 3,300 times the systemic concentration anticipated for topical ocular use in humans).

14 CLINICAL STUDIES
Clinical efficacy was evaluated in 2 conjunctival allergen challenge (CAC) studies (237 patients). BEPREVE (bepotastine besilate ophthalmic solution) 1.5% was more effective than its vehicle for relieving ocular itching induced by an ocular allergen challenge, both at a CAC 15 minutes post-dosing and a CAC 8 hours post dosing of BEPREVE.

The safety of BEPREVE was evaluated in a randomized clinical study of 861 subjects over a period of 6 weeks.

16 HOW SUPPLIED/STORAGE AND HANDLING
BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% is supplied in a white low density polyethylene plastic squeeze bottle with a white controlled dropper tip and a white polypropylene cap in the following size:
5 mL (NDC 24208-629-02)
10 mL (NDC 24208-629-01)

STORAGE
Store at 15° – 25°C (59° – 77°F).

17 PATIENT COUNSELING INFORMATION
17.1 Topical Ophthalmic Use Only
For topical ophthalmic administration only.

17.2 Sterility of Dropper Tip
Patients should be advised to not touch dropper tip to any surface, as this may contaminate the contents.

17.3 Concomitant Use of Contact Lenses
Patients should be advised not to wear a contact lens if their eye is red. Patients should be advised that BEPREVE should not be used to treat contact lens-related irritation.

Patients should also be advised to remove contact lenses prior to instillation of BEPREVE. The preservative in BEPREVE, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of BEPREVE.

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Under license from:
Senju Pharmaceutical Co., Ltd.
Osaka, Japan 541-0046

the cornea would help this patient.' So I think American surgeons will want to do this—and they will do it.

"My advice to those surgeons would be: If you want to minimize damage and get the best possible result when treating a patient who has previously undergone refractive surgery, start off by doing it as a two-step procedure," he says. "Tell these patients that this is the way you plan to proceed. Tell them, 'You have an irregular cornea, but it's so irregular that if we do a laser vision correction procedure to improve your topography, I have no idea what the impact will be on your prescription, so I can't compensate for it right away. Instead, I'll correct the cornea first and make it regular. Then we'll wait six months. In the interim, you can wear spectacles or contact lenses to address your interim refraction, and because we will have improved your corneal surface, you'll find that your corrected vision is better than before. Once we get to six months, we'll measure your refractive error again and do a wavefront-optimized procedure to fix just the refractive component.' "

Dr. Cummings points out that the refractive impact of a given treatment has a lot to do with the difference between what the ablation profile indicates will happen at the center versus at the periphery of the ablation zone. "If you're ablating 15 µm in the center and nothing at the edge, you're creating 1 D of refractive change," he explains. "If you're doing 30 µm in the middle and 15 µm at the edge, you're also creating 1 D of refractive change. The same is true if you're ablating 100 µm in the middle and 85 µm at the edge; you're creating 1 D of refractive change. These are some of the things you'll learn to think about when predicting the impact of smoothing the cornea."

Dr. Cummings explains that dividing the procedure into two parts allows you to practice predicting the refractive impact of the corneal smoothing. "Every time you do this procedure, look at the higher-order ablation profile," he says. "Enter 'zero refraction' into the portal software; then look carefully at the digital display showing exactly what the laser will be doing to the cornea to regularize it. You may think to yourself, 'This looks a bit like a hyperopic correction. It's changing nothing in the middle but ablating 15 µm in a doughnut shape around the edges. That looks like a 1 D hyperopic correction.' So you make a note in your file saying you think this procedure will cause a 1-D hyperopic correction. If the patient is currently -2 D, you're predicting that this patient will be at -3 D when you review his refraction in six months time."

"Your first patients should be less than 4 D with probably less than 1.5 D of cylinder until you get comfortable with the technology and understand it."
—Karl Stonecipher, MD

Dr. Cummings says it might take as few as 10 cases to become good at predicting the refractive effect of smoothing the cornea—if you attend a course on it and spend some time talking to other surgeons who have mastered it. "One reason taking a course is so important is that there are a number of ways to calculate the impact of corneal smoothing, and you can learn them there," he says. "You may not be an authority in 10 cases, even if you take a course and share other surgeons' experience, but you'll be able to manage the more complicated cases quite well.

"To tell the truth, if all you want to do is learn to compensate for the smoothing, you don't even have to do 10 cases; you just have to understand the principle," he says. "You can learn a lot just from looking at patient files. But doing the treatments, taking a course, working with other surgeons and seeing how your predictions turn out is what will give you confidence. Eventually you'll learn from experience to predict what the refractive change is going to be. In the meantime, doing the surgery in two stages is good for patient expectations, it helps you gain experience, and you're not going to hurt anyone."

Strategies for Success

Surgeons offer these bits of advice to ensure your outcomes are everything you'd like them to be:

• ***Start with easy, lower-diopter cases so you can develop your nomogram.*** "Being part of the FDA clinical trial gave me a chance to develop my nomogram," says Dr. Stonecipher. "A surgeon's biggest fear is not having a nomogram. What numbers do I put in for the first patient? That's why I say to everybody, begin by treating the -1 D and -2-D cases. Work your way up until you feel comfortable with the technology and your results are solid. Because if you go out and treat a -10 on the first day and you make a 10-percent error, you'll be a diopter off. That's the difference between 20/40 and 20/15. But if you make a 10 percent error in a -1 D case, the error will be almost negligible. So your first patients should be less than 4 D with probably less than 1.5 D of cylinder, until you get comfortable with the technology and understand it. That way everybody benefits. You won't be stressed out, and your patients will get great results."

• ***Focus on the diagnosis.*** "Successful use of topography-guided abla-

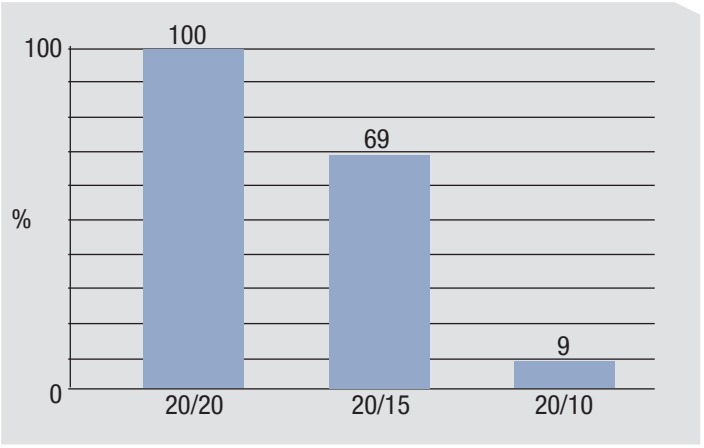
tion depends on understanding the cause of the visual symptoms," says Dr. Reinstein. "Always consider how the ablation profile will change the topography and ask yourself if this makes sense in relation to your diagnosis."

• ***Pay attention to the details.*** "To get a great result you need to pay attention to detail—more so than with a standard procedure," says Dr. Cummings. "In a standard procedure the ablation profile is symmetrical; you can't really make too many mistakes. But when the ablation is not symmetrical, you have to make sure the treatment is perfectly overlaid on the areas you want to treat. Especially when treating complicated eyes, there's no question that you can make things worse if you're not careful."

• ***Remember that good data is crucial.*** "Results of topography-guided treatments will only be as good as the quality of the topography data," says Dr. Reinstein.

• ***If you're considering using topography-guided ablations for all of your primary cases, consider measuring both corneal and whole-eye aberrations.*** "Topography-guided ablations are restricted to addressing irregularities on the front corneal surface, so a wavefront-guided treatment would be more appropriate if the majority of the irregularities were inside the eye," says Dr. Reinstein. "This means that it's important to measure both corneal and whole-eye aberrations if you are considering using topography-guided ablations for all of your primary cases. If you only measure the topography and regularize this, you may inadvertently uncover internal aberrations that the cornea was compensating for."

Outcomes of First 50 Cases (Low Diopter)—UCVA



Initially choosing low-diopter cases to treat allows a surgeon to minimize error and get great outcomes while developing a nomogram. (Data shown is from the first 50 cases treated by Karl Stonecipher, MD.)

Dr. Reinstein says he rarely uses wavefront- or topography-guided ablations in primary surgery cases. (He prefers to use a wavefront-optimized ablation profile, unless there are significant corneal or whole-eye aberrations.) "The reason is that a primary LASIK treatment induces more aberrations than were present before the surgery in the vast majority of patients," he explains. "Therefore, it's more important to focus on controlling the induction of aberrations rather than trying to correct the nascent aberrations, which patients are neurally adapted to. Removing those may not always be a good idea."

He notes that some surgeons do claim to use this technology on all of their patients, and some report improved outcomes. "This could simply be because the base profile of the topography-guided system is better than the standard profile for the laser system they're using," he says. "For example, the topography-guided system might include an improved aspheric/peripheral energy correction function, relative to the currently used wavefront-guided or wavefront-optimized profile. It would not be surprising if this achieved better results than the standard profile."

• ***Don't alter the Q-value.*** One of the things a topography-guided treatment allows the surgeon to do is alter the Q-value, or sphericity, of the cornea. "In most cases, when you're doing a primary procedure on someone's eye, all the patient wants to do is see better," says Dr. Cummings. "In that situation you don't want to alter the Q-value. In a virgin eye, that's the Q-value the patient has always had. His brain is used to it and has learned to function well with it. In fact, one of the advantages of topography-guided treatments is that they tend to cause less of a change in Q-value than wavefront-guided or optimized treatments.

"When you load the data, the laser will tell you what the corneal asphericity is," he continues. "It will give you a Q-value such as -0.3. You want to program the ablation to keep the same Q-value. If you do a standard -3-D wavefront correction, where you're ablating 45 µm in the center and nothing at the edge, the treatment is going to induce some spherical aberration. If your Q-value before the procedure was -0.3, postoperatively it will probably be -0.2 or -0.15. But when using topography-guided ablation, you can target a postoperative Q-value of -0.3. This will help change the asphericity as little as possible. So, when setting up an ablation, make sure your target Q is the same as your presenting Q."

Dr. Cummings notes that if you're trying to treat a problematic eye that previously underwent refractive surgery, you might want to change the Q-value. "However, when you adjust the Q-value, you change the ablation depth and make the refraction less

accurate," he says. "With primary procedures, the one thing the patient wants is an accurate refraction. If you change the Q-value you're guaranteed to get a refractive surprise every time. Leaving the Q-value unchanged gives you your best chance of getting a very accurate result."

• ***Keep "tilt" turned off.*** "Many American surgeons will be using the Alcon Allegretto 400 Hz Eye Q to perform topographic treatments," says Dr. Cummings. "That laser defaults to the setting 'tilt on.' Tilt is a lower-order aberration that compensates for alignment; another way to think of it is as a prismatic correction. When tilt is turned on a procedure typically uses significantly more tissue than when tilt is turned off. So, if you're using the 400-Hz Eye Q, go to that box and unclick it. You don't want tilt as part of your ablation." (Dr. Cummings adds that, in contrast, the 500-Hz laser defaults to 'tilt off.')

• ***Educate staff and colleagues about this technology, not just patients.*** Dr. Stonecipher says it's crucial to educate those you work with—both inside and outside your practice—about the nature and advantages of this surgery. "You have to begin by educating your staff so they can answer patient questions," he says. "At the same time, you have to talk to your affiliates and colleagues and referrals."

Dr. Stonecipher notes that a surgeon's colleagues often don't understand the difference between topography-guided treatments and the other treatments. "If they confuse your patients, the whole point is lost," he says. "I tell them, this new technology not only improves a patient's quantity of vision but also quality of vision. It not only improves your spherical outcome, it improves how well you see, day or night, under low illumination and in different contrasts. Both patients with regular but asymmetric topography and unique corneal surface abnormalities can be treated with this technology.

"Of course, you need to make sure your patients understand this as well," he says. "This is particularly important if you're charging more for the procedure. For example, I might tell a patient, 'You can go to a store and buy an off-the-rack suit, but you may really need one that's tailored for you.' That's an analogy patients understand.

"Today," he adds, "most of our patients are contacting our practice through the Web, so our website has to have this information, too."

• ***Don't combine wavefront and topography-guided ablations.*** "The wavefront data contains the irregularities from the topography," Dr. Reinstein points out. "Combining them would mean treating the corneal irregularity twice."

The Learning Curve

Dr. Reinstein says that the learning curve when undertaking topography-guided ablation is relatively short if you're treating standard eyes. "This is essentially the same as doing a wavefront-guided treatment," he says. "You obtain a scan, import it and the software calculates the ablation based on this data. In contrast, the learning curve for treating therapeutic patients is quite long, but this is almost entirely about learning to select the appropriate patients. In other words, it's the diagnostic process that involves a significant learning curve."

"Alcon is putting together a group of previous users who participated in the clinical trials, an advisory panel to help train doctors," notes Dr. Stonecipher. "When you're being trained you'll go to Alcon to get the software and unlock Contoura. You'll be required to do an online assessment. Then a trainer will come and show you how to use it and which patients to choose, and help you get through your first cases. Alcon is doing everything they can to make sure this has a good outcome."

Dr. Reinstein believes that topography-guided ablation may have an impact on the future success of refractive surgery in general, particularly because of its ability to undo undesirable corneal effects that sometimes accompany laser refractive surgery. "I believe the main reason a majority of people still don't want to have refractive surgery done is that they're afraid that if something goes wrong we won't be able to fix it," he says. "The truth is, with the currently available custom ablation profiles based on wavefront aberrometry and corneal topography and our understanding of epithelial masking and the therapeutic use of transepithelial phototherapeutic keratectomy, we're able to repair the majority of irregular corneas. As this message spreads and more surgeons become comfortable diagnosing and treating therapeutic patients, I'm confident that this will be accompanied by an increased public confidence in laser eye surgery as a whole." REVIEW

Dr. Cummings is a consultant to Alcon Laboratories and WaveLight GmbH. Dr. Reinstein is a consultant to Carl Zeiss Meditec. Dr. Stonecipher is a consultant to Alcon.

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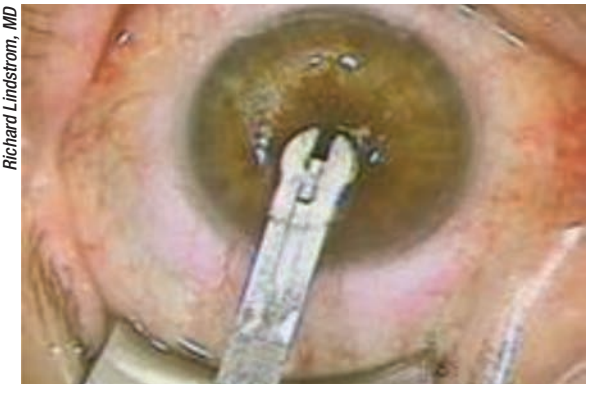
Update on Corneal Inlays for Presbyopia

Michelle Stephenson, Contributing Editor

One approved, two in trials, the inlays offer differing mechanisms of action.

Presbyopia is the most common refractive error and currently affects approximately 2 billion people worldwide.[1] Corneal inlays are one of the newest options for treating presbyopia, and their biggest advantage is that they are additive and do not remove any tissue. This allows patients to be treated with any advanced procedures that may be developed in the future.

"Emmetropic presbyopes are the hardest patients to treat," says John Hovanesian, MD, who is in private practice in Laguna Hills, Calif. "These patients have had good distance and near vision their entire lives and don't want to wear reading glasses. Most of these patients, typically the younger ones, have a bias against monovision, which would be the only other option."



Richard Lindstrom, MD

Figure 1. Presbia's insertion tool places the Flexivue Microlens into the pocket.

Currently, three corneal inlays are in various stages of development. The Flexivue Microlens (Presbia) is a refractive inlay that alters the index of refraction by using a bifocal optic. The Raindrop (ReVision Optics) is a reshaping inlay that changes corneal curvature, and the Kamra (AcuFocus) inlay, which was recently approved by the Food and Drug Administration, employs small-aperture optics to increase the depth of focus.

All are implanted in the nondominant eye. "All of the inlays are considered modified monovision, because they are all intended to be done in a single eye. One of the advantages of this is that you retain better distance vision while still gaining good near vision," says Richard Lindstrom, MD, who is in private practice in Minneapolis.

Each of the inlays has advantages and disadvantages. "One of the advantages of all of the inlays is that they are removable and, for the most part, reversible. It's not like a corneal laser procedure, which creates a multifocal corneal shape that is irreversible," adds Michael Gordon, MD, who is in private practice in La Jolla, Calif.

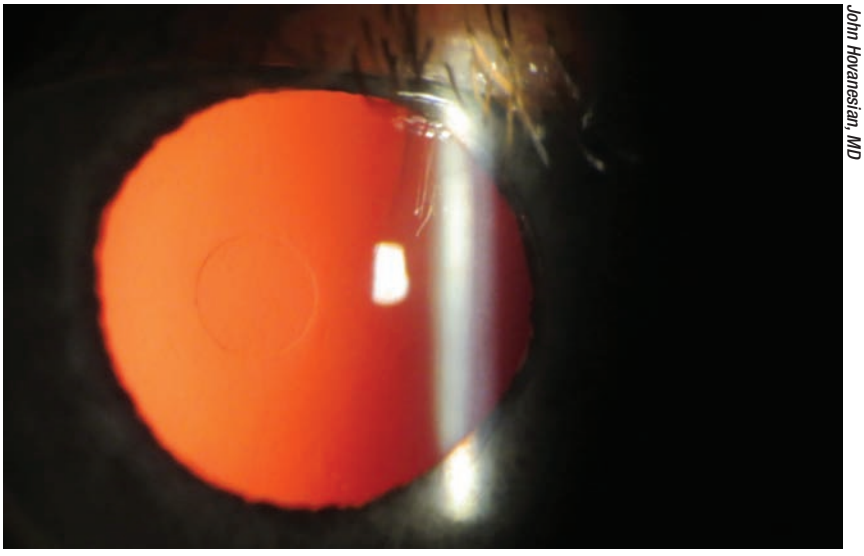
This article has no commercial sponsorship.

Flexivue Microlens

The Microlens is a transparent, hydrogel-based, concave-convex lens. It has a plano central area to provide distance vision, surrounded by rings with different add powers to provide intermediate and near vision. It is 3 mm in diameter and 15 to 20 µm thick, depending on the additional power. The central 1.8 mm diameter is plano, and the inlay power ranges from +1.25 to +3.0 D in 0.25-D increments. There is a 0.15-mm hole at the center of the inlay that facilitates oxygen and nutrient transfer into the cornea. This inlay is placed in a pocket created in the cornea using a femtosecond laser.

In a study conducted in Greece, 47 patients were implanted with the Flexivue Microlens and were followed for 12 months.[2] One year postoperatively, patients' mean uncorrected near visual acuity significantly improved from 0.68 ±0.03 logMAR to 0.14 ±0.9 logMAR in the operated eyes and from 0.53 ±0.13 logMAR preoperatively to 0.13 ±0.13 logMAR binocularly. UCNVA of the operated eyes was 20/32 or better in 75 percent of patients 12 months after inlay implantation, and mean uncorrected distance visual acuity in operated eyes significantly decreased from 0.06 ±0.09 logMAR preoperatively to 0.38 ±0.15 logMAR, but it did not change significantly binocularly.

Dr. Gordon participated in Flexivue's clinical trial. "We have had great success with the Flexivue in my hands in the clinical trial," he says. "Most people love it. We are seeing great patient acceptance. They are reading glasses-free. They do not have issues driving at night from glare. The beauty is that it is a refractive inlay, meaning that it comes in powers. Younger presbyopes can have a lower-power implant. As these patients get older, the lower-power implant can be removed, and a higher-powered one can be implanted. The Flexivue has a lot of potential, I believe, and is probably 1.5 years away from approval. It's reversible. It's upgradable. It's very well-tolerated, and it's easy to implant. I have been impressed with the Flexivue both as a product and as a surgical procedure."



John Hovanesian, MD

Figure 2. The Raindrop inlay.

Raindrop

This corneal inlay is a clear, permeable, positive meniscus-shaped hydrogel implant with a diameter of 2 mm, a center thickness of 32 µm, and approximately the same refractive index as the cornea. While it has no refractive power, it alters the eye's refractive power by increasing the central radius of curvature of the part of the cornea overlaying the implant. It is thinner at the edge than it is at the center, so when implanted, it creates a hyperprolate corneal shape, which results in a multifocal cornea. Oxygen and nutrients freely pass through the highly permeable hydrogel material used for the inlay.

Two studies have been conducted recently, and both used keratotomy to create a flap with a diameter greater than 8 mm and a depth of 130 to 150 µm using a femtosecond laser.[3,4] An inserter for the Raindrop inlay is provided by the manufacturer, and the inlay is placed on the stromal bed and correctly positioned over the center of the pupil. Then, the flap is replaced over the inlay.

In one study, 19 presbyopic emmetropes were implanted with the inlay, and 12-month postoperative results were reported.[3] All patients achieved UCNVA of 0.2 logMAR or better in the operated eye. Mean UCNVA was better than 0.1 logMAR at all visits, including the final follow-up after 12 months. Additionally, all patients achieved a binocular UCNVA of 0.18 logMAR or better. By one month postoperatively, the mean binocular UCDVA was 0.01 logMAR and remained at this level or better until 12 months postoperatively.

Mean photopic contrast sensitivity in the eye with the inlay was similar to preoperative levels at both the six-month and 12-month follow-up visits.

All participants in this study completed a patient questionnaire concerning spectacle wear and satisfaction. Twelve months after implantation of the inlay, 95 percent of patients said that they were satisfied or very satisfied with their near and intermediate vision. All patients reported that they were very satisfied with their distance vision and the overall visual outcome.

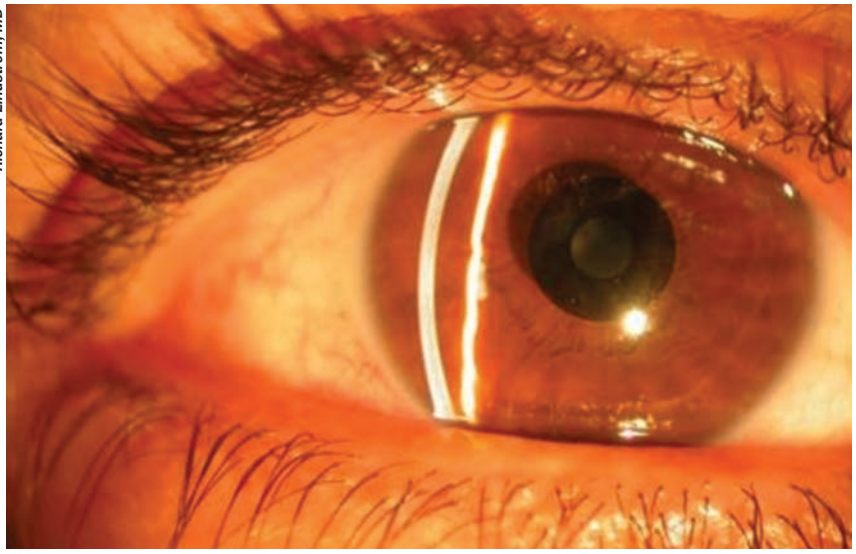

Richard Lindstrom, MD

Figure 3. The Kamra inlay.

Additionally, 84 percent reported rarely, if ever, wearing glasses.

The second study included 16 hyperopic presbyopic patients who were implanted with the Raindrop inlay immediately after laser corneal correction of the hyperopia.[4] Mean UCNVA in the implanted eye was 20/21 (Snellen) ±0.04 (logMAR) after 12 months, and mean uncorrected intermediate visual acuity was 20/26 ±0.07. Uncorrected distance visual acuity was 20/31 ±0.14 after 12 months, and mean binocular UCNVA was 20/21 ±0.03 after 12 months. Additionally, mean binocular UCIVA was 20/26 ±0.08, and mean UCDVA was 20/19 ±0.11 after 12 months.

Patient satisfaction questionnaires were also completed by all patients in this study. Fourteen of the 16 patients said that they were satisfied or very satisfied with their near, distance and overall vision.

"The Raindrop has finished clinical trials, and data are being submitted to the FDA," Dr. Lindstrom says. "It works similarly to presby-LASIK. There is some loss of distance vision with this approach, and it looks like you only lose a line or two at distance and you gain three to four lines at near, so it is a reasonable trade-off. It has similar advantages and disadvantages to a multifocal IOL or contact lens, so most eye doctors are familiar with the optics."

Kamra

The Kamra is currently the only FDA-approved corneal inlay. The current version is a 5 µm thin microperforated artificial aperture made of polyvinylidene fluoride with incorporated nanoparticles of carbon. It has a total diameter of 3.8 mm and a central aperture of 1.6 mm. The inlay has 8,400 holes that range in size from 5 to 11 µm in diameter to allow water and nutrition flow to prevent corneal thinning and epithelial decompensation.

The Kamra inlay is based on the pinhole effect, and it increases depth of focus and consequently improves near and intermediate visual acuity. Because it doesn't split light between near, intermediate and distance focal points, patients maintain their binocular summation even though the inlay is only implanted in the nondominant eye.

Currently, the inlay is implanted in a lamellar pocket created with a laser that is 220 µm or deeper. Creating a pocket with a femtosecond laser reduces the impact on corneal nerves and reduces the risk of dry eye postoperatively.

Minoru Tomita, MD, PhD, of the Shinagawa LASIK Center, Tokyo, and colleagues have conducted two large studies using the Kamra inlay.[5,6] One study included 223 eyes in 223 patients who had previously undergone LASIK and then were implanted with the current version of the Kamra inlay.[5]

The patients' mean age was 53.6 years (range: 44 to 65 years), and mean manifest spherical equivalent was –0.18 D (range: –1.00 to +0.50 D). The mean UCDVA in the operated eye decreased from 20/16 preoperatively to 20/20 after the inlay had been implanted for six months. Mean UCNVA improved from J8 to J2. Patients' dependence on reading glasses and their satisfaction with vision without reading glasses significantly improved by six months postoperatively.

An earlier study conducted by Dr. Tomita and colleagues included 360 eyes in 180 patients who underwent simultaneous corneal inlay implantation and LASIK to treat presbyopia in patients with hyperopia, myopia or emmetropia.[6] Preoperative UCDVA and UCNVA were significantly different between the three groups of patients, while no significant difference was seen six months postoperatively.

Hyperopic presbyopic patients had an improvement of three lines in UCDVA and seven lines in UCNVA at six months after implantation. Emmetropic presbyopic patients had an improvement of one line in UCDVA and six lines in UCNVA, and myopic presbyopic patients had an improvement of 10 lines in UCDVA and two lines of UCNVA.

Postoperatively, patient satisfaction with regard to spectacle independence and overall vision was significantly increased in hyperopic and emmetropic patients. However, it was not significantly increased in myopic patients

who had good UCNVA preoperatively.

"The Kamra uses small-diameter aperture optics and hyperfocality," Dr. Lindstrom says. "This is basically the optical system that is used in a disposable camera that allows a decent picture at distance, intermediate and near. The eye needs to be set slightly myopic. The ideal target for the Kamra would seem to be -0.75. You get a close to 3-D increase in depth of focus, which allows functional distance, intermediate and near vision. The negative is that if you use small-diameter aperture optics in a dusky mesopic environment, you still have a small aperture, so things are dimmer in a low-light environment. You need significant light for this system to operate well. That's why you only do it in one eye."

"One consideration with this implant is that it is dark in color," Dr. Hovanesian adds. "If it is centered over the pupil, it looks beautiful, but in lighter-colored eyes when viewed from the side, sometimes it can show. It works very well in terms of achieving near vision while not too badly degrading distance vision."

He also explains that all three implants have some need for follow-up, and the follow-up care for these patients is not as simple as with LASIK. "You need to be watchful for signs of intolerance or signs of dry eye, and there is an explant rate of about 10 percent. This is better than LASIK because our alternative to this procedure is to just give a patient monovision, and of course monovision degrades the patient's distance vision in the treated eye," he says.

Although the three inlays have different mechanisms of action, they all look promising. "All of these approaches work," Dr. Lindstrom says. "Each one arguably has some features that one doctor might like over another. I'm an advocate of all of these. I'd love to see them all get approved." REVIEW

Dr. Gordon is an investigator for Presbia and serves on its Medical Advisory Board. Dr. Lindstrom is a board member at AcuFocus. Dr. Hovanesian is an investigator for ReVision Optics.

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- Analyze new research that illustrates the key role that inflammation plays in the genesis of DME and macular edema secondary to RVO.
- Engage in discussions related to emerging issues in glaucoma, including risk assessment, imaging, management and progression assessment.
- Manage glaucoma using newer pharmaceutical agents.
- Discuss the newest glaucoma surgical devices, including those used in patients undergoing cataract surgery.
- Utilize advanced technologies and techniques in refractive cataract surgery, including femtosecond laser and new ultrasound fluidics.
- Master advanced technology IOLs, improving patient selection, surgical technique and postoperative management.
- Outline current management techniques for ocular surface diseases such as dry eye and keratitis.
- Discuss the rationale for anti-VEGF therapy and steroids in posterior segment diseases including age-related macular degeneration and diabetic macular edema.
- Navigate issues relating to patient compliance/adherence with eye-drop medications.
- To understand the facial aging process and gain knowledge of possible treatments for rejuvenation.

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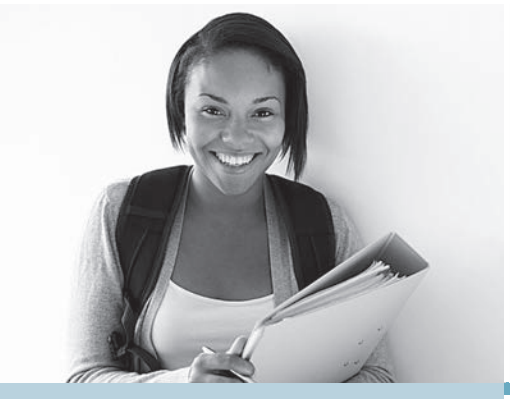

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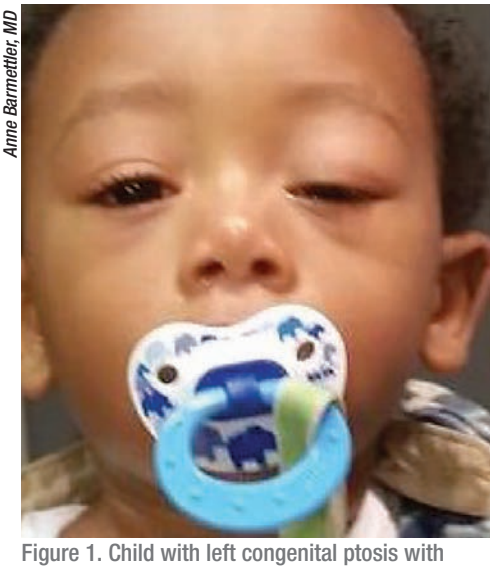
Ptosis: Diagnostic Tips & Surgical Options

Congenital blepharoptosis can occur in isolation or in conjunction with other ophthalmic and systemic findings.

Janice Liao, MD, New York City

Congenital blepharoptosis, or ptosis, is defined as an abnormally low upper eyelid noted within the first year of life. There is no gender or racial predilection. The exact incidence is unknown, although in the United States, Gregory Griepentrog, MD, and colleagues reported an incidence of childhood ptosis of 7.9 per 100,000 in Olmstead County, Minn., over a 40-year time period, with 90 percent presumed to be congenital.[1] In a large population-based study in China, Dr. Dan-Ning Hu and colleagues reported a 0.18-percent incidence of congenital ptosis out of nearly 250,000 patients examined.[2] Because these studies were done in relatively homogeneous populations, however, the results should not be extrapolated to racial/ethnic groups.

The majority of congenital ptosis is unilateral, and it can occur as an isolated phenomenon or in association with other ocular or systemic findings.[1,3-8] Although the etiology is classically thought to be myogenic in nature, more recent reports have suggested that disordered innervation during embryonic development may be the underlying cause.[6] Additionally, Mohammed Alshehri, MD, and colleagues examined Müller muscle in a series of 12 patients with congenital ptosis and found structural abnormalities compared to six control patients with aponeurotic ptosis.[9] Several genes have been implicated in isolated congenital ptosis, including autosomal dominant inheritance and X-linked dominant inheritance.[3,6] Congenital ptosis can be associated with Blepharophimosis, ptosis, and epicanthus inversus (BPEI) syndrome; Duane Retraction syndrome; congenital fibrosis of the extraocular muscles; Marcus-Gunn jaw-winking syndrome; Congenital Horner's syndrome; and strabismus, among others.[1,3-8]



Anne Barmettler, MD

Figure 1. Child with left congenital ptosis with absent left upper lid crease, using compensatory chin-up position.

Evaluation

Take a thorough history on every child who presents with ptosis. Inquire about the age of onset and any fluctuations or progression, pupil asymmetry, motility or alignment abnormalities, trauma or allergic reactions. Additional history should focus on medical history, including birth and development, family history and review of systems. Photographs of the child at a younger age or of family members may be helpful.

On examination, first observe the child, looking for anomalous head position, including compensatory chin-up position, and spontaneous frontalis use *(See Figure 1)*. Obtain visual acuity and cyclo-

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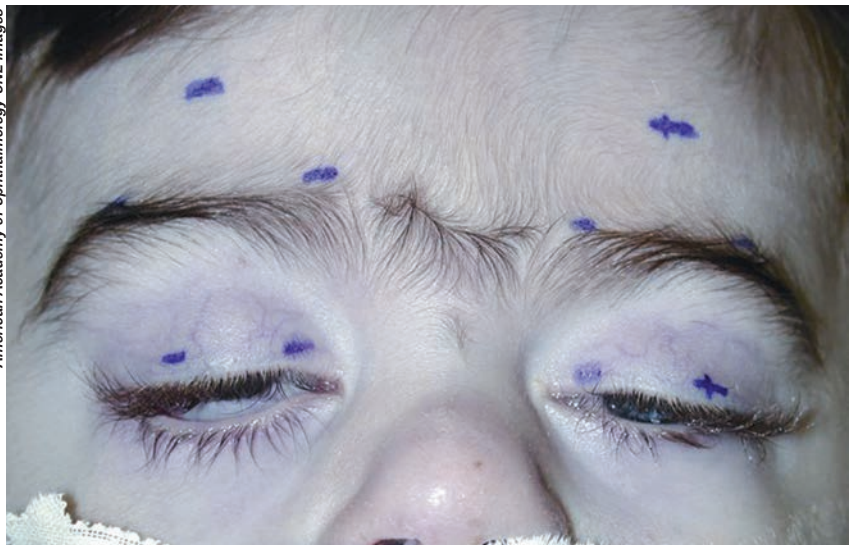
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Figure 2. Patient with bilateral congenital ptosis, marked for frontalis sling in pentagonal pattern.

plegic refraction, and assess pupils, looking for anisocoria, motility and alignment. With the head in neutral position, the frontalis immobilized to maintain the brow in normal anatomic position, and the patient fixating at distance, hold a ruler vertically next to the eye. Measure the distance between the upper lid margin and the corneal light reflex to the nearest 0.5 mm for margin reflex distance (MRD)1, and the distance between the lower lid margin and the corneal light reflex for MRD2. Ptosis is considered mild at ≤2 mm, moderate at 3 mm and severe at ≥4 mm, as classified by Crowell Beard, MD.[15]

In the same position, with the frontalis fixated, measure levator function in mm as the excursion of the upper lid margin from maximal downgaze to maximal upgaze. Levator function is subdivided into excellent (≥13 mm), good (8 to 11 mm), fair (5 to 7 mm), and poor (≤4 mm).[7,10] Look for lid lag—poor movement of the lid with the globe—in downgaze. In unilateral cases, the ptotic side will often be higher in downgaze due to poor motility of the fibrotic levator muscle. Assess frontalis function and the amount of lagophthalmos.

Consider Hertel exophthalmometry if pseudoptosis secondary to contralateral proptosis is a concern, although this can be difficult in young children. Proptosis can be assessed grossly from a worm's eye view. Palpate the eyelids and orbital rims for masses, and examine the lids for erythema or edema and lid crease. The lid crease is often poorly formed or absent with congenital ptosis, in contrast to the higher lid crease typically seen with involutional aponeurotic ptosis.

Determine whether the patient has an intact Bell's phenomenon, as a poor Bell's phenomenon increases the risk of exposure keratopathy after surgical intervention. A complete anterior segment exam, especially of the tear lake, corneal surface integrity and iris coloration, and dilated fundus exam should be completed as well.[7]

Differential Diagnosis

The differential diagnosis includes traumatic ptosis; mechanical ptosis; neurogenic ptosis; aponeurotic ptosis; myasthenia gravis; blepharochalasis; chronic progressive external ophthalmoplegia; preseptal or orbital cellulitis; allergic dermatitis; orbital mass; conjunctivitis; corneal foreign body or ulcer; and pseudoptosis.

Management

Congenital ptosis is most concerning for its amblyogenic potential, due to visual axis obstruction, anisometropia or associated strabismus. Various studies have reported amblyopia incidences of 14 to 48 percent for all types of congenital ptosis.[11] However, parents may also be concerned due to poor cosmesis and subsequent psychosocial effects. If amblyopia is minimal or responds well to occlusion or penalization therapy, and the child can compensate with either frontalis use or mild chin-up position, surgery is typically delayed until age 4 to 5. At this age, the upper face and frontonasal complex growth is complete, and more accurate measurements can be obtained.[12] However, if amblyopia worsens, the patient is noncompliant with amblyopia therapy, compensatory mechanisms do not develop, or the chin-up position is excessive or interferes with mobility, surgery is performed sooner.[12]

Surgical Options

The surgical method depends on both the severity of ptosis and the amount of levator function. Several common options will be discussed; the Fasanella-Servat procedure and the Müller muscle-conjunctival resection will not be covered here as they are most useful in mild ptosis with good levator function, which is not characteristic of most cases of congenital ptosis. Congenital ptosis as part of syndromes such as BPEI and Marcus-Gunn jaw-winking syndrome require more complicated surgical planning and are outside the scope of this article.

Frontalis Sling

Frontalis sling is one of the most commonly used operations for poor levator function. The upper lid is linked to the frontalis, such that contracting the frontalis will simultaneously elevate the lid. There are multiple variations in technique. The sling can be placed in pentagon *(See Figure 2)*, single-triangle, or double-triangle configuration via supraciliary stab incision or lid crease incision.[3,7] The material can be sutured to the tarsal plate, which was recently found by Dr. Ibrahim Bulent Buttanri and colleagues to produce a higher success rate than unsutured silicone rods, with a non-statistically significant higher success rate using braided polyester versus monofilament polypropylene.[13]

The material for suspension can also vary, including autogenous or banked fascia lata; silicone rods; polyester; collagen; silk; stainless steel; monofilament nylon; polytetrafluoroethylene; and polypropylene.[3] Some surgeons consider autogenous fascia lata the best material, due to its biocompatibility and longevity, although it requires a second surgical site and patients must be at least 3 years old to provide a graft of adequate length.[3] Banked fascia lata, although felt to be a good alternative to autogenous fascia lata, has a long-term success reported only around 50 percent, possibly due to early resorption.[14] Silicone rods are one of the most frequently used alloplastic material as their elastic nature allows both for good eyelid height *(See Figure 3)* and complete eyelid closure, although as with all alloplastic materials, there is a risk of infection, inflammation, granuloma formation and extrusion.[3,14]

Overall, the frontalis sling is considered effective and well-tolerated, and has the advantage of being adjustable postoperatively, depending on the material used. In addition to those mentioned above, potential risks include lagophthalmos, lid crease distortion and poor lid-globe apposition.

Levator Resection, Advancement

Levator resection and advancement can be considered in patients with levator function ≥5 mm.[3,7] Levator resection can be approached either anteriorly or posteriorly, although the anterior approach provides better exposure and the ability to reform the lid crease, and allows for greater degrees of levator resection.[7] After the levator is exposed, it is either plicated or resected, then sutured to the tarsal plate with partial-thickness bites, typically with nonabsorbable sutures.[3,7] The sutures can be initially tied in temporary fashion and adjusted to the desired contour and height. There are various methods to calculate the amount of levator to resect. Intraoperatively, you can set the upper lid margin at the superior corneal limbus for severe ptosis and mid-pupil for mild ptosis with good levator function.[7] Alternatively, quantitative algorithms have been published based on the severity of ptosis and degree of levator function, including a simple recommendation to resect 4 mm of levator for every 1 mm of ptosis.[3] Of note, some surgeons will still use a levator resection, with or without a tarsectomy, for patients with severe ptosis and poor levator function, with reported good success.[3]

Whitnall Sling

The Whitnall sling procedure involves maximal levator resection, up to Whitnall's ligament, combined with suturing of the superior tarsal edge to Whitnall's ligament with either absorbable or non-absorbable sutures. It can be used in cases of moderate to severe ptosis with poor to fair levator function.[3,7] A superior tarsectomy can be performed as well, with an estimated 1 to 1.5 mm of additional lid elevation expected from a 5-mm resection.[3] This is often recommended as cases of isolated Whitnall sling have been reported to have a high incidence of late undercorrection.[3] However, patients

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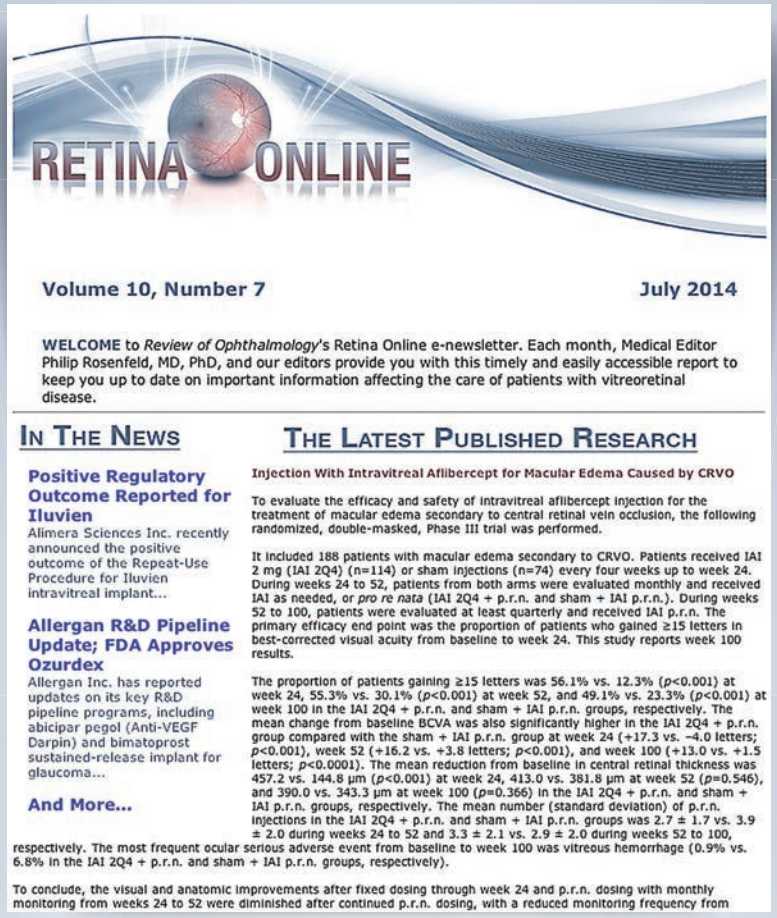

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THE LATEST PUBLISHED RESEARCH

Injection With Intravitreal Aflibercept for Macular Edema Caused by CRVO

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

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

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

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

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REVIEW® of Ophthalmology

Anne Barmettler, MD

Figure 3. A child with left congenital ptosis status post left frontalis sling, with improved left eyelid position and presence of lid crease.

with maximal or supermaximal levator resection commonly have significant lagophthalmos in the immediate postoperative period and must be counseled on frequent lubrication.[7]

Modified Tarsal Resection

An alternative for patients with fair levator function is a modified tarsal resection with graded levator advancement, as described by Sarit Patel, MD, and colleagues. From an anterior approach, the levator aponeurosis is exposed and disinserted from the tarsus, then separated from Müller muscle. The anterior face of the tarsus is exposed. A predetermined amount of tarsus and Müller (in a 1:2 ratio) to be excised is marked, depending on the amount of ptosis, then tarsus, Müller muscle and conjunctiva is resected en bloc. The inferior edge of Müller muscle and conjunctiva is then advanced to the new superior tarsal border with absorbable sutures. Levator aponeurosis is then advanced to the anterior face of the tarsus and adjusted to set the upper lid margin at the superior corneal limbus. All patients had mild lagophthalmos in the immediate postoperative period only, with good results in 25 of 30 patients (30 of 36 lids).[10]

Congenital ptosis can occur in isolation or in conjunction with other ophthalmic or systemic findings. It can be both amblyogenic and a cause of psychosocial distress. Although some cases can be monitored and managed with amblyopia treatment until the child is older, surgery should be done sooner for worsening amblyopia or compensatory positioning that is excessive or interferes with function. Because the levator muscle is often anomalous and poorly functioning, surgical management can be challenging and should be approached on a case basis. REVIEW

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Real-World Utilization of Anti-VEGF Agents

How 'real world' clinical experience with anti-VEGF drugs in treating three FDA-approved indications differs from clinical trial results.

Tom Berenberg, MD, and Szilárd Kiss, MD, New York City

Anti-vascular endothelial growth factor agents have become the standard of care for the treatment of neovascular age-related macular degeneration, retinal vein occlusions and diabetic macular edema. Pivotal clinical trials have shown dramatic improvements in vision associated with anti-VEGF agents and, correspondingly, the clinical utilization of anti-VEGF agents has trended upward.[1] However, despite the abundance of evidence that more frequent injections lead to the best visual outcomes, clinicians are, on average, treating patients substantially less frequently. This article will review "real-world" usage of anti-VEGF medications for three Food and Drug Administration-approved intravitreal indications: AMD; RVO; and DME.

AMD

Anti-VEGF therapy was first approved for intraocular use in neovascular age-related macular edema. Ranibizumab was initially approved in the United States for neovascular AMD in 2006, the same year as the pivotal ANCHOR[2] and MARINA[3] trials were published. These large prospective trials reported that monthly ranibizumab injections led to +11.3 and +7.2 Early Treatment of Diabetic Retinopathy letter gains overall at 12 months, respectively. Less-frequent injection dosing in PIER,[4] which dosed patients monthly for three months and then quarterly up to month 12, revealed an initial +4.3-letter improvement at month three then a total -0.2 decrease by month 12 after less-frequent dosing was initiated. Similarly, in EXCITE,[5] less-frequent dosing led to fewer letter gains compared to the pivotal Phase III trials. Patients in EXCITE were treated monthly for the first three months then switched to quarterly dosing or maintained on monthly dosing. Those remaining on monthly ranibizumab dosing for the 12 months achieved +8.3 letters versus the two quarterly groups, which gained +4.9 and +3.8 letters.

The two-year CATT data appear to support the findings of less-frequent injections resulting in fewer letters gained. In CATT, patients reassigned from monthly to PRN administration after the first year had a reduction in vision (-1.8 letters in the ranibizumab group and -3.6 letters in the bevacizmuab group; p=0.03) compared with patients that continued on the monthly regimen.[6,7] Monthly regimens in the ranibizumab and bevacizumab groups led to gains of +8.8 letters and +7.8 letters at 24 months, respectively, versus +6.7 and +5.0 letters in the p.r.n. groups. Compared to a maximum of 26 injections in the fixed monthly dosing, p.r.n. groups averaged 12.6 treatments and 14.1 treatments over the two years. The IVAN[8] and HARBOR[9] prospective trials also revealed small visual acuity differences between the monthly and p.r.n. groups (<three letters), which were not statistically significant.

Despite the data in the literature of the apparent benefit of frequent anti-VEGF dosing, large retrospective analyses of claims from that time period show an apparent under-utilization of anti-VEGF agents.[1,10,11] Nancy Holekamp, MD, and colleagues analyzed United States claims data from 2006 to 2010

This article has no commercial sponsorship.

for ranibizumab and bevacizumab use for neovascular AMD.[1] In the 2006 and 2007 cohorts (n=8,767), mean annual numbers of bevacizumab or ranibizumab injections were 4.7 and 5.0 respectively. In the 2008 to 2010 cohorts (n=10,259), mean annual numbers of injections were 4.6, 5.1 and 5.5 for bevacizumab; and 6.1, 6.6 and 6.9 for ranibizumab. In an international real-life utilization study, the mean injection numbers in Canada, France, Germany, Ireland, Italy, the Netherlands, the UK and Venezuela were also lower than in the large prospective clinical trials.[10] Data from 2009 to 2011 were analyzed in these eight countries for 2,227 patients with neovascular AMD. Overall, patients received a mean of 5.0 injections in the first year of treatment and 2.2 injections in the second year. This corresponded to a mean change in visual acuity of +2.4 and +0.6 letters in years one and two, respectively. Of note, this study suggests that in countries where patients received more frequent injections, the visual acuity gain was higher. This ranged from the lowest-ranking country, Italy, with a net loss of -2.1 letters at year two (zero gain at year one) with a two-year mean of 5.2 injections to the highest-ranking country, the UK, with a net gain of +4.1 letters at year two (+6.0 letters at year one) with a two-year mean of 9.0 injections.

Additionally, clinicians are seeing neovascular AMD patients and ordering diagnostics tests much less frequently than in the clinical trials.[11] In an analysis of more recent U.S. claims data, while the mean number of injections increased from 2008 to 2010, less than 23 percent and less than 40 percent of patients had at least 10 annual ophthalmologist visits in the bevacizumab and ranibizumab-treated patients, respectively. Less than 14 percent and less than 21 percent of patients had at least 10 optical coherence tomography scans in these respective groups for the 2010 cohort. These real-world data reveal that patients are being seen less frequently, are receiving fewer injections, and are gaining fewer letters than patients in the prospective clinical trials.

Despite mounting evidence that monthly monitoring and more frequent injections lead to better and more sustained visual outcomes, practitioners are underutilizing anti-VEGF therapy in patients with neovascular AMD, RVO and DME.

RVO

Ranibizumab was FDA-approved for use in central retinal vein occlusion and branch retinal vein occlusion in 2010. The use of monthly anti-VEGF when compared to the standard-of-care (observation for CRVO and focal laser as needed for BRVO) in RVO was associated with significant improvement in visual acuity in both the BRAVO[12] and CRUISE[13] studies. In both studies, patients received either sham injections or monthly ranibizumab dosing (0.3 mg or 0.5 mg) for the first six months followed by p.r.n. dosing. Vision improved by +16.4 and +18.3 letters in the BRAVO treatment groups compared to +12.1 in the sham group, with an average of 8.4 injections in the 12 months. In the CRUISE study, vision improved by +13.9 letters in both dosing arms of the treatment groups versus +7.3 letters in the sham group with an average of 8.8 injections administered. Although fewer pivotal trials were conducted in RVO than in neovascular AMD, data from the extension phases of BRAVO, CRUISE and HORIZON[14] suggests a similar association between dosing frequency and visual improvement.

In a claims analysis from 2008 to 2011, a total of 885 BRVO and 611 CRVO patients were included. In the 2008, 2009 and 2010 cohorts, mean annual injections were 2.5, 3.1 and 3.3 for BRVO and 3.1, 3.1 and 3.5 for CRVO respectively.[15] Visual acuity data for this claims analysis is not available; however, patients clearly received less frequent dosing than suggested by the results of BRAVO and CRUISE. In addition, patients in these cohorts saw their ophthalmologists infrequently, averaging between 5.1 to 5.6 visits in the BRVO groups and 5.8 to 6.5 visits for the CRVO patients.

DME

Anti-VEGF therapy was approved for the treatment of diabetic macular edema in 2012 and therefore, we have the least understanding of its real-world clinical utilization. Nevertheless, the same pattern of apparent underutilization can be seen when clinical use data is compared to prospective pivotal trial data. As with AMD and RVO, large studies for anti-VEGF therapy in DME also suggest that better visual acuity comes with more frequent injections. RESOLVE,[16] RISE/RIDE[17] and DRCR.net protocol T[18] used more frequent injection regimens and achieved greater mean numbers of letters gained over 12

months compared to studies like RESTORE[19] or DRCR.net Protocol I[20] with less-frequent p.r.n. dosing regimens. In RESOLVE, there was an average of 10.2 injections with a +10.3-letter gain (-1.4 letters for sham group). RISE/RIDE had monthly injections with +10.9 ±12.5 letter gain versus +2.3 ±2.6 for the sham groups. DRCR.net protocol T averaged between nine and 10 injections across the aflibercept, bevacizumab and ranibizumab groups with overall letter gains ranging from +9.7 to +13.3.

By contrast, RESTORE patients averaged 6.8 to 7.3 injections with a +6.4 to +6.8 letter gain versus +0.9 for the laser alone group. While in DRCR.net protocol I, patients in the injection or injection plus prompt laser averaged nine and eight injections respectively, with a +9.0 letter gain in both groups.

In analyses of real-world data, the mean number of injections for DME appears to be considerably less than the prospective trials. A claims analysis revealed between 2.2 and 3.6 injections per year for newly diagnosed DME patients.[15] These numbers are in stark contrast to the mean numbers in the large clinical trials noted above. Furthermore, only 31.2 percent of patients with newly diagnosed DME received three or more injections in the first four months of treatment.[15] Again, the real world use of anti-VEGF medications is substantially less than in clinical trials.

Reasons for Underutilization

There are many factors that may contribute to the lower numbers of injections and office visits seen in clinical practice when compared to prospective studies. Patients in a clinical practice may be inherently different from those enrolled in large clinical trials. The stage of the disease in patients treated in the real world may not be comparable to that in the trials. Practitioners may also be slow to adopt increased dosing regimens, and the claims data analyzed for the clinical utilization data may subsequently capture this lag.

In addition, treatment burden for patients and their caregivers may also play a large role. Many of these patients, especially those with vascular diseases like diabetes or hypertension, have numerous doctors' visits each year and therefore are not willing or able to see their ophthalmologist on a monthly or close to monthly basis.[21] Additionally, there are some studies that have shown that extended treatment protocols, such as treat-and-extend for neovascular AMD, may provide comparable results to monthly retinal evaluations and anti-VEGF injections.

Despite mounting evidence that monthly monitoring and more frequent injections lead to better and more sustained visual outcomes, practitioners are underutilizing anti-VEGF therapy in patients with neovascular AMD, RVO and DME. This underscores the need for further innovation to reduce the burden on patients, caregivers and the health-care system associated with treatment of these disorders. In the future, perhaps sustained-delivery devices or gene therapy may provide a means for reducing office visits and intravitreal injections without sacrificing visual outcomes. REVIEW

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Wintering with Ocular Allergies

A look at the attributes of perennial allergy and therapies designed to combat the chronic inflammation it engenders.

Mark B. Abelson, MD, CM, FRCSC, FARVO, Paul Gomes, and Connie Slocumb, PhD, Andover, Mass.

Although winter can be the season of relief for many who are affected by the allergens that accompany the warmer months of the year, for others it provides no respite. Even worse, many of these patients know that winter allergies represent just one of four seasons of chronic, perennial allergic conjunctivitis. But patients with allergies in winter are an important population for those of us who are concerned with ocular allergy. Not only do they suffer with allergic symptomologies throughout the winter, but these are also the patients most likely to have the most severe responses to summer allergens as well. They're also a population most likely to exhibit a resistance to the current therapies, so they represent a significant unmet therapeutic need. Effective treatments for these patients represent a holy grail of ocular therapeutics.

This month, we examine the attributes of our patients with perennial allergy, and review current and potential therapies that are designed to combat the chronic inflammation often associated with these individuals' allergic response to persistent allergens in their environment.

Dust Mites and Animal Dander

Seasonal allergies such as hay fever are a boom-and-bust process, with symptoms rising and falling with the pollen counts for spring birch, summer grass and fall ragweed. The allergens of winter are, in contrast, omnipresent throughout the year: dust mites; cockroaches; and animal dander. Although avoidance may be a useful strategy for evading seasonal allergens, it is less likely to be achievable for perennial allergens, especially during the winter season. Decreased temperatures during the winter result in an increased amount of time indoors, less exchange of indoor air and, consequently, an increase in exposure to allergens. Use of aggressive hygiene approaches to minimize environmental exposure to these allergens (in particular, to dust mites) hasn't proven to be an effective strategy.[1] Thus, unlike the periodic spikes in seasonal allergens where avoidance can mitigate the level of exposure, the constant presence of perennial allergens results in continual priming of the allergic response, altering the immune reaction to future exposures and leading to a chronic inflammatory state.

In an acute response, high concentrations of allergens such as seasonal pollens trigger IgE-mediated degranulation of mast cells, causing a release of histamine and other pro-inflammatory mediators; these activate local histamine receptors and initiate the classic hyperemia and pruritus responses of AC. Antihistamines act as direct, pharmacological antagonists of these responses.[2] In contrast, a chronic AC elicited by continuous exposure to lower levels of allergen involves recruitment of secondary immune cells and a more extensive inflammatory response. Under these conditions physical barriers to allergens become compromised, and subsequent allergen exposures elicit an exacerbated response; proteolytic activity expressed by many common perennial antigens may play a role in this process.[3]

Recent evidence has also provided clues to prevalence of perennial parasite allergy: Significant similarities in epitopic-like regions (the epitope is the part of an antigen that's recognized by the immune system) in parasite proteins and the most common allergenic protein domain families provide an explanation for off-target effects of

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IgE-mediated immune reactions.[4] It may be that in the absence of infection, the highly specialized immune system components that have evolved to combat the effect of metazoan parasites switch to a collateral mode, becoming hyper-responsive to similar proteins such as dust mite group II allergens, Der p 2 and Der f 2 which, in turn, share structure homology with some components of grass expansin allergens.[5]

Chronic mite and animal dander exposure is the most common source of perennial ocular allergies. Continuous activation and degranulation of mast cells activate cellular-mediated inflammation, structural cells of the corneal and conjunctival epithelium, vascular endothelial cells and fibroblasts. All of these components amplify initial responses and alter future immune responses by priming the antigen recognition sites on dendritic cells. Up-regulation of adhesion molecules on the conjunctival epithelium results in infiltration of eosinophils, neutrophils and lymphocytes into the conjunctiva, leading to subsequent cascades of inflammatory mediators that characterize the persistent clinical inflammation of chronic allergic conjunctivitis. Perennial allergies thus can constitute a perfect storm of ocular distress, a vicious cycle in which the continuous exposure to allergens prevents reestablishment of a healthy conjunctival barrier.[6]

Therapies

Currently, the only potent anti-inflammatory agents available to treat the chronic inflammation associated with PAC are topical corticosteroids, particularly glucocorticoids used for the treatment of severe or chronic ocular allergy.[2] Although traditional topical glucocorticoids such as dexamethasone and prednisolone are known to be highly effective, the potentially serious adverse side effects of ocular hypertension, glaucoma and cataracts limit their use to short-term therapy for only the most severe forms of AC.[5] It's generally thought that a two to three week course of steroid therapy is required to break the chronic allergic cycle, but patients will be susceptible to bacterial or viral infections during that time. Newer-generation compounds are preferred over older GC agonists; these so-called "soft steroids" are designed to have a reduced biological half-life, allowing for a more precise timed delivery of therapeutic. For example, loteprednol has an ester bond replacement, causing it to be labile to conversion to an inactive metabolite, yielding a shorter therapeutic half-life and a more focused treatment window.[7]


Dust mites are the primary source of perennial indoor allergens.

One approach to improving current steroid therapy has been to dissect the anti-inflammatory effects of steroids away from their adverse side effects. This labor has borne fruit in the form of a class of drugs called selective glucocorticoid receptor agonists, or SEGRAs, which have been designed to target the glucocorticoid receptor without the collateral effects responsible for toxicity.[8] One such drug, Mapracorat, was shown in preclinical studies to selectively drive glucocorticoid receptor mediated anti-inflammatory effects with a diminished ability to promote the gene transactivation thought to be responsible for many adverse steroid effects such as ocular hypertension.[9] Unfortunately, this selective efficacy has not been demonstrated in several clinical trials. But while interest in Mapracorat may have waned, the goal of a selective, safe glucocorticoid agonist remains.

The mast-cell hyperplasia observed in states of chronic PAC is known to be reduced only by repeated rather than acute steroid treatment, indicating that sustained drug release is critical to its efficacy.[10] Thus, another avenue being explored for selectively targeting the glucocorticoid receptor is changing the drug pharmacokinetics through novel drug-delivery techniques. Ocular Therapeutix has developed an intracanalicular depot system that releases a lower yet sustained dose of dexamethasone. Preliminary studies in a guinea pig model for chronic allergy demonstrated that multiple dexamethasone treatments were effective in suppressing both the chronic inflammatory score and mast-cell hyperplasia. These results led to its clinical program, and a successful clinical Phase II study. Phase III development of this depot steroid for chronic ocular allergy is imminent.

Non-steroidal anti-inflammatories are also approved for treatment of allergic conjunctivitis. They are less effective than antihistamines for acute disease, but several recent trials suggest they may be more effective if used in longer courses, comparable to steroid treatment regimes.[11]

Immunomodulatory agents also provide a steroid-sparing alternative for allergic conjunctivitis, but have yet to obtain Food and Drug Administration approval for the treatment of ocular allergy.[12] Members of this drug class act by inhibiting calcineurin and have less-severe side effects than steroid treatment. Examples of immunomodulatory agents include cyclosporine A, pimecrolimus and tacrolimus. Although these agents are effective and have a better safety profile than steroids, they have had limited therapeutic success due to their low water solubility and lipophilic nature, result-

ing in challenging topical formulations and poor ocular penetration. Other treatments in the pipeline include the identification of new targets and sites of therapeutic intervention. For example, kinase inhibitors such as PRT2761 (Portola Pharmaceuticals) target the spleen tyrosine kinase that's the link between IgE-antigen binding and subsequent events in the allergic cascade.

While antihistamines are thought of as therapy for acute allergy, newer generations have anti-inflammatory properties that may provide a higher efficacy for perennial allergy sufferers. The best example of this is alcaftadine, a long-acting histamine antagonist that has been shown to be clinically superior to the most-prescribed drug in this class, olopatadine.[13] A proposed mechanism underlying this superiority was described in preclinical studies, where alcaftadine demonstrated an ability to reduce inflammatory cell infiltration through the stabilization of conjunctival epithelial tight junctions; it's also been shown to antagonize multiple histamine receptor subtypes.[13,14] It's been proposed that an added benefit of this front-line reinforcement might be a reduction in the ability of the allergen to enter and activate the allergic cascade within the ocular tissue.

Clinical Models

The difficulty of studying AC in humans has been a substantial hurdle in developing new agents, particularly those that target chronic inflammation.[15] Seasonal trials that focus on a recapitulation of a natural setting are limited by unpredictable allergen levels and placebo effects. The clinical evolution of AC is unpredictable, and manifestations are dramatically modified by external stimuli, such as the specific type and prevalence of allergen. Uncontrollable intrinsic and extrinsic variables during a clinical trial such as sensitivity to allergen and comorbidities (intrinsic), allergen exposure and patient compliance (extrinsic) collectively contribute to a heterogeneous population with an unstable baseline for study. Also, the phenomenon of "placebo benefit" can have as much as a 70-percent effect on signs and symptoms due to dilution or washing away the allergen.[16]

The conjunctival allergen challenge model was developed for the evaluation of anti-allergic compounds to address these shortcomings.[17] Subjects are tested for ocular sensitivity by instilling allergen in the eye at increasing doses until a moderate to severe, but still modifiable, allergic response is produced. Originally designed to model acute allergy, the CAC model has been modified in order to target the chronic inflammatory response associated with PAC. To provoke the chronic inflammatory response, multiple doses of allergen challenge are delivered to invoke a late-phase allergic response and increase levels of cellular infiltrates. Thus, repetitive allergen challenge has provided a model for the study of the efficacy of anti-inflammatory therapeutics in subjects with chronically inflamed tissue. *(Gomes et al. IOVS 2006;47:ARVO E-abstract 4978)* This approach can be brought closer to real-world exposure in environmental chambers (such as the Ora Allergen Biocube) designed to provide precise control over allergen exposure in a more natural delivery modality.

Other Options

Research into mechanisms of chronic allergy and inflammation remains the key to improving therapies, but it's also sometimes worthwhile to consider the tools at hand and ask, "Is there a better way?" An approach that's been successful in treatment of glaucoma, for example, is combination therapy: pairing two drugs with different mechanisms of action to yield a therapeutic with greater efficacy and safety. Lower concentrations of each ingredient mean reduced adverse effects. With an improved understanding of the cells, mediators and immunological events that occur in chronic ocular allergy, we are in a better position to identify and explore potential combination therapies; perhaps a combined antihistamine-calcineurin inhibitor would provide the balance needed to treat the whole chronic allergy patient. We expect that some degree of balance between therapeutic development and clinical progress will provide the key to more effective treatments for winter allergies. REVIEW

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Stabilizing the Cornea with Intacs

Intracorneal ring segments can be great for stabilizing keratoconus, but be ready for the insertion challenges.

Soosan Jacob, MS, FRCS, Chennai, India

In some conditions, when no cure is available, sometimes simply preventing further progression can be enough to help the patient. In this vein, the use of Intacs intracorneal ring segments (Addition Technology, Lombard, Ill.) in moderate keratoconus cases can often help improve the patient's quality of vision and, more importantly, help slow or stop the progression of the disease, especially when used in combination with corneal cross-linking. As with any corneal procedure, however, especially one involving the use of a device, a breakdown in technique can lead to intraoperative difficulties or postoperative complications. In this article, I'll share my experience with Intacs and their possible pitfalls, to help flatten your learning curve.

Planning the Procedure

In patients with keratoconus, placing intracorneal ring segments shortens the arc length of the corneal curvature and creates an artificial limbus within the cornea. The presence of the ring segments redistributes biomechanical stress forces more evenly, thus helping decrease progression of keratoconus, although not as much as corneal cross-linking. Ring segments also improve topography and reduce corneal irregularity, often improving vision.

Though Intacs placement can be beneficial, it's not for every patient with keratoconus; it works best when the patient's condition is neither too mild nor too extreme. In mild cases, the use of Intacs isn't necessary, and a cross-linking treatment is often enough. On the other hand, in a severe case, the segments don't provide much benefit and a deep anterior lamellar keratoplasty would be preferable.

The location of the cone will determine the need for one or two segments, or if one should use symmetric or asymmetric segments (i.e., a thick segment and a thin segment). For central or global cones, symmetric segments are useful. For eccentrically located cones, either single-segment placement inferior to the cone or an asymmetric placement with a thicker segment below the cone and a thinner one above it could be useful.

If the cone is centrally located, the ring segments may be centered on the pupil. For an eccentric cone, I try to decenter the Intacs slightly toward the apex of the cone, while still remaining centered within the pupil. Excessive decentration should be avoided to prevent visual symptoms such as glare and haloes in scotopic conditions.

The femtosecond laser is a reliable means to create channels for the Intacs. I program the depth to about 75 to 80 percent of the minimum pachymetry in the implantation zone. The inner and outer diameters will depend on the type and thickness of the segments being implanted. A smaller optic zone as well as thicker segments give a greater flattening effect. Segments that fit well in their channels also have more effect as compared to segments lying in oversized channels. The entry incision is usually placed on the steep axis and oversized by 0.1 mm as compared to the channel thickness.

Proper Insertion

Although the channels are created by a laser, the segments are inserted by hand, so there is an art to it.

To insert the first segment, slide it into the entry incision perpendicular to the channel you've created and then,

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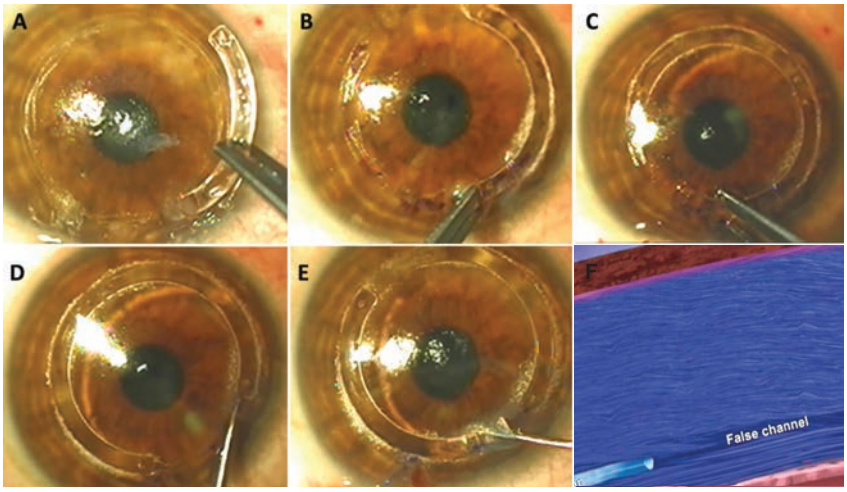

Steps of the turnaround technique. Figure A: A false channel is inadvertently created. B: The segment is turned around and pushed in. C, D: The second segment used as an instrument to push the first forward. E: The final position of both segments. F: When the segment approaches the false channel from the opposite side, it flattens out the obstructing internal lip and thus crosses the point of resistance.

at the base of the incision, turn it 90 degrees and begin inserting it into the channel. A possible error is to not go down fully to the bottom of the channel before turning the segment sideways. The other mistake that can occur is not holding the segment parallel to the surface of the cornea while feeding it into the channel. If the segment is advanced before reaching the bottom of the entry incision, or if advanced when held angled posteriorly or anteriorly, a false channel may be created.

Dealing with False Channels

A false channel is where the segment begins tunneling into the corneal tissue adjacent to the actual channel. Signs that you've inadvertently created a false channel are increasing resistance to your insertion to the point where it may stop entirely, as well as radiating folds at the edge of the segment. The false channel has an internal lip of tissue that separates it from the laser-created channel, blocking the path. In addition to the obvious concern that the false channel results in the inability to implant the segment, it also invites complications such as neovascularization, segment migration and corneal melt.

All is not lost. By using a maneuver I described, the "turnaround technique," one can still properly position the segments. On encountering resistance to implantation or on seeing corneal folds at the advancing edge, the surgeon stops trying to push forward. Instead, the segment is removed, turned around, and then inserted into the entry incision from the opposite direction. Since the femtosecond laser channel is a circumferential 360-degree channel, the segment will continue around until it's fully in. The second Intacs segment is then used as an instrument to push the first segment the rest of the way. When the first segment reaches the location of the false channel, it's coming from the opposite direction and will therefore flatten the lip and close the false channel. Final positioning can be done with a reverse Sinskey hook used in the positioning hole. In the end, both segments will then lie in their proper positions. (For a video of the technique, visit http://tinyurl.com/h8ugvwf.)

For asymmetric segments, the first segment is pushed in from the opposite side and the second segment is used to push it to its final position.

The segments are always pushed in following the arc of bubbles created by the femtosecond laser. If you're facing difficulty in inserting the segments, and anticipate a delay in final implantation, it's wise to mark the channel arc with a fine-tipped marking pen on the surface of the cornea so that even when the bubbles have dissipated completely, the segments can still be pushed in following the inked arc.

False-channel Complications

It's important to recognize and react to false channels when they occur, as continuing to push a segment into the false channel can end in undesirable final positions, such as the segment straddling the entry incision or being too deep, too superficial or on an uneven plane of implantation. In some situations, implantation may have to be abandoned because of an inability to push the segment. Blind pushing can also lead to anterior or posterior perforation of the segment. Complications that can ensue include stromal necrosis and melt, anterior chamber perforation and neovascularization. Neovascularization generally traverses the entry incision and sometimes tracks down the channel, and it's generally innocuous unless the patient requires a corneal graft later, in which case it can increase the risk of rejection.

Stromal necrosis and melt can lead to infection, and the best response in such a case may be to remove the segment. Stromal necrosis, though it may be deep, is generally localized over the segment and may require removal of the segment with the application of cyanoacrylate glue over the melt. REVIEW

Dr. Jacob is director of Dr. Agarwal's Refractive and Cornea Foundation at Dr. Agarwal's Eye Hospital and Eye Research Center. She has no financial interest in Intacs.


Managing Glaucoma with ICE Syndrome

Because of the other issues associated with ICE syndrome, many standard glaucoma treatments are ineffective.

Paul A. Sidoti, MD, and Jonathan Schulhof, MD, New York City

Iridocorneal endothelial syndrome, or ICE syndrome, is a primary abnormality of the corneal endothelium. In ICE syndrome, abnormal corneal endothelial cells proliferate, forming a membrane that migrates out over the anterior chamber angle and the iris; eventually, that membrane contracts, resulting in iris abnormalities and secondary angle-closure glaucoma. Healthy endothelial cells do not proliferate; so far, no one has definitively determined the cause of the cellular abnormality that leads to proliferation in ICE syndrome.

The incidence of secondary glaucoma in patients with ICE syndrome is fairly high, and its management can be very challenging; it's often accompanied by corneal edema and requires multiple surgeries. Generally, ICE syndrome occurs unilaterally, and it's commonly associated with corneal edema and iris abnormalities, including atrophy, stretch holes, nodules and pupillary distortion. Affected patients tend to be young, with no known comorbidities.

Glaucoma associated with ICE syndrome is recalcitrant and often difficult to control. As a result, modification of standard surgical techniques is necessary to optimize outcomes. Here, we'd like to offer some strategies that can help you make the best of this challenging condition.

Surgical Options

Because glaucoma secondary to ICE syndrome frequently involves extensive synechial angle closure, medications are often not sufficient to control the intraocular pressure. Likewise, laser trabeculoplasty is often unsuccessful, despite angles that appear open. Laser trabeculoplasty targets the trabecular meshwork cells; in ICE syndrome, the endothelial membrane or peripheral anterior synechiae preclude access to the meshwork cells. Transscleral cyclophotocoagulation can be effective, although it doesn't address the primary outflow obstruction. We tend to reserve it for end-stage disease and for patients who don't want or can't have incisional surgery.

Because medicinal therapy is often inadequate and the utility of laser is limited, surgical procedures tend to be the treatment of choice. However, the newer Schlemm's canal-based procedures such as Trabectome and iStent are not feasible in most ICE syndrome patients, and they are unlikely to achieve lasting results even when areas of open-appearing angle exist, due to continued endothelial membrane proliferation. Procedures that bypass the trabecular outflow pathway altogether, such as trabeculectomy with mitomycin-C and aqueous shunt surgery, are considerations. Of these, we favor tube shunts over trabeculectomy, based on our personal experience and the limited data in the published literature.

What the Data Shows

To compare the potential value of these procedures, it's worth looking at the data reported in the literature. One study published in 2000 reported the outcomes of trabeculectomy with mitomycin-C performed on 10 ICE syndrome patients.[1] At a mean follow-up of 14 months, the success rate—defined as an IOP less than 21 mmHg—was 80 percent. However,

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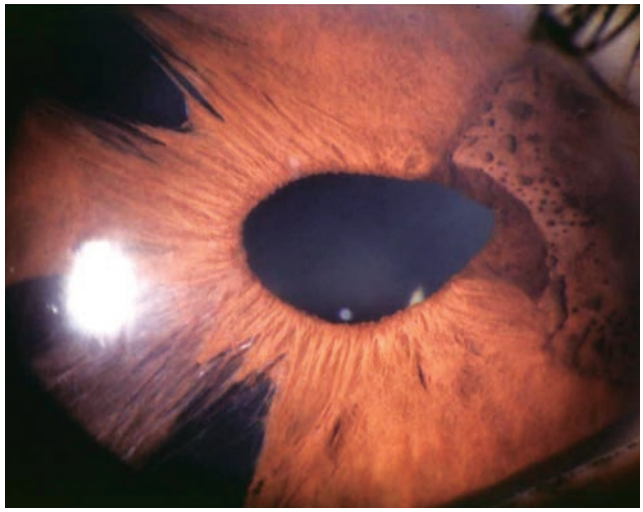
this follow-up period was short by glaucoma standards. For comparison, another study published in 2001 reported the results of trabeculectomy performed with either mitomycin-C or 5-fluorouracil on 12 ICE syndrome patients; at five years, using the same criteria, the success rate was only 29 percent.[2] (Of course, it's not uncommon to have an increasing number of patients fail after trabeculectomy the longer you follow them, but ICE syndrome patients tend to have a much greater failure rate than standard open-angle glaucoma patients would have.)



In addition to corneal edema, ICE syndrome is commonly associated with iris abnormalities, including atrophy, stretch holes, nodules and pupillary distortion, and the incidence of secondary glaucoma is high.

ICE syndrome patients have a number of risk factors that can lead to failure of trabeculectomy. They tend to be younger than the average glaucoma patient, which means they have more robust healing and may scar more easily; the proliferating membrane associated with ICE syndrome may block the internal ostium; many of these patients have had prior surgeries, which can add to their risk of failure; and these patients often need other surgeries in tandem with or subsequent to the glaucoma surgery, such as cataract surgery or corneal transplantation. That combination can put even a well-functioning filter at risk.

Aqueous shunts have also demonstrated limited success in ICE syndrome patients, but they tend to do better than trabeculectomies. A 1999 study in which 10 ICE syndrome patients underwent tube implantation had a five-year success rate of 75 percent (although tube revision or repositioning was required in three of the patients).[3] Another study published in 2001 followed 21 patients who received tube shunts; at five years their success rate was 53 percent.[2] While these were retrospective studies, there is reason to believe that the long-term success rate of tube implant surgery is superior to that of trabeculectomy.

When shunts fail in ICE syndrome, they can do so for a variety of reasons. For example, the capsule can become excessively thick. (This can happen in any tube-shunt patient, but the tendency for this to occur may be greater in ICE syndrome patients than in patients with other types of glaucoma.) Also, the proximal tube ostium can become blocked, either by the endothelial membrane or by the iris, because of progressive anterior synechiae formation. This accounts for the need to reposition tubes in some patients; if the iris gets pulled up into the tube, for example, the tube may become occluded and need to be repositioned into the ciliary sulcus or the pars plana. Leaving the tube long so that it extends far away from the anterior chamber angle and the iris can often prevent these issues.

To summarize, tubes often work better in ICE syndrome patients because they tend to be more resilient than trabeculectomy; they are less prone to failure due to subconjunctival or episcleral scarring (which is especially important given the younger age of these patients); they are less affected by inflammation; and they are less affected by prior, concurrent or subsequent surgery. All of these things are common concerns in ICE syndrome patients.

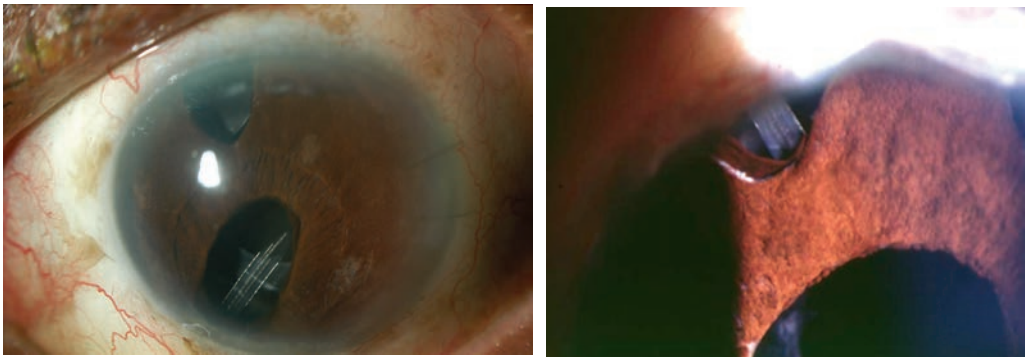
Assessing the Eye

Clearly, in ICE syndrome patients, the location of tube placement is critical. The standard choices for placement would be the anterior chamber, the ciliary sulcus, or through the pars plana into the anterior vitreous cavity. The surgical approach that makes the most sense will vary.

Preoperative assessment is always critical. Perform gonioscopy to look for the location and height of the peripheral anterior synechiae. Locating the synechiae can help to guide your tube placement to locations where the angle is still open. (Although the membrane of proliferating cells can be visualized on pathologic specimens, it's translucent and can't be visualized clinically.)

If the patient is phakic, note the status of the lens. Does the patient have a cataract, or is the lens clear? If the patient is pseudophakic, note the type of lens and the status of the posterior capsule. (If the patient is aphakic, that presents different options and needs; we'll discuss those shortly.)

The presence and degree of corneal edema is also important to assess. If the cornea is clear and without evidence of edema, you may want to perform specular microscopy to assess the cell count and morphology of the cells. This will help you predict the



Choice of tube location in the prescence of ICE syndrome is critical to preventing the tube from becoming occluded by proliferating endothelial cells. One option is to place the tube so that the tip lies within a preexisting iris defect, as shown above.

likelihood that the patient will need a corneal transplant in the near future. If the patient does have corneal edema, you may need to perform a corneal transplant, Descemet's stripping automated endothelial keratoplasty or Descemet's membrane endothelial keratoplasty. In any case, you have to be able to see through the cornea well enough to do the glaucoma surgery and any other concomitant surgery.

It's also important to assess pupil size and configuration, and the location of any vitreous, particularly in aphakic or pseudophakic patients. If vitreous is present in an area that might allow it to sneak into the tube tip postoperatively, perform a vitrectomy and remove that vitreous at the time of tube placement.

Placement of the Tube

If the cornea is clear and the anterior chamber angle is open (as it might be in a Chandler's syndrome patient) with no visible synechiae, the tube can be positioned in the anterior chamber. While leaving the tube tip long can help prevent occlusion, it's also important in the event that the tube needs to be repositioned to the sulcus or pars plana at a future time. Creating a curved course for the extraocular portion of the tube, between the endplate and the insertion site, will also allow a little extra tube length should you need it for future repositioning.

If concurrent cataract surgery is being performed, the tube can be positioned in the anterior chamber, the ciliary sulcus or the pars plana. Ciliary sulcus or pars plana placement is generally preferred in pseudophakic and aphakic patients, as a way to decrease the potential risk of corneal decompensation requiring transplantation. However, in order to put the tube through the pars plana and into the anterior vitreous cavity, a concurrent vitrectomy is required, adding more surgery to your procedure.

In ICE patients, it's especially important to maximize the distance between the tip of the tube and the posterior surface of an already compromised cornea. Additionally, as mentioned earlier, longer tube length can minimize the potential for occlusion of the proximal ostium by iris or endothelial membrane.

Regarding iris contact, we agree with some surgeons that resting on the iris is preferable to touching the cornea, but in ICE syndrome patients we think it's equally important that the tube not touch the iris because of the underlying disease process. The synechiae tend to pull the iris forward, toward the angle and the cornea. Contact between the tube and the iris may accelerate synechiae formation. So, if the tube is too deep in the anterior chamber, the iris will get pulled up and potentially occlude the tube. In addition, the membrane on the surface of the iris can overgrow the proximal tube tip; contact between the iris and tube tip may facilitate that overgrowth. So ideally you should make sure the tube tip is close to, but above the surface of the iris. (Or, as mentioned earlier, it can be positioned within an iris defect or iridectomy when one is present in an appropriate location, to minimize the risk of occlusion.)

Sometimes the iris may have an existing stretch hole or surgical iridectomy. In that situation you can position the tube within the iridectomy so that it's far away from the cornea and not on top of the iris, minimizing the risk of occlusion. Fortunately, silicone is a poor substrate for membrane growth, so the membrane will only block the tube if the opening is contacting the iris or immediately adjacent to it.

Diffuse synechiae may preclude anterior chamber placement and require placement in the sulcus or pars plana. In fact, ciliary sulcus placement is often facilitated when the iris is pulled forward by synechiae, enlarging the sulcus space. However, insertion of the tube into the ciliary sulcus or anterior vitreous cavity necessitates removal of the lens, whether it's clear or not.

We believe that it's important to do a complete pars plana vitrectomy in conjunction with pars plana tube placement, as opposed to a limited anterior vitrectomy (even if the patient doesn't have ICE syndrome), because any residual vitreous will

eventually find its way into the tube opening and block it.

Multiple Surgeries

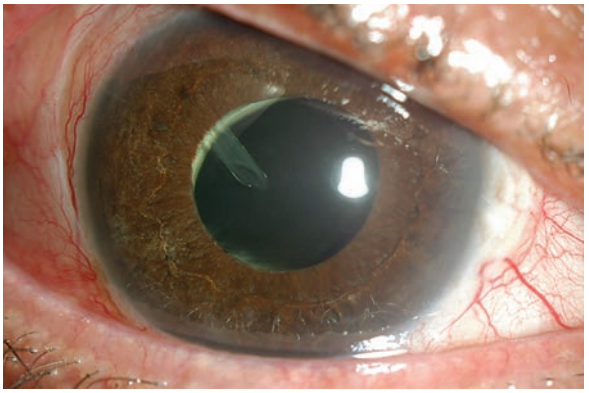
In addition to poorly controlled intraocular pressure, some ICE syndrome patients will have corneal edema that requires a corneal transplant. If you need to do more than one surgery, such as a corneal transplant in addition to the glaucoma surgery—and possibly cataract surgery and a vitrectomy as well—the timing of the surgeries may depend on the extent of the corneal edema and the degree to which it obscures the surgeon's view into the eye.

If the patient has early corneal edema, we prefer to stage the surgeries. As long as the view is good enough to perform the surgery, we'll do the shunt first, sometimes combining it with cataract removal or vitrectomy so we can put the tube through the pars plana. After three or four months, when the pressure is stable and the inflammation has subsided, we'll go back and do the corneal transplant.

This is a good approach because the endothelium of the corneal graft is delicate and may be adversely affected by excessive intraocular inflammation, variable intraocular pressures and potential early postoperative complications, all of which can be associated with combined surgery. On the other hand, graft survival can be enhanced by performing corneal transplantation alone in an eye that is quiet with a stable and well-controlled intraocular pressure several months after aqueous shunt surgery. Fortunately, most of these patients have a healthy, well-seeing fellow eye, so rapid visual rehabilitation of the eye with ICE syndrome is less of a concern.

Of course, in some cases you can't see well enough to do any intraocular surgery because the corneal edema is substantial. If that's the situation, you may need to do the surgeries concurrently—first, do the corneal transplant; then perform a vitrectomy, remove the cataract (if the patient is still phakic) and implant the tube in the sulcus or pars plana. Our bias is to place the tube in the pars plana in this situation, but that's just our preference; others prefer to put the tube in the sulcus.

If you intend to perform DSAEK or DMEK, the issue of needing a gas bubble following the surgery is a consideration when a tube is present; however, when using a non-valved drainage device with a temporary ligature, no air or gas should exit through the tube. If a valved drainage device is used, temporary ligation of the tube would be necessary to prevent premature leakage of the gas from the anterior chamber prior to adherence of the graft. With a pars plana tube, even if the tube is fenestrated to allow for some immediate aqueous outflow, an anterior chamber air bubble can be placed simultaneously with the tube implant. So it is possible to perform DSAEK or DMEK concurrently with the glaucoma surgery, although, as already noted, we would prefer to stage the procedures.



In many pseudophakic patients, the tube can be placed within the ciliary sulcus, as seen above. If the patient is phakic, the lens must be removed prior to placement in the sulcus or anterior vitreous cavity.

Hoping for a Cure

Of course, secondary glaucoma doesn't occur in every ICE syndrome patient. However, even those who don't develop secondary glaucoma may still develop corneal edema and require a corneal transplant for visual rehabilitation. Meanwhile, when glaucoma does develop because of angle closure, managing it appropriately can be crucial to maintaining the patient's vision.

Ideally, we'd like to be able to address the underlying cause of the ICE syndrome by correcting the endothelial cell abnormality and preventing these cells from proliferating. Resolving the problem at the cellular level would provide a true long-term solution for these patients and eliminate the problem of secondary glaucoma. It is our hope that this will happen at some point in the near future. REVIEW

Dr. Sidoti is a professor of ophthalmology and deputy chair for clinical affairs in the department of ophthalmology at New York Eye and Ear Infirmary of Mount Sinai and the Icahn School of Medicine at Mount Sinai in New York City. He has previously received speaking honoraria from NeoMedix. Dr. Schulhof is a glaucoma fellow in the department of ophthalmology at New York Eye and Ear Infirmary of Mount Sinai and the Icahn School of Medicine at Mount Sinai in New York City.

1. Lanzl IM, Wilson RP, Dudley D, Augsburger JJ, Aslanides IM, Spaeth GL. Outcome of trabeculectomy with mitomycin-C in the iridocorneal endothelial syndrome. Ophthalmology 2000;107:295-297.
2. Doe EA, Budenz DL, Gedde SJ, Imami NR. Long-term surgical outcomes of patients with glaucoma secondary to the iridocorneal endothelial syndrome. Ophthalmology 2001;108:1789-1795.
3. Kim DK, Aslanides IM, Schmidt CM, Spaeth GL, Wilson RP, Augsburger JJ. Long-term outcome of aqueous shunt surgery in ten patients with iridocorneal endothelial syndrome. Ophthalmology 1999;106:1030-1034.

OCTA vs. Traditional Imaging in AMD

A European study has demonstrated a high level of correspondence between different choroidal neovascularization patterns identified using optical coherence tomography angiography and treatment decisions established on conventional multimodal imaging in patients with exudative age-related macular degeneration. While fluorescein angiography remains the gold standard for determining the presence of leakage, OCTA may offer a noninvasive option for monitoring CNV.

The study was a prospective case series of 80 eyes of 73 consecutive patients (39 women, 34 men) with exudative AMD (mean age: 79.4 ±5.3 years) diagnosed with different types of CNV (58 Type 1; two Type 2; six mixed Type 1 and Type 2; three retina angiomatous proliferation; 11 AMD-related polyps). The data obtained from traditional multimodal imaging, based on fluorescein angiography, indocyanine green angiography and OCT were used to assess the need for treatment; the data obtained from OCTA was used to identify two different patterns of CNV. Traditional multimodal imaging and OCTA findings were then compared to evaluate possible correspondence between treatment decision and CNV aspect on OCTA.

A CNV lesion was identified as Group A (requiring treatment) in 58 eyes (72.5 percent) in traditional multimodal imaging. With OCTA, 59 eyes (73.7 percent) had lesions defined as Pattern 1; the remaining 21 (26.3 percent) were defined as Pattern 2. There was a 94.9-percent correspondence between the Pattern 1 CNV on OCTA and the Group A cases on conventional multimodal imaging. A 90.5-percent correspondence was also computed between Pattern II CNV on OCTA and Group B (not requiring treatment) cases on conventional multimodal imaging. There was a high interobserver agreement ($p<0.05$) both for treatment decision in conventional multimodal and for Patterns (1 or 2) defining on OCTA imaging analysis.

Retina 2015;35:2219-2228.
Coscas G, Marco L, Coscas F, Gagini C, Souied E.

No Long-term Protection from NSAIDs after Cataract Surgery

A review of the available data shows a lack of level 1 evidence to support long-term benefit of prophylactic topical nonsteroidal anti-inflammatory drugs in preventing vision loss from cystoid macular edema after cataract surgery. Although dosing of NSAIDs before surgery may hasten the speed of visual recovery in the first several weeks after cataract surgery, there is no evidence that this practice affects long-term visual outcomes. However, because there is no uniform method of reporting CME in the literature, standardized reporting of CME based on OCT may allow for more uniform quantification of its incidence and more reliable assessment of treatment outcomes.

Literature searches of the PubMed and the Cochrane Library databases were last conducted on January 21, 2015, with no data restrictions. The searches retrieved 149 unique citations. The first author reviewed the abstracts of these articles and selected 27 articles of possible clinical relevance for full-text review. Of these 27 articles, 12 were deemed relevant to analyze in full. Two additional articles were identified from the reference list of the selected articles, and another article was identified from a national meeting. The panel methodologist assigned ratings of level of evidence to each of the selected citations.

NSAID therapy was effective in reducing CME detected by angiography or optical coherence tomography and may increase the speed of visual recovery after surgery when compared directly with placebo or topical corticosteroid formulations with limited intraocular penetration. However, the use of NSAIDs did not alter long-term (≥three months) visual outcomes. Furthermore, there was no evidence that the benefits observed with NSAID therapy could not be obtained similarly with

equivalent dosing of a corticosteroid. The reported impression that there is a pharmacologic drug synergy from the use of both an NSAID and a corticosteroid is not supported by the literature.

Ophthalmology 2015;122:2159-2168.

Kim S, Schoenberger S, Thorne J, Ehlers J, Yeh S, Bakri S.

Treat-and-Extend vs. Monthly Dosing for Neovascular AMD

A prospective, randomized, controlled trial using a treat-and-extend neovascular age-related macular degeneration management strategy with ranibizumab resulted in visual and anatomic gains comparable with those obtained via monthly dosing.

Sixty patients with treatment-naïve neovascular AMD with Early Treatment Diabetic Retinopathy Study best-corrected visual acuity from 20/32 to 20/500 (Snellen equivalent) were randomized 1:2 to receive intravitreal 0.5 mg ranibizumab monthly or according to a treat-and-extend protocol. The treat-and-extend patients were treated monthly for at least three doses, until resolution of clinical and spectral-domain optical coherence tomography evidence of exudative disease activity; the interval between visits then was individualized according to a strict prospective protocol. Main outcome measures were mean ETDRS BCVA change from baseline.

At baseline, mean age was 77 years (range: 59 to 96), mean BCVA was 20/60 (Snellen equivalent) and mean central retinal thickness was 511 µm. Fifty-seven eyes (95 percent) completed month 12, at which point mean BCVA improved by 9.2 letters in the monthly cohort and 10.5 letters in the treat-and-extend cohort (p=0.60). The mean number of injections administered through month 12 was 13.0 and 10.1 (r: seven to 13) in the monthly and treat-and-extend cohorts, respectively (p<0.0001). Among the treat-and-extend patients, seven (18 percent) were maximally extended; four (10 percent) demonstrated fluid at every visit; and at month 12, 18 (45 percent) had achieved an extension interval of eight weeks or more; the mean maximum extension interval between injections after the first three monthly doses was 8.4 weeks (r: four to 12 weeks). Most treat-and-extend patients who demonstrated recurrent exudative disease activity (17/24, 71 percent) were unable to extend beyond their initial maximum extension interval.

Ophthalmology 2015;122:2514-2522.

Wykoff C, Croft D, Brown D, Wang R, Payne J, et al.

Predicting Wet AMD Patient Response to Ranibizumab

Consistent with other published reports, this retrospective exploratory analysis of the HARBOR study identified several baseline predictors associated with visual acuity outcomes at month 12 with ranibizumab treatment in patients with wet age-related macular degeneration: lower baseline best-corrected visual acuity; younger age; a smaller total choroidal neovascularization leakage area; a smaller area of occult CNV; and presence of subretinal fluid. Subretinal fluid thickness >118.25 µm at baseline predicted requiring more ranibizumab injections in the first 12 months of treatment.

Researchers used a retrospective, exploratory analysis of multicenter, randomized, controlled trial data, culling patients aged ≥50 years with subfoveal wet AMD who had best-corrected visual acuity measured at baseline and month 12 for the study population. Intravitreal ranibizumab 0.5 mg was administered monthly (n=249) or as-needed after three monthly loading doses (n=251). The main outcome measures that served as a basis for baseline predictors of visual acuity outcomes at month 12 were BCVA change from baseline at month 12; the proportion of patients with a BCVA gain of ≥15 ETDRS letters from baseline at month 12; and the proportion of patients with a Snellen equivalent of 20/40 or better at month 12 in the ranibizumab 0.5-mg monthly and 0.5-mg PRN groups. A post hoc analysis of the total number of injections in the first 12 months of patients receiving ranizibumab 0.5 mg PRN was also performed. Only variables that were statistically significant (p<0.05) remained in the final statistical model.

Am J Ophthalmol 2015;160:5:1014-1023.

Regillo C, Busbee B, Ho A, Ding B, Haskova Z.

Antibiotic Resistance in Ocular Pathogens in the United States

During the first five years of the Antibiotic Resistance Monitoring in Ocular Microorganisms surveillance study, methicillin resistance was present among staphylococcal isolates from ocular infections, with many strains demonstrating multidrug resistance. These findings are consistent with resistance trends reported for nonocular staphylococcal isolates. Overall ocular resistance did not grow during the five-year study period.

ARMOR was performed at an independent central laboratory, with the goal of reporting resistance rates and trends among common ocular isolates collected during the first five years of the study. Clinical centers across the United States were invited to submit ocular isolates of *Staphylococcus aureus*, coagulase-negative staphylocci (CoNS), *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Pseudomonas aeruginosae*. Isolates were collected from January 1, 2009 through December 31, 2013, and analyzed from January 16 to May 15, 2015.

Minimum inhibitory concentrations

(continued on page 81)

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His ophthalmologist's concern over a potential cerebrovascular event prompts a patient to seek further help at Wills Eye.

Melissa Sieber, MD, and Mark Moster, MD

Presentation

A 32-year-old Caucasian male presented with an acute onset of partial temporal visual field loss in the left eye over a period of a few days. The patient saw an ophthalmologist who, in the setting of an otherwise normal ocular exam, was concerned the patient was having a cerebrovascular accident. During a brief hospitalization, CT and MRI findings were thought to be due to atypical migraines. He did note a history of migraines and was having regular headaches that would last about one hour with visual "floaters." According to the patient and records, there were no other neurological deficits at that time. Further stroke workup was negative. Upon routine follow-up a year and a half later, he continued to have his headaches as previously described but noted stable vision with no new changes. On review of systems, he noted occasional vertigo, which would last days to weeks at a time. He also reported decreased hearing in both ears with an increase in fatigue. He denied any weakness, numbness or loss of balance.

Medical History

Medical history was significant for hypertension, depression, gastroesophageal reflux disease, atypical migraines and Meniere's disease (diagnosed at age 26). Ocular history included congenital dyschromatopsia and mild myopia. Surgical history was notable for prior appendectomy and cholecystectomy. He denied current tobacco (noted a prior 15 pack-year history), alcohol or illicit drug use. Employment included secretarial work.

Medications include aspirin 81 mg p.o. daily, amlodipine 10 mg-benazepril 20 mg p.o. daily, clonazepam 0.5 mg p.o. b.i.d. as needed for anxiety, ranitidine 25 mg p.o. daily, meclizine 25 mg p.o. b.i.d., and Zoloft 100 mg p.o. daily.

Examination

Initial presentation revealed a completely normal systemic and ocular exam with the exception of temporal field defect in the left eye by confrontation visual fields.

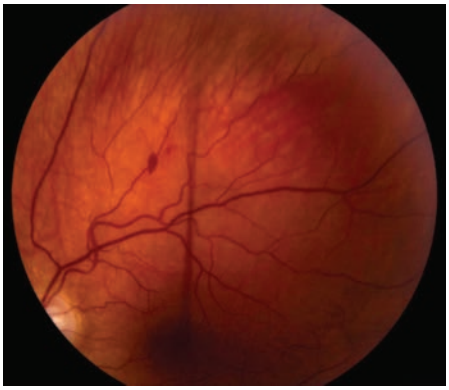

Figure 1. Fundus photo of the left eye demonstrating a retinal hemorrhage superiorly.

On follow-up examination a year and a half later, vital signs were stable and within normal limits. The patient was oriented to person, place and time but was somewhat drowsy during the visit with a slow thought process. Ocular exam revealed best-corrected visual acuity to be 20/20 OU. He denied subjective color or light desaturation. Pupils were equally round and reactive to light without a relative afferent pupillary defect. Amsler grid was full OU. Confrontation visual field was notable for nasal defects in the left eye. Extraocular motility was full OU.

Anterior slit-lamp examination was normal OU. Dilated fundus exam was normal OD and revealed vitreous syneresis, attenuated vessels and a small retinal hemorrhage superiorly *(See Figure 1)* OS.

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

Diagnosis, Workup and Treatment

Initial presentation and symptomatology to the outside hospital and ophthalmologist prompted a stroke workup. CBC, CMP, ESR,° CRP, Factor V Leiden, Protein C, Protein S, ANA, CCP IGG, anti-dsDNA, Lyme, SS-A antibody, SS-B antibody, echocardiogram, electrocardiogram and MRA were all unremarkable. MRI with tiny foci of T2 hyperintensities scattered in the bilateral cerebral white matter *(See Figure 2)* elicited a diagnosis of migraine. Given the patient's history of hypertension, he was started on aspirin 81 mg p.o. daily and cardiovascular risk factors were medically optimized.

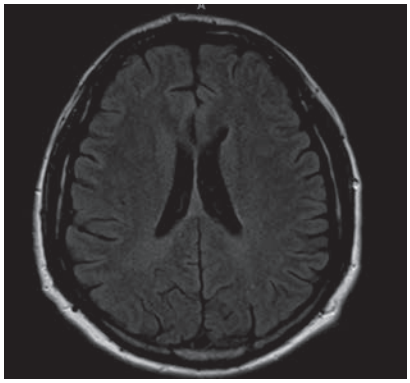

Figure 2. Axial T2-weighted FLAIR MRI on initial presentation with few areas of hyperintensity scattered in the cerebral white matter thought initially to be due to migraine.

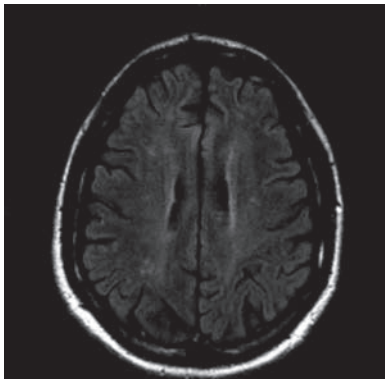

Figure 3. Axial T2-weighted FLAIR MRI from second presentation demonstrating increased white matter hyperintensities compared to the initial MRI (Figure 2).

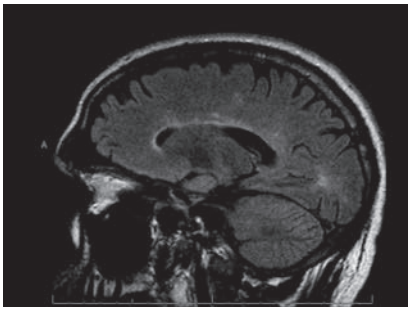

Figure 4. Sagittal T2-weighted FLAIR MRI on second presentation with areas of hyperintense "spoke" lesions along the roof of the corpus callosum, typical of Susac's syndrome.

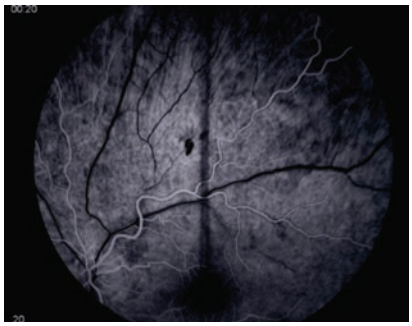

Figure 5. Fluorescein angiography of the left eye demonstrating an arterial filling defect.

On follow-up, the patient's visual symptoms were stable but headaches were still noted to be prominent, which led to a repeat MRI. This MRI showed bilateral cerebral white matter FLAIR hyperintensities with equivocal interval increase *(See Figures 3 & 4)*. These changes were felt to be consistent with multiple sclerosis. Dilated fundus findings of a retinal hemorrhage, however, led to a fluorescein angiography, which demonstrated a branch retinal artery occlusion in the left eye *(See Figure 5)* corresponding to that retinal hemorrhage. The patient likely had a subtle branch retinal artery occlusion on initial presentation that was not appreciated on clinical examination. The BRAOs, MRI changes and symptoms of hearing loss with mental status changes led to the diagnosis of Susac's syndrome.

The patient was started on IV steroids along with an oral steroid taper. He was referred to rheumatology for blood workup and to the Cleveland Clinic's Susac's center for appropriate management.

Discussion

Susac's syndrome is characterized by a clinical triad of encephalopathy, branch retinal artery occlusion and hearing loss.[1] It was initially described in 1979, and a recent review article cited that 304 cases have since been reported.[2] SS is thought to be an autoimmune disease with unclear pathogenesis in which the small vasculature of the brain, retina and inner ear become occluded. It is three times more common in women compared to men without any racial predilection.[3]

Our patient's prior history of Meniere's disease, in addition to atypical migraines, may have indicated early symptoms of Susac's syndrome. He was diagnosed with Meniere's six years prior to initial ocular symptoms and would have vertigo attacks sometimes lasting days to weeks. This is very atypical for Meniere's disease, in which vertigo symptoms usually last only minutes to hours.[4] Additionally, hearing loss in Meniere's is generally unilateral, in contrast to our patient

with bilateral symptoms. Headaches that are migrainous in nature are also common in the setting of microvascular cerebral occlusions that occur with SS. On occasion, due to MRI findings, a misdiagnosis of multiple sclerosis may occur. However, distinguishing features have been described in the literature. Lesions in MS and SS are both most prominent in the white matter and the diseases occur in similar age groups with a female predilection. Headaches and mental status changes, however, are common in SS but are not typical in MS.[5] Encephalopathic changes in MS are generally only seen in the late stages of the disease. The pathognomonic MRI changes of SS occur centrally in the corpus callosum, are "snowball" lesions acutely on T2 and FLAIR, followed by the chronic "punched out holes" seen on T1.[6] Radial "spoke" lesions arising from the roof of the corpus callosum are also common in SS, as noted in our patient. In MS, lesions known as Dawson's fingers are perpendicular to the corpus callosum rather than within the corpus callosum as seen in SS.

Ophthalmic manifestations of SS arise from the occurence of peripheral branch retinal artery occlusions. These often occur in both eyes, over multiple episodes, and can be either subclinical or result in noticeable decrease in vision. Since the disease often occludes small peripheral arterioles, fundoscopy may be normal with fluorescein angiography being the more sensitive modality for diagnosis.[7] Our patient likely had a BRAO on initial presentation causing a visual field defect that was missed by initial dilated eye exam. This suggests that fluorescein angiography may be helpful with routine monitoring of disease status. Spectralis OCT may be used as another diagnostic tool, as those with SS show scattered intraretinal scarring that spares the outer nuclear layer and photoreceptor layers.[8]

Appropriate treatment of SS is still under debate but many experts agree that acute events in SS may be treated with high-dose IV steroids along with gradual oral taper. Cyclophosphamide and intravenous immunoglobulins are other common choices.[9] In general, aspirin is also helpful in these patients as it improves microvascular blood supply.[9]

In conclusion, Susac's syndrome is an extremely rare condition but should be considered in patients with branch retinal artery occlusion with auditory and mental status changes. Magnetic resonance imaging, fluorescein angiography and audiology may be helpful in both diagnosis and clinical monitoring. Other ancillary tests including rheumatologic blood testing, visual field testing and OCT may also aid in the diagnosis. Clinical suspicion and appropriate testing are essential as early diagnosis may be important to limiting the sequelae in this clinical entity. REVIEW

The authors acknowledge the assitance of Adam Flanders, MD.

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8. Ringelstein M, Albrecht P, Kleffner I, Bühn B, et al. Retinal pathology in Susac syndrome detected by spectral-domain optical coherence tomography. Neurology 2015;85(7):610-8.
9. Gross M, Eliashar R. Update on Susac's Syndrome. Curr Opin Neurol 2005;18(3):311-314.

(continued from page 75)

for various antibiotic classes were determined by broth microdilution according to the guidelines of the Clinical and Laboratory Standards Institute. Minimum inhibitory concentrations were interpreted as susceptible, intermediate or resistant based on established break points.

A total of 3,237 ocular isolates (1,169 *S. aureus*, 992 CoNS, 330 *S. pneumoniae*, 357 *H. influenzae* and 389 *P. aeruginosa*) were collected from 72 centers. Methicillin resistance was found among 493 *S. aureus* isolates (42.4 percent; 95 percent confidence interval, 39.3 percent to 45.1 percent) and 493 CoNS isolates (49.7 percent; 95 percent CI, 46.5 percent to 52.9 percent) and methicillin-resistant isolates had a high probability of concurrent resistance to fluoroquinolones, aminoglycosides or macrolides ($p<0.001$). Multi-drug resistance to at least three additional antibiotic classes was found in 428 methicillin-resistant *S. aureus* isolates (86.8 percent) and 381 methicillin-resistant CoNS isolates (77.3 percent). All staphylococcal isolates were susceptible to vancomycin. Resistance among *S. pneumoniae* isolates was highest for azithromycin (113 isolates; 34.2 percent) whereas resistance among *P. aeruginosa* and *H. influenzae* isolates was low against the antibiotics tested. Staphylococcal isolates from elderly patients were more likely to be methicillin-resistant, as were *S. aureus* isolates obtained from the southern United States ($p<0.001$). Methicillin resistance among staphylococci did not increase during the five-year study period ($p\leq0.22$) and small decreases in resistance to ciprofloxacin among CoNS and methicillin-resistant CoNS and to tobramycin among CoNS ($p\leq0.03$) were found.

JAMA Ophthalmol 2015;133:12:1445-1454.
Asbell P, Sanfilippo C, Pillar C, DeCory H, et al.

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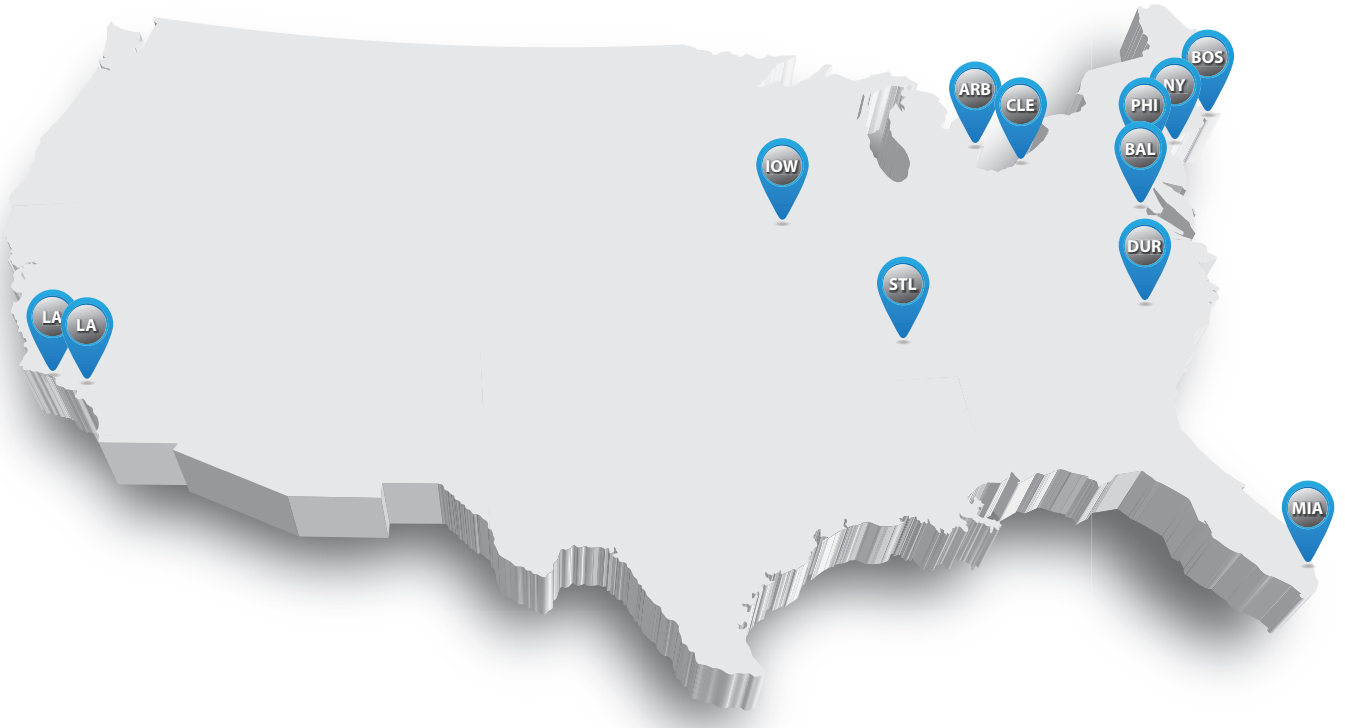

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