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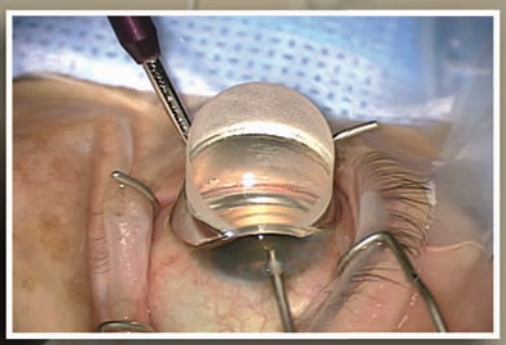

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REVIEW NEWS
Volume XXI • No. 6 • June 2014

JHU Team Suggests a New View On Photoreceptors and Vision

A type of retina cell plays a more critical role in vision than previously known, a team led by Johns Hopkins University researchers has discovered.

Working with mice, the scientists found that the ipRGCs—an atypical type of photoreceptor in the retina—help detect contrast between light and dark, a crucial element in the formation of visual images. The key to the discovery is the fact that the cells express melanopsin, a type of photopigment that undergoes a chemical change when it absorbs light.

"We are quite excited that melanopsin signaling contributes to vision even in the presence of functional rods and cones," postdoctoral fellow Tiffany M. Schmidt said.

Dr. Schmidt is lead author of a recently published study in the journal *Neuron*. The senior author is Samer Hattar, associate professor of biology in the university's Krieger School of Arts and Sciences. Their findings have implications for future studies of blindness or impaired vision.

Rods and cones are the most well-known photoreceptors in the retina, activating in different light environments. Rods, of which there are about 120 million in the human eye, are highly sensitive to light and turn on in dim or low-light environments. Meanwhile the 6 million to 7 million cones in the eye are less sensitive to light; they drive vision in brighter light conditions and are essential for color detection.

Rods and cones were thought to be the only light-sensing photoreceptors in the retina until about a decade ago when scientists discovered a third type of retinal photoreceptor—the ipRGC, or intrinsically photosensitive retinal ganglion cell—that contains melanopsin. Those cells were thought to be needed exclusively for detecting light for non-image-dependent functions, for example, to control synchronization of our internal biological clocks to daytime and the constriction of our pupils in response to light.

"Rods and cones were thought to mediate vision and ipRGCs were thought to mediate these simple light-detecting functions that happen outside of conscious perception," Dr. Schmidt said. "But our experiments revealed that ipRGCs influence a greater diversity of behaviors than was previously known and actually contribute to an important aspect of image-forming vision, namely contrast detection."

The Johns Hopkins team along with other scientists conducted several experiments with mice and found that when melanopsin was present in the retinal ganglion cells, the mice were better able to see contrast in a Y-shaped maze, known as the visual water task test. In the test, mice are trained to associate a pattern with a hidden platform that allows them to escape the water. Mice that had the melanopsin gene intact had higher contrast sensitivity than mice that lack the gene.

"Melanopsin signaling is essential for full contrast sensitivity in mouse visual functions," said Dr. Hattar. "The ipRGCs and melanopsin determine the threshold for detecting edges in the visual scene, which means that visual functions that were thought to be solely mediated by rods and cones are now influenced by this system. The next step is to determine if melanopsin plays a similar role in the human retina for image-forming visual functions."

Additional Vision-Related Cost of Cigarette Smoking

Cigarette smoking and male sex are significant risk factors for developing ocular sarcoidosis, according to a new study presented at the 2014 American Thoracic Society International Conference.

Sarcoidosis is a disease in which inflammation produces granulomas in organs throughout the body, most often in the lungs, but also in the eyes, lymph nodes or skin. Ocular sarcoidosis, which can lead to blindness, affects 25 to 50 percent of sarcoidosis patients.

"Risk factors for ocular sarcoidosis have not been well-studied," said lead author Adam Janot, MD, of the Virginia Commonwealth University School of Medicine in Richmond. "Accordingly, we reviewed the cases of 109 patients with biopsy-proven sarcoidosis and identified independent risk factors for developing ocular morbidity."

Of the 109 patients, 21 had ocular sarcoidosis. A significantly higher percentage of patients with ocular sarcoidosis were smokers (71.4 vs. 42 percent,

p=0.027) and were male (57.1 vs. 26.1 percent, p=0.009). Median duration of sarcoidosis was 10 years among patients with ocular sarcoidosis and four years among those without (p=0.031).

In analyses adjusting for age, race, sex and other factors, tobacco exposure was associated with a greater than fivefold risk of developing ocular sarcoidosis (odds ratio 5.24, p=0.007, 95% CI 1.58 to 17.41) and male sex was associated with a greater than sevenfold risk (odds ratio 7.48, p=0.002, 95% CI 2.152 to 26.006). Disease duration was no longer significantly associated with developing ocular sarcoidosis in the multivariate analysis. "Our study is the first to correlate smoking and male sex as risk factors for developing ocular manifestations of sarcoidosis," said Dr. Janot. "If confirmed in other studies, this information may give some insight into the pathology of the disease, can be useful in guiding treatment, and it adds ocular sarcoidosis to the numerous adverse health consequences of tobacco use."

Trinity Scientists Tie IL-18 to AMD

Scientists at Trinity College Dublin report a breakthrough with important implications for sufferers of age-related macular degeneration. The group found that a component of the immune system, IL-18, acts as a guardian of eyesight by suppressing the production of damaging blood vessels behind the retina at the back of the eye. In addition, in pre-clinical models, it was shown that IL-18 can be administered in a non-invasive way, which could represent a major improvement on the current therapeutic options that are open to patients.

"We were initially concerned that IL-18 might cause damage to the sensitive cells of the retina, because it is typically linked to inflammation. But surprisingly, we found that low

Droplet Lens Makes Smartphone a Microscope

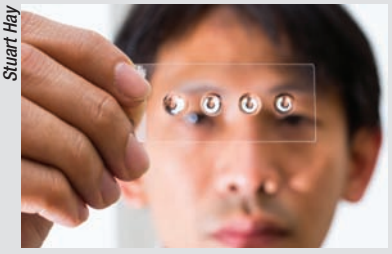
Australian scientists have invented a simple and cheap way of making a high-powered lens that can transform a smartphone into a high-resolution microscope.

Costing less than a cent, the lenses promise a revolution in science and medicine in developing countries and remote areas.

The lens fabrication technique was invented by Dr. Steve Lee from the Australian National University Research School of Engineering, who collaborated with Dr. Tri Phan from Sydney's Garvan Institute of Medical Research to find ways to transform the lentil-sized lens into a medical imaging tool.

The lenses are made by using the natural shape of liquid droplets. "We put a droplet of polymer onto a microscope cover slip and then invert it. Then we let gravity do the work, to pull it into the perfect curvature," Dr Lee said.

"By successively adding small amounts of fluid to the droplet, we discovered that we can reach a magnifying power of up to 160 times with an imaging resolution of four micrometers." The polymer, polydimethylsiloxane, is the same as that used for contact lenses, and it won't break or scratch.



Stuart Hay

Dr. Steve Lee inspects PDMS droplet lenses on a slide

"It would be perfect for the Third World. All you need is a fine-tipped tool, a cover slip, some polymer and an oven," Dr. Lee said.

The first droplet lens was made by accident. "I nearly threw them away. I happened to mention them to my colleague Tri Phan, and he got very excited," Dr Lee said. "So then I decided to try to find the optimum shape, to see how far I could go."

Dr. Lee and his team worked with Dr. Phan to design a lightweight 3D-printable frame to hold the lens, along with a couple of miniature LED lights for illumination, and a coin battery.

The technology taps into what the scientists are calling a "citizen science revolution," which is rapidly transforming owners of smartphones into potential scientists. There are also exciting possibilities for remote medical diagnosis.

Dr. Phan said the tiny microscope has a wide range of potential uses, particularly if coupled with the right smartphone apps. "This is a whole new era of miniaturization and portability—image analysis software could instantly transform most smartphones into sophisticated mobile laboratories," Dr. Phan said.

"I am most able to see the potential for this device in the practice of medicine, although I am sure specialists in other fields will immediately see its value for them."

Dr. Lee said the low-cost lens had already attracted interest from a German group interested in using disposable lenses for tele-dermatology.

"There are also possibilities for farmers," he said. "They can photograph fungus or insects on their crops, and upload the pictures to the Internet where a specialist can identify if they are a problem or not."

The lensmaking technology is described in the latest issue of *Biomedical Optics Express*.

doses had no adverse effects on the retina and yet still suppressed abnormal blood vessel growth," said Sarah Doyle, assistant professor in immunology at Trinity, who is the first author on the paper.

Dry AMD accounts for the majority of cases, but wet AMD causes more than 90 percent of blindness, generally central, associated with the disease. Because central vision accounts for almost all of our daytime visual acuity, wet AMD sufferers experience severe and profound day-to-day challenges.

The Trinity scientists found that IL-18 directly inhibits vascular endothelial growth factor production, and that it can work as effectively as the current treatment—intravitreal injection—when administered via a non-invasive intravenous injection in pre-clinical settings.

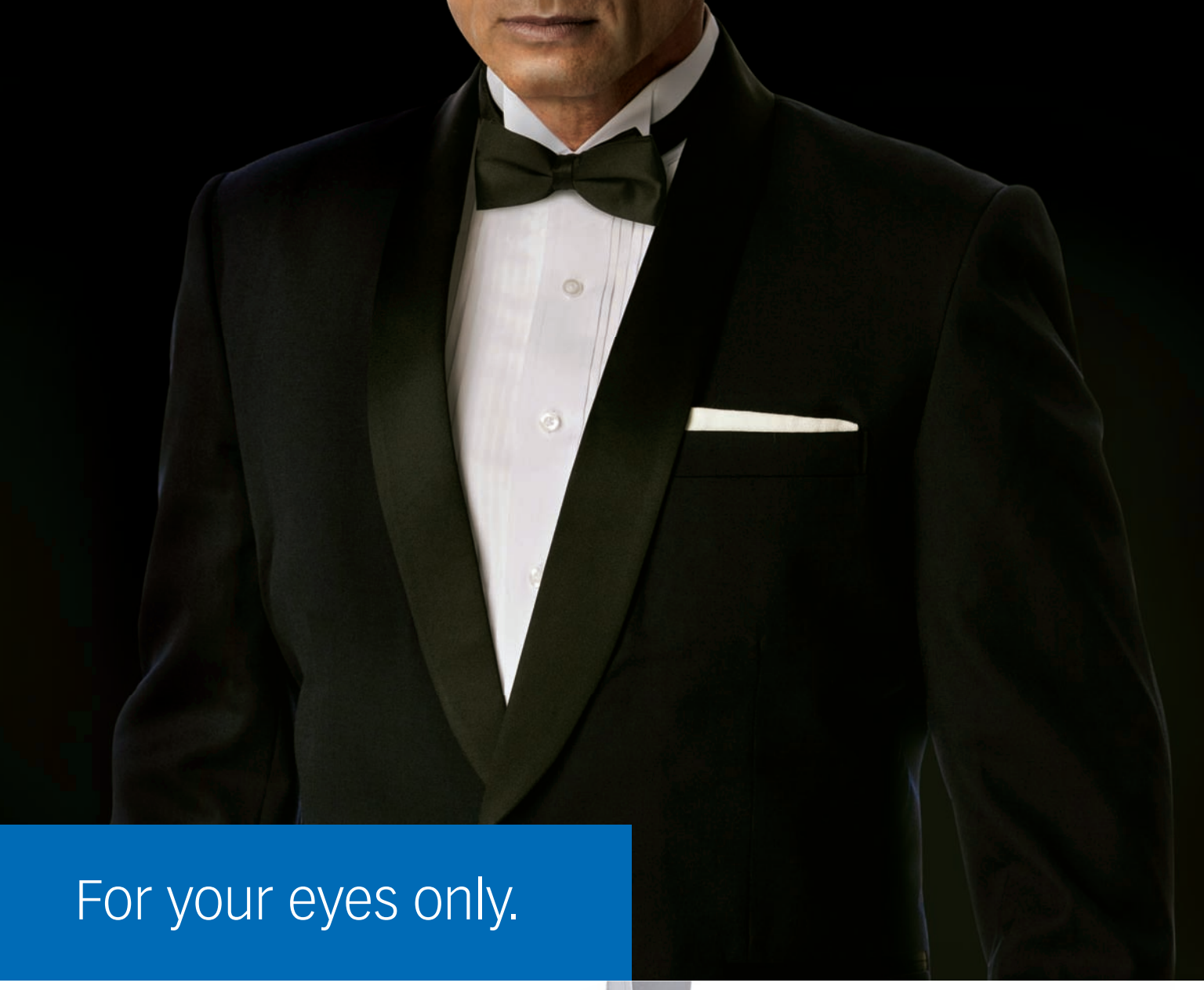
The research was published online in the international journal, *Science Translational Medicine*.

Orphan-Drug Status for Humira For Uveitis

AbbVie announced that the Food and Drug Administration granted Humira (adalimumab) orphan drug designation for the treatment of non-infectious intermediate, posterior, or pan-uveitis, or chronic non-infectious anterior uveitis, a group of rare but serious inflammatory diseases of the eye. AbbVie is investigating the efficacy and safety of Humira for the treatment of non-infectious uveitis, and the clinical program is in Phase III development. Humira is not currently approved to treat any form of uveitis.

Uveitis encompasses several inflammatory eye diseases. The associated inflammation causes damage of eye tissue leading to reduced vision and/or vision loss. While the exact cause of uveitis is unknown, this condition can be caused by an infection, autoimmune disease, medication, surgery or trauma to the eye. Symptoms of uveitis may include vision loss, blurred vision, eye pain and redness, as well as sensitivity to light. It is estimated that uveitis accounts for 10 to 15 percent of all cases of total blindness in the United States.

"Few well-characterized treatment options are available for patients suffering from uveitis, and the orphan drug designation recognizes the significant unmet need that exists within this disease," said Scott Brun, MD, vice president, Pharmaceutical Development, AbbVie. "AbbVie remains committed to the ongoing development of Humira to treat a variety of autoimmune diseases where patients have the potential to benefit." REVIEW



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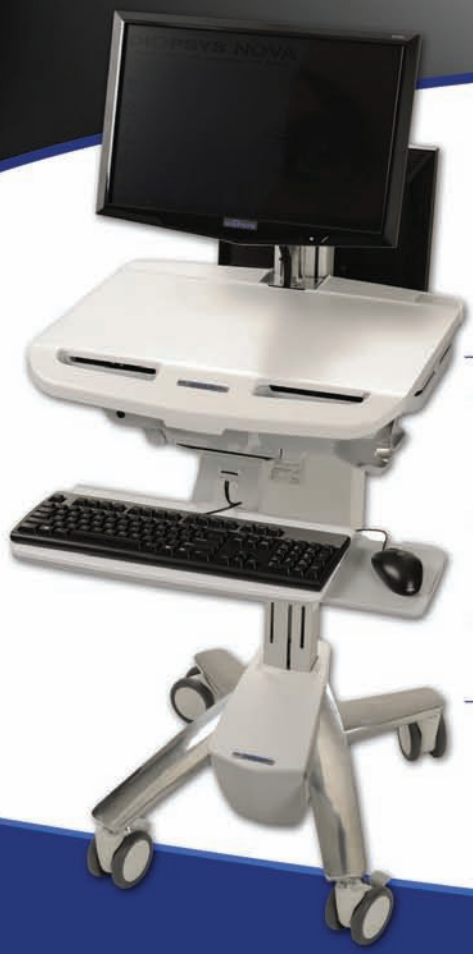

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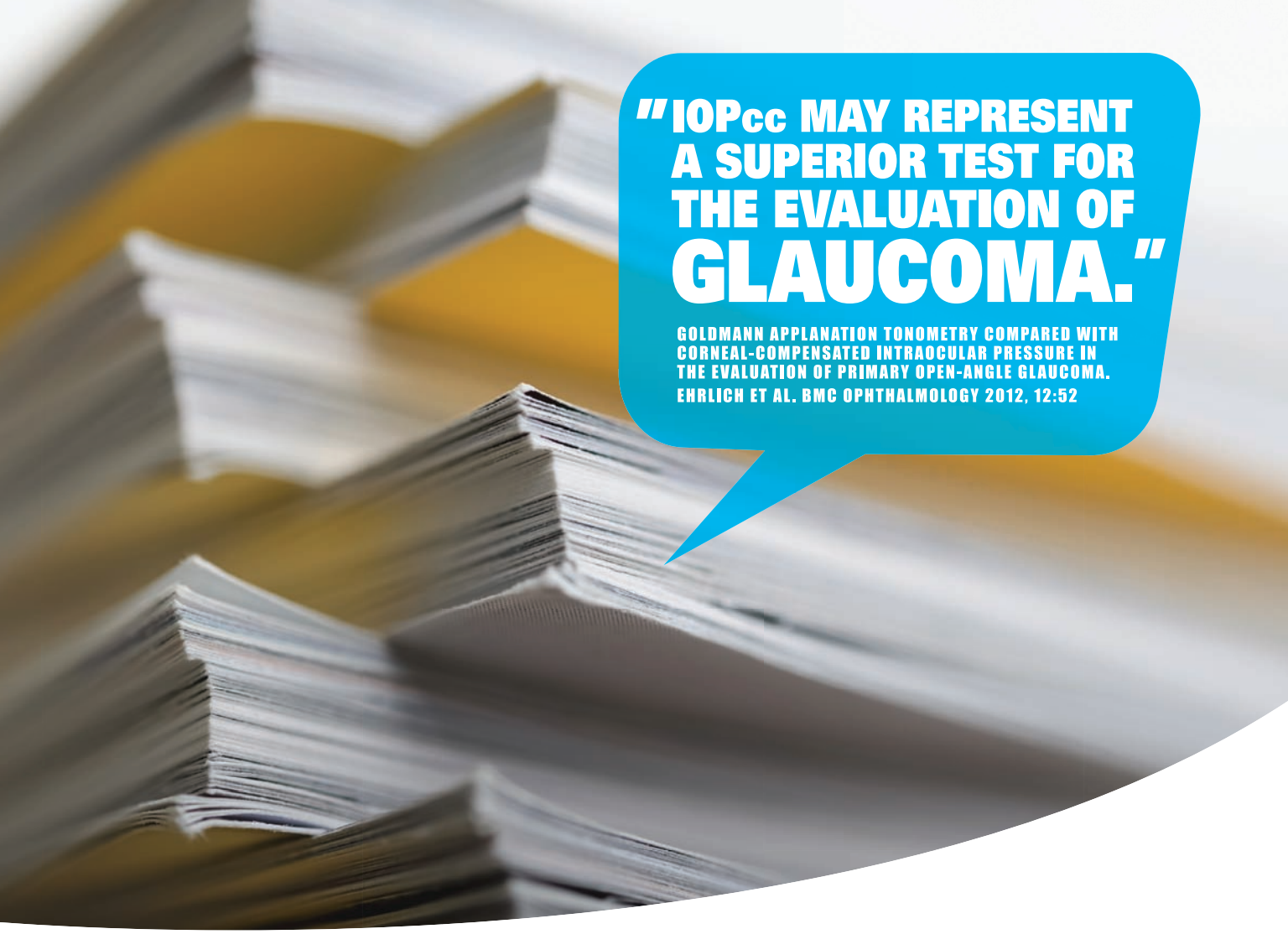

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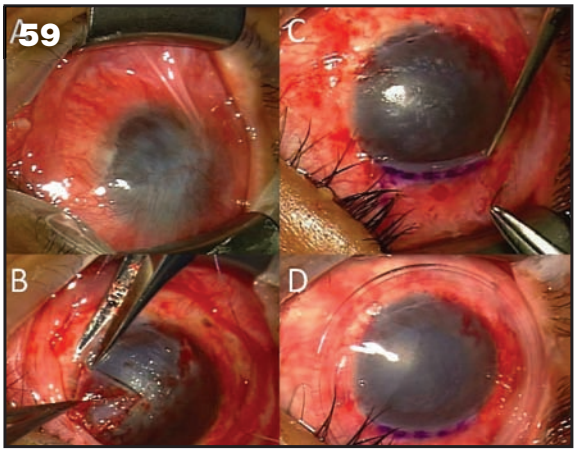

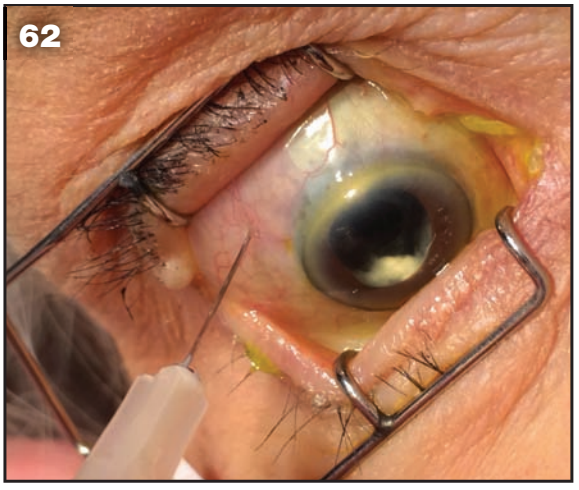

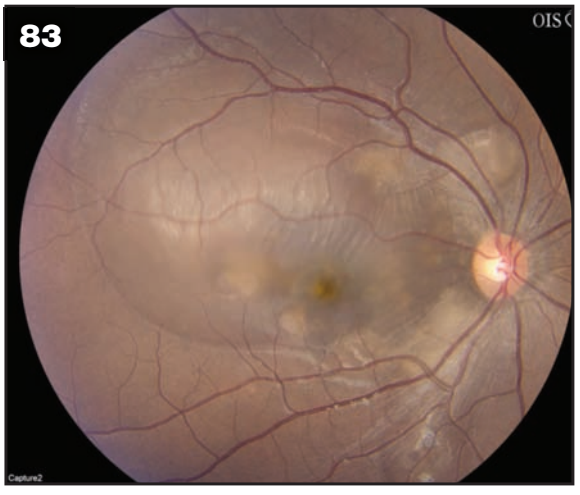

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REVIEW® of Ophthalmology

REVIEW Editor's Page

Christopher Glenn, Editor in Chief

Pushing the Adherence Rock Up the Hill

With the return of the annual Glaucoma Issue comes the unwelcome challenge of opening that issue with something definitive to say about the state of the disease and its treatment. I've swung and missed on about a dozen of those annual challenges so far, so you'd think I'd learn.

All of the usual treatment challenges remain and, as regularly happens, are reinforced by ever-growing bodies of data. Most recently, two studies from *JAMA Ophthalmology*.

One described an effort at the Wilmer Eye Institute to electronically monitor hundreds of patients over three months for their adherence to prostaglandin therapy. Results were expectedly spotty. About 80 percent of patients reported using their meds three-quarters of the time. Most of the remainder were deemed nonadherent, and were less likely to be able to name their glaucoma medication, less likely to agree that remembering to use the medication was easy, and more likely to agree with the sentiment that eye drops can cause problems.

A second study by the same researchers looked at the effectiveness of voice or text messages as an intervention to improve adherence. The patients deemed non-adherent in the first study were randomized to an intervention (daily messages, either text or voice, reminding patients to use their glaucoma medication) or no intervention. The median adherence rate in the intervention group increased from 53 percent to 64 percent. There was no change in the controls. Patients in the intervention agreed the reminders were helpful and that they would continue to use them outside the study. Implementing the intervention was estimated to cost about $20 per year per patient.

The sad state of glaucoma drug adherence seems to just go on and on. Any effort to push closer to solutions is worthy and this is in no way meant to detract from this work but if you substitute fax for text message, studies with results much like these might have easily been published in 2002. Perhaps the more widespread availability of today's handheld technology will make a dent where old media couldn't. Or there's another approach.

Microincision glaucoma surgeries have been on the scene for a couple of years now. At the outset they may have suffered the expected resistance or at least suspicion that accompanies any glaucoma surgery in the presence of an "effective" medical option like the prostaglandins. But the past few years have given surgeons the time to test some of these procedures. Even if you are skeptical, especially if you are skeptical, I invite you to take in the experience of the early users and see whether one of these procedures has a place in your practice.

Or you can wait for next year's adherence reports.

Donna McCune, CCS-P, COE, CPMA

Consider This Before Joining an ACO

Patients and providers can both benefit under a Shared Savings Program alternative to the standard fee-for-service practice.

Q What drives the Centers for Medicare & Medicaid Services to consider alternatives to paying providers under the current Medicare system?

A CMS believes that a shift in how providers are paid must occur to preserve the Medicare system. With 75 million baby boomers transitioning to Medicare starting in 2011, many question the continued viability of the current system. The *Medicare Trustees Report 2013* indicates a depleted Medicare Trust Fund in 2026, which was recently updated from 2024.

Q Are Accountable Care Organizations one such alternative payment system?

A ACOs are a form of a Shared Savings Program, which is an alternative approach to the current standard fee-for-service Medicare payment system. Shared Savings Programs reward providers who reduce cost, meet specific quality standards and continue to deliver high-quality care to patients.

Q Are Shared Savings Program concepts aligned with the Affordable Care Act?

A The Affordable Care Act created both the Medicare Shared Savings Program and the concept of ACOs. The ACA supports the purpose of these programs and states that the SSP "promotes accountability for a patient population and coordinates items and services under Part A and B, and encourages investment in infrastructure and redesigned care processes for high quality and efficient service delivery."

Q Will this Shared Savings Program save CMS dollars?

A CMS actuaries estimate a $940 million savings in four years, but this is less than 1 percent of the anticipated expenditures during that time. Long term, regulators hope for a shift in practice patterns that will ultimately lead to greater savings.

Q Is an ACO just another kind of health maintenance organization?

A No. A key difference between ACOs and HMOs is that providers run an ACO while insurance companies run HMOs.

Q How are Accountable Care Organizations structured?

A The structure of an ACO loosely resembles a health maintenance organization. An ACO is a provider network that coordinates to give quality care and reduce cost. Groups of

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INDICATIONS AND USAGE

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

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

WARNINGS AND PRECAUTIONS

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

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

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

DRUG INTERACTIONS

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

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

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

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

ADVERSE REACTIONS

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

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

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BRIEF SUMMARY

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

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ADVERSE REACTIONS

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

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

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

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

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

DRUG INTERACTIONS

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

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

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

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

OVERDOSAGE

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

NONCLINICAL TOXICOLOGY

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

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

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

PATIENT COUNSELING INFORMATION

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

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

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

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

Rx Only

Revised: 11/2011

Based on package insert 71816US15C

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physicians, hospitals and other healthcare providers come together to form an ACO. Once formed, the ACO must establish a governing body, complete an application for CMS and satisfy several requirements. An ACO must serve at least 5,000 Medicare fee-for-service patients, and providers must participate for at least three years.

Q Do different ACO models exist?

A Yes. ACOs must decide whether to participate in a one-sided model or a two-sided model. A one-sided model, also known as an "upside risk category of shared savings," permits sharing in the savings without liability for any losses. The two-sided model, "upside and downside risk category of shared savings," provides an opportunity for a greater savings share, but also holds the ACO accountable for losses. Specific loss thresholds exist to cap the ACO's loss sharing rate.

Q Will participating providers face reduced reimbursements on their claims if they join an ACO?

A No. Unlike HMOs, where physicians generally take lower reimbursement rates, ACO participants continue to receive the same payments under the Medicare Physician Fee Schedule.

Q What motivates a provider to join an ACO if reimbursement rate are the same as their MPFS rates?

A The motivator to participate in an ACO is the potential to receive a bonus. ACOs that save on the cost of care while maintaining quality share the savings with CMS. CMS will develop the metrics and benchmarks and perform periodic assessments of the ACO's performance.

In theory, if a group of providers can reduce duplication of services, only order necessary diagnostic tests and utilize preventative measures, then an ACO can improve care for the chronically ill and simultaneously lower cost. To better coordinate care, and with the beneficiaries' permission, ACOs will be able to obtain Medicare claim data for beneficiaries from CMS.

Q How will quality of care be measured?

A Measures of quality currently exist within the CMS bonus systems for the Physician Quality Reporting System, the now expired E-Prescribing program and Electronic Health Records. Therefore, ACOs do not have to reinvent quality measures, and many ophthalmologists and optometrists are already familiar with these quality measures, as shown by their high rate of participation in existing programs. The primary focus associated with quality will be on the following:

- patient experience;
- care coordination;
- patient safety;
- preventive health; and
- at-risk populations.

Q What if an ACO doesn't meet performance and savings benefits?

A It is possible that ACOs that do not make necessary benchmarks or savings targets will have to pay a penalty. ACOs that are unable to save money may also have to make further investments to address areas that are limiting their ability to make required benchmarks.

Q Must providers participate in an ACO?

A Participation in a Medicare ACO is voluntary, although CMS hopes that practitioners will see a benefit to joining.

Q Has CMS released any information about the money saved by ACOs?

A Yes. In January, CMS announced that ACOs saved $380 million in the first year of operation. Of the 114 Shared Savings Program ACOs that participated, 29 percent generated enough savings to be eligible for bonuses totalling $126 million.

Q Are patients required to join an ACO?

A No. Patients do not "join" an ACO; physicians do. Medicare fee-for-service patients continue to see Medicare providers as they always have. Some Medicare patients are assigned to an ACO, but patients may choose their providers without regard to the physician's participation or nonparticipation in an ACO.

Q May ophthalmologists and optometrists join more than one ACO?

A The final rule from CMS restricts providers of primary-care services to just a single ACO; however, specialists may join more than one ACO. This is ostensibly good news for eye-care providers, but there has been a glitch with specialists trying to enroll in more than one ACO: CMS limits practices that file claims with Evaluation and Management codes to one ACO. Consequently, many specialty societies are working with CMS to address this issue. REVIEW

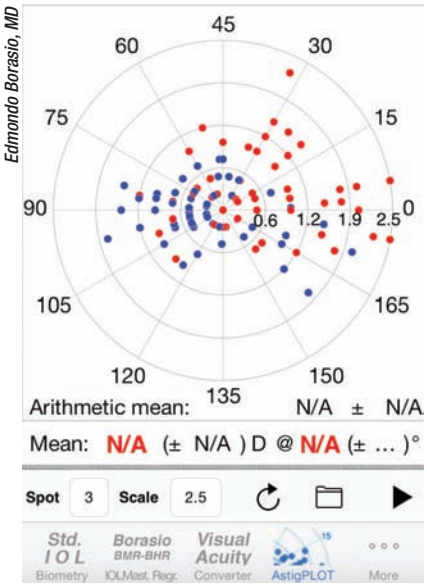
Ms. McCune is vice president of the Corcoran Consulting Group. Contact her at DMcCune@corcoranccg.com.


Smartphones Take On Astigmatism

Surgeons say you can make use of a powerful tool you almost always have with you to help tame patients' cylinder.

Walter Bethke, Managing Editor

A maxim among photographers states that "The best camera is the one you have with you," implying that no amount of expensive equipment is going to help you if it's sitting back at your house. Along those lines, ophthalmologists are discovering that the device most of them always have with them—their smartphone—may be useful for any number of tasks in and out of the clinic. One of these tasks is dealing with astigmatism, in terms of marking a toric intraocular lens patient's axis as well as calculating the surgically induced astigmatism. In this article, we'll look at three devices and apps, developed by surgeons, that harness the power of smartphones to help wrangle astigmatism.



The Astig PLOT app can graph patients' pre- and postop astigmatism and calculate your surgically induced astigmatism.

Astig PLOT

Astig PLOT is an app created by Edmondo Borasio, MD, head of cornea and refractive surgery at Moorfield's Eye Hospital in Dubai, United Arab Emirates, as a handheld method for surgeons to analyze astigmatism in a group of eyes. The application plots preop/postop astigmatism, aggregate astigmatism, surgically induced astigmatism and mean astigmatism. The program also supplies the standard deviation of the mean astigmatism and the surgeon's SIA.

To use Astig PLOT, the surgeon enters the input values into a comma-separated value file that he uploads to the application. "The surgeon enters pre- and postoperative K values, or refractions, and their respective meridians, or axes, and the program will calculate the mean arithmetic and mean vector SIA," explains Dr. Borasio. "The program shows the SIA in terms of sphere magnitude, cylinder magnitude and meridian/axis, and also shows the conversion of the SIA to Cartesian (x,y) notation. Cartesian notation is needed when calculating the mean of multiple individual SIAs."

Dr. Borasio says he developed the application after running into annoying impediments with statistical analysis programs. "I was fed up with using standard statistical analysis programs in which I had to format the graph, change the scale and reformat the axes each time I used them," he explains. "The Astig PLOT graphs are autoscaling to the highest value in the series, but also allow you to choose a custom scale if, for example, you wish to compare two graphs from two different series. In such a case, you would choose the same value for both graphs. There is also an option to plot on the same graph the individual patient results of two different series, which is useful for making a visual comparison. For example, the two

series could be pre- and postoperative astigmatism values of the same series or they could be the postoperative astigmatism from two different series in order to determine which of two techniques induced less astigmatism and achieved more consistent results."

Astig PLOT is available for iOS 4.3 or later on the Apple App Store, and costs $19.99. For information, visit edmondoborasio.com.

Steinert/Oliver Marker

The Steinert/Oliver Smart Phone Marker from Rhein Medical is the brainchild of Stanford University's Roger Steinert, MD, and Alejandro Oliver, MD, of Timmins and District Hospital in Timmins, Ontario, Canada. Rather than a software application, it's the fusion of an instrument and a smartphone. "We'd been looking to use smartphones as levels for toric lenses and toyed with several adapters for the different phone brands," explains Dr. Oliver, "There are so many phones out there, however, that it made it challenging to find one adapter that worked for all of them. So, we got the idea that we can hook the instrument to the earphone jack because, no matter what brand of smartphone you have or which generation it is, it has an earphone jack, and the earphone jacks are exactly the same across the board."

To use the marker, the surgeon downloads one of many level apps available and plugs the marker into the earphone jack. The level app will indicate when the marker is being held exactly horizontally level, allowing the surgeon to mark the patient's eye before surgery. "My preference is to mark the zero to 180 axis," says Dr. Oliver, "So, I basically mark at 3 o'clock and 9 o'clock. I mark this axis bedside after the patient's been through all the paperwork and before he's gotten any dilating drops. Then, in the operating room, I use a Mendez ring and a marker to mark the meridian of the astigmatism. You'll get a very durable mark, but you have to make sure the patient doesn't rub his eye after you've made it. This is especially true if there's lidocaine gel on the ocular surface. Alternately, you could also use the smartphone to mark the desired IOL axis in one step. To do that, however, you sometimes have to hold your hand in certain awkward positions. But, if you're OK with holding your hand like that, you can do the mark once and that's it; you won't have to bother making additional marks in the OR."

Alejandro Oliver, MD

The Steinert-Oliver Smart Phone marker fits into the earphone jack of a phone and uses a digital level to help mark the eye.

The kind of level application the surgeon uses can have an effect on the ease of use, and possibly the accuracy, of marks made with the instrument. "There are a lot of level apps out there for smartphones," says Dr. Oliver. "My preference is not the bubble-level app, but instead a level app with an actual dial. The bubble app is a little too qualitative for me—you can be off by a few degrees and not be

A New Online Algorithm to Help Diagnose Uveitis

The etiology of uveitis can be tricky to elucidate. It may involve a large differential diagnosis and require multiple lab tests. Ophthalmologists at the Medical University of South Carolina Storm Eye Institute have developed a simple algorithm to assist comprehensive ophthalmologists in the differential diagnosis and testing for uveitic patients. The algorithm goes through a series of simple questions about the particular patient and then delivers a likely differential and recommended testing. Disease entities are then linked into the American Academy of Ophthalmology EyeWiki website to provide more quality information quickly. It provides a great starting point for ophthalmologists to provide excellent care to the patient.

The algorithm has been developed into an online and mobile application, which is available free to all ophthalmologists. It is formatted for full web browsers, iPhone and Android operating systems. The developers hope the application helps ophthalmologists to hone both their differential diagnoses and the testing ordered.

The team that developed the algorithm includes George Magrath, MD, MBA, Andrew Reynolds, MD, Reid Turner, MD, and Lynn Poole Perry, MD, PhD. They invite all ophthalmologists to give the application a try and give them your feedback, as they are continually working to improve the application. Their goal is to provide a practical and useful tool to assist comprehensive ophthalmologists with the care of uveitic patients. The application is available at diagnoseuveitis.com. Contact Dr. Magrath at magrath@musc.edu.

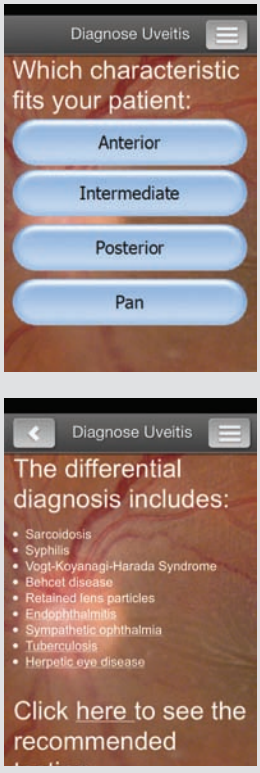
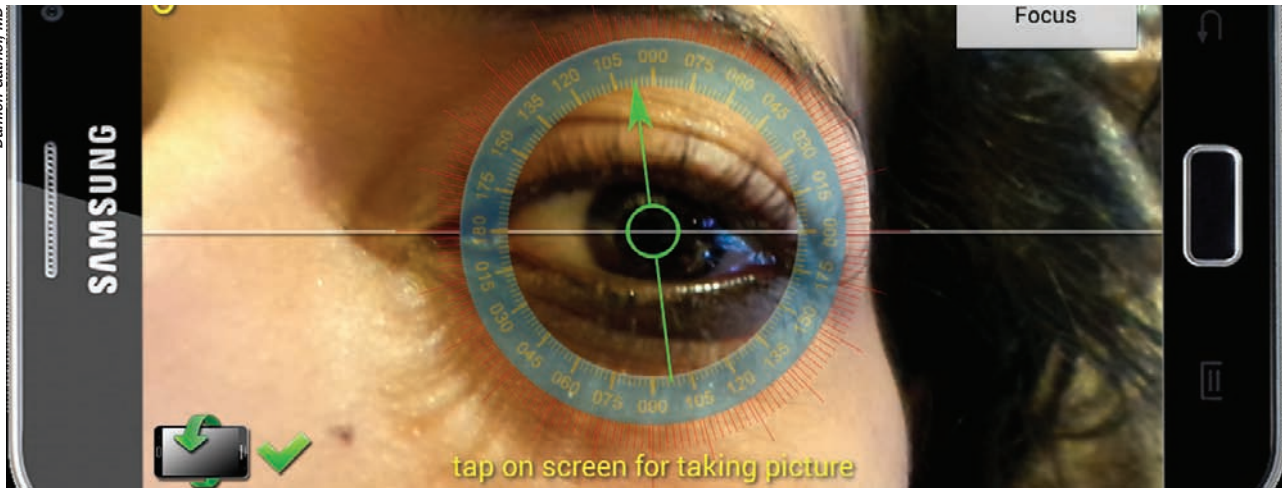


Figure 1. The Diagnose Uveitis application helps with differential diagnoses.



The Toreasy app for astigmatic axis marking uses smartphones' built-in accelerometers and gravity sensors to give a perfectly level horizontal line for use in marking the zero/180-degree axis without having to physically touch the patient's eye.

able to really tell. Therefore, a level app that has actual continuous gradations in degrees is ideal, since you get a quantity."

As with any kind of measurement, the axis marking process is only as good as the accuracy of the smartphone level application that you use in conjunction with the marker, so Dr. Oliver says it's important to make sure that when the smartphone says it's horizontal it actually is in that orientation. "There have been reports about errors with the accelerometers of certain devices that will lead to incorrect measurements," says Dr. Oliver. "Each level app you download has a calibration mode you can use. You want to make sure the level makes sense, so either use the device's calibration function or just take a level you have at home and make sure when the phone reads itself as horizontal it actually is."

The marker costs $295. For information, visit rheinmedical.com or call 1 (800) 637-4346.

Toreasy

Paris ophthalmologist Damien Gatinel says he developed the noncontact Toreasy astigmatic axis application to try to overcome sources of error that can crop up when patients move or tilt their heads. "When you mark the eye with a pendulum marker, you are trying to align the axis of the marking system with a horizontal orientation as perfectly as you can, so you'll at least know where the zero/180 axis is," he says. "But this relies on your marking skills, and the patient will sometimes rotate his head to try to make you more comfortable with your manual marking. But this rotation, unfortunately, introduces more error."

To try to eliminate having to touch the patient to acquire the axis, Toreasy takes advantage of smartphones' built-in accelerometers and gravity sensors. "Toreasy will constantly track the zero/180 direction on the screen using a bar that is unaffected by any rotation or tilt that you introduce by holding it. It will always give a level line. So, looking through the phone's display, you face the patient and ask him to slightly tilt his head until the zero/180 line goes through both pupils. This is the proper head orientation. You then ask the patient to stay still and you zoom in on one eye and take a snapshot. You then examine the picture you've taken and find a vessel or other mark on the eye and use an on-screen reticle to mark its position. The app will mark it on the screen and give you the landmark's position in degrees. If there are no vessels or prominent ocular structures that you can easily find, you can use a pen to place a mark on the eye wherever you want before you capture the image and place the reticle on that. Either way, you'll know exactly where that mark is in relation to the zero/180 axis in degrees.

"Then, at the time of surgery, you use a Mendez ring and the smartphone's images to mark the intended axis of the IOL," Dr. Gatinel continues. "You can do this because once you know that the blood vessel landmark is a certain number of degrees away from the horizontal line or the IOL axis, it's easy to move from that location to the proper IOL axis and mark it." To avoid obscuring important ocular landmarks, the degree ring on the Toreasy display is slightly transparent.

Dr. Gatinel says that, after having used the Toreasy marking system for a while, he's learned that the farther away the anatomic landmark is from the center of the image, the more precise the degree mark will be. "If you pull the reticle arrow using your

(continued on page 77)

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References: 1. Liew M, Zhang M, Kim E, et al. Prevalence and predictors of Sjögren's syndrome in a prospective cohort of patients with aqueous-deficient dry eye. *Br J Ophthalmol.* 2012;96:1498-1503. **2.** Kassan SS, Moutsopoulos HM. Clinical manifestations and early diagnosis of Sjögren syndrome. *Arch Intern Med.* 2004;164(12):1275-1284. **3.** Sjögren's Syndrome Foundation. Sjögren's Syndrome Foundation. 2013. Available at http://www.sjogrens.org. Accessed September 5, 2013. **4.** Shen L, Suresh L, Lindemann M, et al. Novel autoantibodies in Sjögren's syndrome. *Clin Immunol.* 2012;145:251-255.

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Time to Join the MIGS Movement?

Christopher Kent, Senior Editor

Microincision glaucoma surgeries are changing the way surgeons think about treating this disease.

In recent years, glaucoma treatment has relied heavily on medications and lasers. Surgical options—primarily trabeculectomy and tube shunts—have been reserved for patients with advanced disease, because the level of risk associated with those procedures is far greater than those associated with medications and laser treatments. Resorting to surgery has only made sense when a patient was in serious trouble.

Now that is changing, thanks to the development of new surgical procedures that involve far less risk: the microincision glaucoma surgeries, or MIGS. Current options in this category include the iStent, the Trabectome and endoscopic cyclophotocoagulation, or ECP (although not everyone considers ECP a MIGS procedure). In addition, several more MIGS options are in the pipeline. Suddenly, because of the low risk associated with these procedures, using surgery to address mild, early cases of glaucoma is becoming a valid option. Furthermore, because they can be performed through a cataract incision, surgeons are using these procedures as adjuncts to cataract surgery. In many ways, it's a revolution in glaucoma treatment—one being felt by surgeons who would seldom have attempted to treat glaucoma with surgery in the past.

Brian Francis, MD, MS, professor of ophthalmology in the Glaucoma Service at the Doheny Eye Institute, Geffen School of Medicine, University of California, Los Angeles, has used all of the current MIGS options. "A good working definition of MIGS would be glaucoma surgeries that are appropriate for mild to moderate glaucoma, done through a small incision, that combine well with cataract surgery and typically are extremely safe," he says. "Their IOP-lowering ability is augmented when they're combined with cataract surgery. And, they generally don't limit your future options, in terms of traditional filtering surgery, because they don't scar the conjunctiva. In fact, some people include the lack of a bleb in their definition of MIGS." (He notes that most doctors do not consider canaloplasty to be a MIGS procedure because of the need for external dissection.)

Here, Dr. Francis and three other surgeons with extensive MIGS experience offer their thoughts on how these procedures compare to each other, why they're worth adopting, and what the future may hold.

Working With the iStent

Thomas W. Samuelson, a founding partner and attending surgeon at Min-

This article has no commercial sponsorship.

nesota Eye Consultants in Minneapolis and an adjunct associate professor of ophthalmology at the University of Minnesota, was an investigator in the initial United States PMA/IDE trial of the iStent, which is implanted in Schlemm's canal as a means of allowing more aqueous to reach the collector channels into which the canal drains. As a result, he's been implanting them for six or seven years. "The idea behind the iStent is improving physiological outflow," he explains. "The way the iStent accomplishes that is by utilizing the physiological outflow system.

"There are many advantages to this approach, but the most significant advantage by far is safety," he continues. "In the United States premarket approval trial, patients were randomized to cataract surgery alone or cataract surgery plus iStent. There was no difference in adverse events between the groups. So, the addition of the iStent did not adversely affect visual outcomes or subject the patient to a greater frequency of side effects as compared to phacoemulsification alone. The safety of the iStent was clearly established.

"In terms of efficacy, both groups in that trial had improved IOP following the surgery, but the patients receiving an iStent were statistically more likely to either be off medications completely or require fewer of them," he notes. "So that was the benefit: Patients achieved a modest reduction in pressure and medication use without being subjected to significant risk. That's an option we didn't have in the past, prior to the MIGS procedures. It's an excellent adjunct to our surgical offerings." *(For advice on using the iStent in surgery, see the sidebar on p. 28.)*

One issue that has been raised in connection to the iStent is whether implanting more than one will produce a better result. Some work by surgeons such as Ike Ahmed, MD, in Toronto, suggests that this may be the case. "Many surgeons believe that placing two iStents will cause a greater pressure reduction because a greater portion of the outflow system is influenced," says Dr. Samuelson. "Likewise, that's part of the reason for the development of the Hydrus device [still in the pipeline]; it's an 8-mm stent, so it covers a much broader segment of the trabecular meshwork and Schlemm's canal. It should bring more collector channels into play, hopefully providing greater efficacy." Dr. Samuelson notes, however, that the potential superiority of using multiple iStents hasn't been clinically proven in a randomized trial. "It makes sense intuitively, but we need more data to support and further delineate that approach, especially to help guide us on the ideal location to implant," he says.

Dr. Samuelson points out that the second-generation iStent, currently under development, is designed to allow two iStents to be implanted at the same time. "You can put two in while only entering the eye once," he says. "However, there's no reason to be apologetic if you only put in one iStent. That was the protocol in the U.S. trial; and frankly, putting in more than one iStent is generally not covered by third-party payers. So patients will be on the hook for the cost of the second device."

John Berdahl, MD

When preparing to implant an iStent (left) tilt the microscope 30 degrees and the patient's head 30 degrees away from you (right). Have the patient look in the direction of the contralateral ear. Then apply the gonioscope, insert viscoelastic and do fine focusing.

Using the Trabectome

In the Trabectome procedure, the surgeon uses a disposable handpiece equipped with irrigation and aspiration ports to perform bipolar cautery on the trabecular meshwork, ablating a portion (or all) of the meshwork as a means to increase aqueous outflow. "The Trabectome is definitely a MIGS procedure," says Dr. Francis. "It's angle-based; it has an extremely good safety profile; it's very effective in mild-to-moderate glaucoma and when combined with cataract surgery. The fact that it doesn't require placing a foreign body such as a stent inside the eye doesn't disqualify it; in fact, that may be an advantage."

Dr. Francis offers advice for surgeons considering adopting the Trabectome:

• ***Learn the goniosurgical approach.*** "This is important for both the Trabectome and the iStent," says Dr. Francis. "This is a different type of surgery. I'd recommend increasing your use of gonioscopy in the clinic so you become very familiar with the trabecular meshwork and angle landmarks. Also, practice using a goniosurgical lens with your cataract patients. When you're finishing up a standard cataract surgery, take a couple of minutes to tilt the head and microscope in

the manner you would if performing gonio surgery; place the goniolens on the eye and practice looking at the angle. I think that's probably the most helpful thing you can do; it helps you get used to that view. When you're ready to do the surgery, the fewer things that are novel, the better."

• ***Pick appropriate patients.*** "When selecting patients for this procedure, be sure they have mild to moderate glaucoma, have a target pressure in the mid-teens and can tolerate medications after surgery, should they be needed," he says.

• ***Do careful goniotomy on each Trabectome patient before surgery.*** "You need to know what the patient's angle looks like before you go in there," he says.

• ***Make sure you're in the trabecular meshwork.*** "The main thing is that you need to hit the target tissue," says Dr. Francis. "In most cases you can do this because the angle landmarks are usually clear and the trabecular meshwork usually has some degree of pigment.

"There are a couple of tricks you can use if the trabecular meshwork is not readily visible," he continues. "One is to actually decompress the eye, letting it become hypotonous for about 10 seconds. That allows blood to reflux into Schlemm's canal. Then, even after you repressurize the eye, there's a nice red stripe defining the trabecular meshwork. It makes it very easy to see the target. Also, if you're confused about the angle landmarks, you can look at other parts of the eye. Usually the inferior segment of the angle is the easiest to identify because it has some pigment in the trabecular meshwork. So in a pinch, look inferiorly, locate the trabecular meshwork and follow the anatomy around to the nasal quadrant."

• ***Learn to know when you've gone too deep.*** "It's easy to go too deep," says Dr. Francis. "If this happens, you'll feel the resistance and see the eye rotating because the tip is probably digging into the outer wall of Schlemm's canal. When you're correctly ablating the trabecular meshwork, there's almost no resistance; the device moves very easily through the tissue. That's one reason the company requires wet-lab training; you learn to recognize the feeling that lets you know you're in the right area."

• ***Flare the internal opening of the corneal incision.*** "This means instead of going straight in with the keratome blade, once you're inside, you turn the blade side to side," Dr. Francis explains. "It makes the internal opening larger than the external opening. That allows you to move the instrument side to side inside the eye without tugging on the corneal tissue. That, in turn, allows you to do more ablation.

Pearls for Implanting the iStent: Ready, Set, Go!

Get Ready:

• Familiarize yourself with the intraoperative angle anatomy. Visualizing the angle is more difficult during surgery, so becoming familiar with this experience is the most important thing you can do.

Get Set:

• Tilt the microscope 30 degrees away from you.
• Tilt the patient's head 30 degrees away from you.
• Adjust the oculars.
• Have the patient look at his contralateral ear.
• Apply the goniolens and insert viscoelastic. Make sure to insert an appropriate amount of viscoelastic—enough to prevent corneal folds. A cohesive viscoelastic placed adjacent to the stent is ideal.
• Do fine focusing.

Go:

• Don't Go Yet! Practice the motion of iStent insertion using a Sinskey hook. A good time to do this is at the end of your cataract day.
• Let the goniolens float on the eye; don't press down on it. Pressing down on the lens can cause folds, which will make it hard to see during the procedure.
• Be deliberate. Don't poke at the trabecular meshwork; it will bleed and viscoelastic will escape from the chamber.
• Place the stent as if placing your foot into a slipper. Place the toe in first; then slide the foot in; then push the heel down.
• Approach Schlemm's canal with the device at about a 15-degree angle relative to the canal. If the angle is too steep, you'll engage the posterior wall of the canal.
• Adjust your approach based on whether you're placing a right or left stent. Some surgeons prefer a forehand or backhand maneuver.
• Sliding in should occur without too much resistance. If you meet too much resistance, change the angle of the stent.
• Release the torque. If you don't release the torque, the inserter can flick the stent out of the canal when the stent is released.
• Push the button.
• Nudge the stent forward and push it down into the canal.
• Thoroughly remove the viscoelastic. Retained viscoelastic can cause IOP spikes, so remove it thoroughly—including any trapped behind the IOL.

— John Berdahl, MD, Sioux Falls, S.D.

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

Dosage and Administration
The recommended dosage is 1 drop in the affected eye(s) once daily in the evening. TRAVATAN Z® Solution should not be administered more than once daily since it has been shown that more frequent administration of prostaglandin analogs may decrease the IOP-lowering effect. TRAVATAN Z® Solution may be used concomitantly with other topical ophthalmic drug products to lower IOP. If more than 1 topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.

IMPORTANT SAFETY INFORMATION
Warnings and Precautions

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

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

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

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

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

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

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

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

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

For additional information about TRAVATAN Z® Solution, please see Brief Summary of full Prescribing Information on adjacent page.

References: 1. Lewis RA, Katz GJ, Weiss MJ, et al. Travoprost 0.004% with and without benzalkonium chloride: a comparison of safety and efficacy. J Glaucoma. 2007;16(1):98-103. **2.** Gross RL, Peace JH, Smith SE, et al. Duration of IOP reduction with travoprost BAK-free solution. J Glaucoma. 2008;17(3):217-222.

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TRAVATAN Z®
(travoprost ophthalmic solution) 0.004%

TRAVATAN Z®

(travoprost ophthalmic solution) 0.004%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

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

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

CONTRAINDICATIONS
None

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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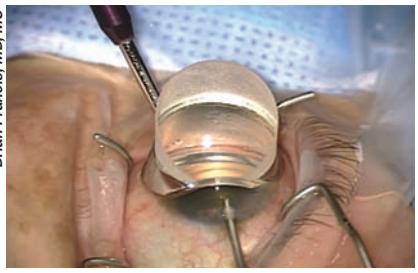
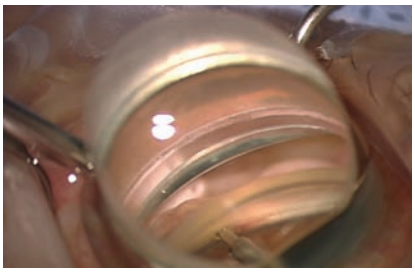




Using the Trabectome. Left: The tip of the instrument is inserted with the gonio lens on the cornea. Right: Ablation of the trabecular meshwork in the counterclockwise direction. Note the white appearance of the outer wall of Schlemm's canal to the right of the Trabectome tip, showing that the meshwork there has been ablated.

"Typically, a beginning surgeon can do about three clock hours, or 90 degrees, fairly easily," he continues. "But when you become more comfortable using the device and you have a flared incision, you can ablate as much as five or six clock hours, treating more of the angle. Treating more of the angle does seem to correlate with better lowering of IOP because you're accessing more of the collector channels. However, I don't recommend that surgeons new to the procedure try to ablate five or six clock hours. You'll end up slipping out of Schlemm's canal and causing iris trauma or corneal trauma. Start with what's comfortable and work up to doing larger segments of the angle."

ECP as MIGS

As previously noted, not every surgeon considers ECP—in which fiber optics allow the surgeon to partially coagulate ciliary process tissue from inside the eye, reducing the production of aqueous—one of the MIGS procedures. "I don't know whether I'd classify ECP as a classic MIGS procedure, but it's conceptually similar," says Dr. Samuelson. "It's a less-invasive approach to pressure reduction, and it has considerably less risk than trabeculectomy or aqueous drainage devices. So I think it's reasonable to talk about ECP in the same conversation as MIGS procedures. There are patients in whom ciliary body ablative procedures may be beneficial, so I do believe there's a role for ECP in select patients."

Robert J. Noecker, MD, MBA, believes ECP does qualify. (Dr. Noecker is in private practice at Ophthalmic Consultants of Connecticut in Fairfield and is an assistant clinical professor at Yale University School of Medicine; he has experience with all three of the procedures discussed here.) "You could say ECP was the original MIGS procedure," he notes. "Several things make it MIGS-like. For one thing, when you do it in combination with cataract surgery you're using the same incision you've already made for the cataract surgery, so the risk of infection is no greater than with cataract surgery alone. ECP also lowers eye pressure moderately rather than dramatically, just as the other MIGS procedures do, so there's no chance of hypotony. And, you can combine it with other MIGS procedures. The counter-argument might be made that it does induce inflammation, probably more than cataract surgery alone and more than implanting an iStent. However, I find the inflammation to be very manageable, and if you manage it aggressively everything is fine. ECP is pretty benign when done properly, compared to just about any other procedure."

One factor working against more widespread use of ECP, says Dr. Noecker, is the capital cost involved in purchasing the equipment. "Also, some doctors may still equate using ECP with the issues surrounding transscleral cyclophotocoagulation," he says. "Of course, TCP is a lot more traumatic to the eye than ECP, in terms of causing inflammation and affecting structures we don't necessarily want to affect."

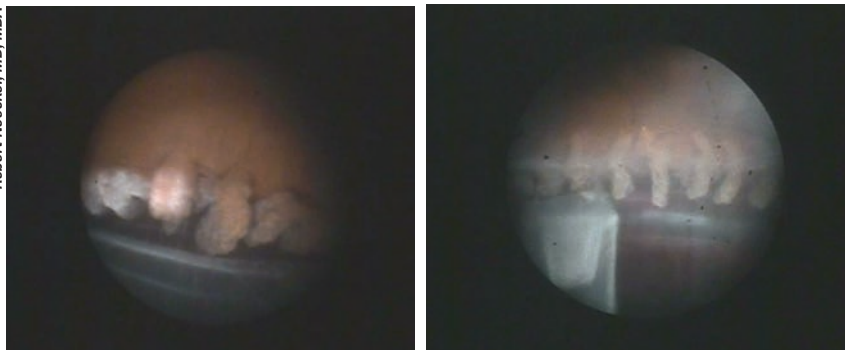
Dr. Francis does see ECP as more versatile than the other MIGS procedures. "ECP can be used in open-angle glaucoma, narrow-angle glaucoma, even neovascular glaucoma," he notes. "And it can be used after another procedure has failed. In other words, if a trabeculectomy or tube shunt has failed, you can go in with ECP and get additional pressure lowering. The other MIGS procedures are generally reserved for first-line surgery."

Dr. Francis adds that the endoscope can be put to other uses as well. "You can use it to view the lens if you have problems with a lens implant," he points out. "You can look at zonular stability if you're trying to decide whether or not to put in a sulcus lens. You can even use it for retinal procedures when you have a corneal opacity and can't see the retina, or when you want to work inside the eye very anteriorly, even anterior to the equator."

Dr. Noecker offers these suggestions when first attempting ECP:

- ***Pick easy cases.*** "Start with a normal-sized eye, not a small eye, and avoid eyes that have other problems," says Dr. Noecker. "It's all about recognizing the anatomy, so pick eyes in which the anatomy is easy to work with and you have a good view. If you can't see the anatomy, you don't want to treat."
- ***Be thorough in your treatment.*** "The average eye has about 70 ciliary processes," he says. "If you treat all 70 you'll get the best result. If you only treat 30 of them you won't lower pressure quite as well because there are still a lot of processes making aqueous."
- ***Treat inflammation aggressively.*** "I'm very proactive about control-

Robert Noecker, MD, MBA



ECP can be performed through the capsule or above the bag. Left: The former approach allows for more posterior access to the ciliary processes (turning white with treatment). The gray line is the front of the capsule. Right: Using the above-the-bag approach the processes are visible, but access to the posterior aspect is limited by the bag. (Note the residual cortex from the cataract surgery, only visible because of the endoscopic view.)

ling inflammation," he says. "I give IV steroids at the time of surgery; I put them inside the eye; and I use intensive eye drop therapy right out of the gate. For the first few days postop I use a lot of steroids, and the eyes quiet down very quickly."

Comparing Efficacy

One issue facing surgeons who are interested in adopting one of the MIGS procedures is deciding which one to adopt. Of course, there are a number of ways to compare procedures; one of the most obvious ways is to compare their efficacy and risk of complications. This is difficult to do definitively, because so far there's no clinical data from head-to-head, randomized, controlled comparisons of the MIGS procedures. (Dr. Noecker also believes surgical results of the different MIGS procedures are difficult to compare because the results are somewhat surgeon-dependent.)

Dr. Noecker does see some differences in terms of risks and complications. "I'd say the iStent induces the least inflammation," he says. "It's very small and goes into a relatively small part of the trabecular meshwork. It's usually a very atraumatic insertion, so in terms of inflammation, I treat those patients no differently than those who are getting straightforward cataract surgery. Trabectome would come in second in terms of inflammation; it does cause a little bit. ECP probably causes the most inflammation, although it certainly is manageable.

"Trabectome also comes with a risk of bleeding, which can mess up the patient's vision in the short term," he continues. "I wouldn't use the Trabectome with a monocular patient because there's a chance you'll get blood in the eye that will interfere with his vision for a few weeks. With iStent there's a very low occurrence of that, although you still have to be careful with people who are on blood thinners; even iStent patients can get hyphemas postoperatively. If you look at morbidity or visual downside, I'd say that ECP is probably the most favorable of the three.

"In terms of efficacy, my impression after having done all three procedures is that ECP is the most efficacious thing I do, followed by Trabectome and the iStent," Dr. Noecker says. "The short-term efficacy achieved with the Trabectome may be comparable to what you get with ECP, but I see more failures with the Trabectome long term. That's probably a result of the mechanism by which it works. You're cauterizing away a strip of the trabecular meshwork, which eliminates resistance at the angle. That can be very effective in the short term, but anytime you're cauterizing something, at a cellular level you're going to get chronic inflammation. You're creating a cleft, and the body doesn't like to leave clefts alone. If the body can figure out a way to close it, it will. I think that's why the Trabectome sometimes has late-term failures; over time the healing response catches up in many patients. Of course, if a procedure controls IOP for a few years and minimizes the need for medications, I'd say that's not time badly spent, even if the problem is not resolved forever—as long as the cost isn't too great."

Dr. Noecker admits that ECP and iStent can also fail in some patients. "I've been doing ECP for a long time," he says. "I've had patients in whom one treatment lasted forever; they've come back time and time again and never needed any further treatment. But I've also had patients who needed another therapy after a couple of years. Failures will happen with any procedure, so I think it's the rate of failure that's important. Right now we don't know what the rate of failure will be for the iStent; it's only been commercially available for about a year. In my hands, it seems to be pretty stable in the first year. Beyond that we have some clinical trial information, but not much real-world information."

In terms of efficacy, Dr. Samuelson agrees that Trabectome and iStent probably have similar pressure-reducing capabilities, at least in the short term. "Long term, I prefer the minimally invasive approach of the iStent," he says. "The Trabectome procedure involves more tissue destruction; you're ablating and removing tissue, so it's doing more to the eye. In contrast, an iStent does very little to the eye. Of course, that doesn't mean it's necessarily a better procedure; those who advocate the Trabectome feel that procedure offers some advantages as well.

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"In terms of the efficacy of ECP, I've often used ECP as a means to help manage pressures that aren't responding enough to other approaches," he continues. "If I place an aqueous drainage device and the pressure is too high, sometimes I'll use ECP to lower the pressure further instead of putting a second tube shunt in. Brian Francis from USC has published on this approach."

Dr. Samuelson says he suspects the iStent is the safest of the MIGS options (including ECP). "Without a comparative trial, of course, that's only conjecture," he says. "However, the iStent is the only one that's gone through a United States PMA trial. No other glaucoma device in history has gone through the scrutiny that the iStent had to go through as part of its FDA approval process. So we can say that we know with confidence, based on a very well-controlled, PMA trial, that there are few if any serious adverse effects from the iStent. We don't have that same kind of data for ECP or Trabectome—although in my experience they are safe, and the data that's available suggests they are safe."

Comparing Skills Sets

"Clinicians probably underestimate the learning curve for these devices, based on videos and lectures they've seen," says Dr. Samuelson. "However, it's definitely within the purview of most skilled anterior segment surgeons to master the iStent, for example, in 20 cases or so. It depends in part on how far apart in time you do the procedures. If you only do one a month, it will take you a while to become good at it. But if you do several on your first day and do several more within a week or two, I think you can master it fairly quickly. The important thing to understand is that there is a learning curve, and it's important not to underestimate that.

"For example, you wouldn't want to do your first iStent case on a day when your schedule is overbooked and time is tight," he says. "You want to start when you can take your time. I usually tell new surgeons that whatever their normal cataract time is, they should allow two or three times that much for their first phaco-iStent procedure. Later on it will go much faster, but at the outset it's better to not feel stressed during the procedure."

Dr. Samuelson believes the first few cases with the Trabectome are a little bit easier than the first few with the iStent. "Both the Trabectome and iStent do require very skilled intraoperative gonioscopy," he notes. "In general, they're comparable, but because the iStent requires placement of a device in a very specific location and orientation, I think it's a little bit more challenging. I'd say that ECP is probably the easiest of the three, although not by a great amount."

Dr. Noecker notes that the iStent, Trabectome and ECP all require some special skills. "To use the Trabectome or iStent you have to use intraoperative gonioscopy," he explains. "That's a separate skill that does require some practice, even though some of us use gonioscopy in the office on every single patient every single day. The reality is that doing it in the OR is a little bit different; it takes a while to learn to do it reproducibly, and the first time you try it can be very unnerving. ECP also involves a different skill set; you have to get used to how it looks on the TV monitor when you move your hand and use the tools inside the eye, but you can learn that quite readily."

Dr. Francis agrees. "Performing ECP is a bit different from what we're used to in ophthalmology," he says. "With the microscope we have a 3-D view, limited to what we can see from the front of the eye. With ECP, you can go anywhere inside the eye that the endoscope can go, but instead of looking through the microscope you're looking at a 2-D screen."

"All of the MIGS procedures require some special skills," adds Dr.

SLT vs. MIGS

With selective laser trabeculoplasty being the most high-profile surgical advance in recent glaucoma history, comparisons to MIGS should be expected. Robert J. Noecker, MD, MBA, in private practice at Ophthalmic Consultants of Connecticut in Fairfield and an assistant clinical professor at Yale University School of Medicine, says he doesn't think of MIGS as an alternative to SLT, but that they can be additive. "I see SLT as something to do before the patient has to go to the OR," he says. "I think SLT is the safest thing I do in glaucoma care, and I use it in many patients as a first-line treatment, even before medications. That said, it doesn't work in everybody, and it doesn't lower eye pressure in people who really have serious glaucoma.

"These days, if a glaucoma patient already has vision loss, I need to lower the eye pressure by at least 30 percent," he notes. "Sometimes that happens with SLT, but a lot of people don't get that result. I think many patients should have SLT in the office first, just because it's very safe. If the patient ends up needing to go to the OR, adding a MIGS procedure to a pressure drop from SLT might be sufficient to keep the patient from needing something more invasive in the future."

"SLT is even less invasive than MIGS because it doesn't require entering the eye," notes Thomas W. Samuelson, MD, a founding partner of Minnesota Eye Consultants in Minneapolis and an adjunct associate professor of ophthalmology at the University of Minnesota. "However, I hope we'll get a longer-lasting effect with these procedures than we might with SLT. They're really completely different procedures."

—CK

Noecker, "but they're all learnable."

Financial Pros and Cons

"I'd say the Trabectome is probably the most expensive in terms of capital investment, at least in the short term," says Dr. Noecker. "You have to buy the device and you have reusable costs, too. With ECP you have to buy the laser and endoscope, but you can use the endoscope for different applications such as retina and glaucoma procedures or manipulating inside the eye. The iStent has the smallest upfront costs; you need a goniolens and the device itself. You can order one and get reimbursed for it relatively quickly."

Dr. Francis concurs. "In terms of costs, the iStent is on a use-by-use basis; you pay for it, you use it," he says. "The Trabectome involves a capital expense for the unit itself and a per-use cost for the disposable handpiece. ECP also has an initial cost for the unit, and there are handpieces to purchase, but the handpieces are not disposable; you can generally get 15 to 20 uses out of each one.

"From the patient's perspective, the MIGS procedures are similar in cost," he adds. "The only significant difference occurs if the surgeon uses more than one iStent during cataract surgery, or if a patient wants an iStent when cataract surgery isn't involved. The iStent is only approved for use with cataract surgery, with a single iStent. Outside of those parameters, the patient has to cover the additional cost."

Dr. Noecker notes that in terms of reimbursement, ECP and the Trabectome have been around for a while. "Claims involving them are rarely rejected," he points out. "They're pretty much covered by commercial insurance and Medicare and Medicaid, although the Trabectome may be a little less likely to be universally reimbursed. The drawback with the iStent is that although it's Medicare-reimbursable right now, it's limited in terms of commercial coverage, and in my experience, it's not covered by Medicaid. So you can't do it on every patient you might want to do it on. The other restriction with the iStent is that it's only approved and reimbursed in combination with cataract surgery, so you won't get reimbursed for implanting it in a patient who has already had cataract surgery. You also may not be reimbursed if the patient has a type of glaucoma other than open-angle glaucoma."

Taking the Plunge

Once you've decided to add MIGS to your armamentarium, surgeons offer these suggestions:

• ***Don't under-prepare.*** "Make sure you do all of the certifying courses that are necessary," says Dr. Samuelson. "Watch lots of videos of the procedure in question."

• ***Practice visualizing before attempting the procedures.*** "With any of these new techniques it's helpful to try pretending that you're going to take the next step without actually doing so," says Dr. Noecker. "With ECP, during a routine cataract surgery, inflate the eye and practice just looking at the ciliary processes with the endoscope. If you'll be using the Trabectome or iStent, practice getting a pristine gonioscopic view so that won't be an issue when you actually begin doing the procedure."

• ***Practice gonioscopy following routine cataract surgery.*** Dr. Samuelson says it's important to master intraoperative gonioscopy before taking on your first case. "Intraoperative gonioscopy is very different from gonioscopy in the office," he points out. "They're not even comparable—there's more difference than similarity. Patient orientation is different; you have to change the orientation of the microscope; and you have to move the patient's head. In the OR the patient is lying down and you're doing something technical with the other hand while doing the gonioscopy. They really are different procedures."

• ***A clear view is the top priority.*** Dr. Noecker notes that when using the Trabectome or iStent, mastering intraoperative gonioscopy and being able to clearly see the target tissue is crucial. "The biggest thing with the Trabectome or iStent is visualization," he says. "In terms of mastering the technique, it really comes down to making sure you're in the right spot. In some cases I'll spend a few minutes making sure I can see what I want to see before commencing the MIGS procedure. Then, placing the stent or doing the Trabectome is relatively straightforward.

"Make sure you turn the patient's head at least 45 degrees," he continues. "You have to tilt the microscope, and you have to have the mirror on the eye and a really good view without striae. Basically, if you have a crystal-clear view, it's going to be an easy procedure. If the view is marginal, it's going to become a big struggle. There's no point in hoping the view will improve during the procedure; visualization can only get worse."

• ***Record your own cases.*** "That will allow you to watch and learn from your own mistakes and successes," notes Dr. Samuelson.

Other Questions

MIGS procedures obviously don't have to be performed at the same time as cataract surgery. What about using them as stand-alone procedures?

Dr. Samuelson notes that to some degree this is uncharted territory, especially with the iStent, although data is quickly being acquired from work completed in Armenia and elsewhere demonstrating the efficacy of the iStent as a stand-alone procedure. "I think there will be a role for these

procedures outside of cataract surgery, but we need more data to help guide us with that," he says. "Currently you can do ECP and Trabectome separately from cataract surgery, but the iStent is not approved for that."

Another question is whether it makes sense to add two MIGS procedures to your repertoire instead of just one. Dr. Noecker sees the different modes of action used by different devices as an advantage in this area. "We've always done a little bit of combining procedures," he notes. "There are times we put two glaucoma drainage devices such as an Ahmed and a Molteno in an eye, for example, because the patient has a really high pressure. MIGS procedures only lower pressure on average by maybe five points—but it's a safe five points. Because the MIGS procedures use different approaches, we can always add a second MIGS procedure that lowers pressure via a different mechanism.

"For example, I often combine ECP and the iStent," he says. "One works via the outflow system, the other works on the inflow system. That addition can get us another five points. This may get us close to the amount of pressure reduction we'd achieve with the riskier traditional procedures that would have caused a lot more bleeding and inflammation, swelling and temporary bad vision."

Dr. Francis believes that all ophthalmologists who treat glaucoma, including general ophthalmologists, should have at least one MIGS procedure in their armamentarium, while glaucoma subspecialists should be versed in two, spanning two different modes of action. "For example, rather than being able to perform both Trabectome and iStent, which work through the same pathway, you might learn to use the Trabectome and ECP, or the iStent and one of the suprachoroidal shunts once they're approved," he says.

Dr. Noecker notes that although having more than one of these procedures in your armamentarium is an advantage, it isn't necessary. "I have a lot of use for these procedures because all of my patients have glaucoma," he says. "I do a half dozen of these cases every surgery day. I think a general surgeon would be happy mastering one, and that's great. It's much better to do one surgery really well than to take on three different surgeries and do them mediocrely—which is more likely to happen if you only get to do the surgery once or twice a month."

The Future Looks Bright

There's no question that the MIGS options bode well for the future of glaucoma treatment. "Many cataract surgeons treat a fair number of patients with glaucoma, but until now surgeons were resistant to combining cataract and glaucoma surgery because the glaucoma surgery could cause problems with the cataract surgery," says Dr. Noecker. "Because the MIGS procedures increase the safety profile of doing combination surgery, I think it will increase the number of glaucoma surgeries that are done, which will help to lower people's eye pressures safely and get them off of eye drops. In many cases, intervention will happen earlier in the disease. I think it will become the norm for any glaucoma patient to have something done at the time of cataract surgery, and that's a good thing."

Dr. Noecker adds that he anticipates a day when better information about the reason for high pressure inside a given eye will allow surgeons to decide which MIGS approach will be most helpful. "We'll be able to tell that one patient has a problem with trabecular resistance, so we'll use a device that bypasses the trabecular meshwork," he says. "Or we may discover that the resistance to outflow is farther back, so the more efficacious solution is a suprachoroidal shunt."

Dr. Francis, for one, sees little value in waiting any longer for such refinements. "Having one or more of the current procedures in your armamentarium will help you no matter what other things come down the pike in the future," he says. "And in terms of waiting, how long are you going to wait? The iStent was just approved a year or two ago, but the Trabectome has been available for six years. At some point you have to adopt one of these procedures or you'll just keep doing trabeculectomies and tube shunts as your primary surgeries.

"I think the time is now to adopt at least one of these procedures in your practice," he concludes. "MIGS is not going away. Any given device or procedure may evolve over time, but this category and the theory behind it are here to stay. That's why I recommend that ophthalmologists adopt at least one of the MIGS procedures."

"This is a very exciting time in glaucoma, to say the least," adds Dr. Noecker. "We had our medication revolution about a decade ago, going from two choices to multiple choices. That allowed us to customize medical therapy according to the patient's risk profile. Now we're seeing a similar revolution in glaucoma surgery. We can weigh the risk-benefit profile of each of the procedures, and just as we do with medical therapy, we can decide which procedure is most appropriate. We can also combine multiple procedures, if necessary. Now, saying a patient needs glaucoma surgery won't just mean one thing."

Dr. Samuelson agrees. "I think the MIGS options are going to keep improving," he says. "It's only going to get better from here." REVIEW

Dr. Francis has consulted for Neomedix and Endo Optiks. Dr. Noecker is a consultant for Endo Optiks and has received research support from Glaukos. Dr. Samuelson has consulted for Glaukos and Endo Optiks. Dr. Berdahl is a consultant for Glaukos.

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What OCT Tells Us About Progression

Walter Bethke, Managing Editor

OCT has made strides as an objective measure of progression, but it still has limitations.

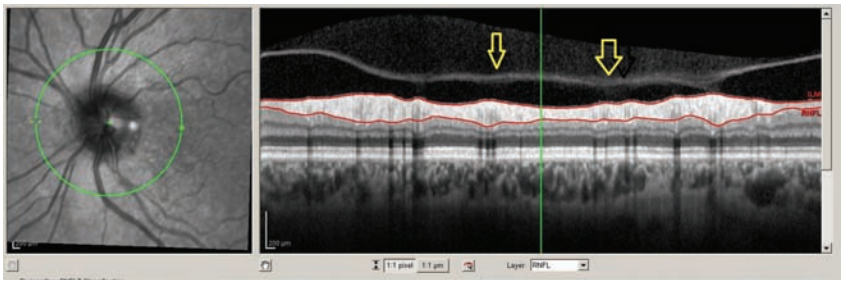
If golf were simple, you'd only need one club to work your way through a course. However, one club won't cut it when you're stuck in the rough or staring down a long fairway. Similarly, ophthalmologists are discovering that multiple tools might be best when trying to track glaucoma progression. Rather than just relying on one method, clinicians use their exam, perimetry and, in an increasing number of cases, optical coherence tomography to put together a picture of the glaucoma patient. Here, experts discuss the strengths and weaknesses of OCT as a progression-tracking tool.

Examining Structures

Surgeons say one of OCT's biggest advantages is its objectivity. Where visual fields rely on patients' subjective responses and stereo disk photos rely on a clinician's judgment, OCT gives a quantitative measurement of structures integral to the mechanism of glaucoma. Here's how physicians use this structural information to track progression.

• ***Retinal nerve fiber layer.*** Clinicians say looking for signs of thinning in the RNFL is probably the most popular way to watch for glaucomatous progression, but this process comes with some caveats. "The thing to keep in mind is there is an intervisit variability inherent to all imaging devices," says Sanjay Asrani, MD, professor of ophthalmology at the Duke University School of Medicine. "Therefore, only when the change is beyond that level of variability do I get concerned. For example, the variability of the Heidelberg Engineering Spectralis machine is 5 µm, which we published in the *Journal of Glaucoma*.[1] Because that's the variability, progression is something I'll

Sanjay Asrani, MD



Vitreous traction (arrows) can make the nerve fiber layer appear thicker. Then, when the traction releases, the apparent "thinning" of the NFL can be miscontrued as progression.

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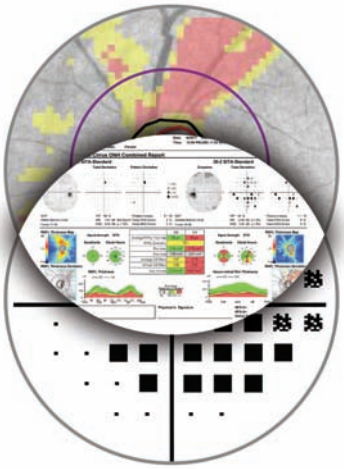

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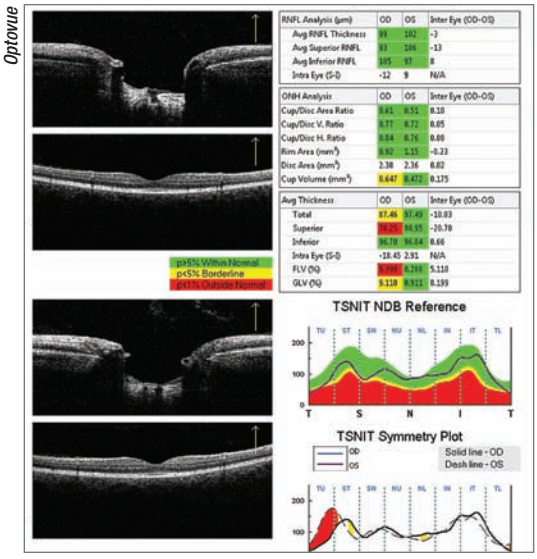
consider as possible if the change in the measurement in a particular quadrant is more than 10 µm. In other words, I wait for two standard deviations of variability before I consider change as a possibility."

As a rule-of-thumb for detecting change, Dr. Asrani says certain areas of the RNFL are more important than others on OCT. "There are two quadrants I really look at when dealing with the RNFL: the superotemporal and the inferotemporal. The display is presented as thickness averages in different quadrants, and the supero- and inferotemporal quadrants are where glaucoma changes occur in the early stage. If the glaucoma progresses dramatically, other quadrants become thinner. In patients in whom the apparent progression is worrisome but I don't want to take the next step of increasing their management of glaucoma until I've confirmed that it's progressed, I might ask them to return in a month for a repeat OCT. It's a confirmation similar to the kind we do in visual fields."

Donald Budenz, MD, chairman of the department of ophthalmology at the University of North Carolina at Chapel Hill, says when you start looking at quadrants rather than the total average thickness, the test/retest variability increases. "We have done some studies, as has Christopher Leung, MD, of the Chinese University of Hong Kong, that have found a test/retest variability of 4.5 to 5 µm for the average RNFL thickness with the Cirrus OCT,"[2] says Dr. Budenz. "But when you slice the RNFL into quadrants, that number goes to 8 µm and then to around 12 µm for even smaller slices. So, if the patient has focal change it won't show up in the average thickness until it's very bad, because you'll be averaging all the other areas that haven't changed. However, if you focus on the site of focal change, or a clock-hour of the RNFL, the test/retest variability is very high, meaning you'd need significant change of 12 to 15 µm before you can conclude it's gotten worse. I think we're better off relying on the statistical progression software provided by the OCT company that's been vetted by the FDA, rather than relying on individual numbers. *(For a look at the progression tools some OCT companies offer, see the sidebar on p. 42.)*



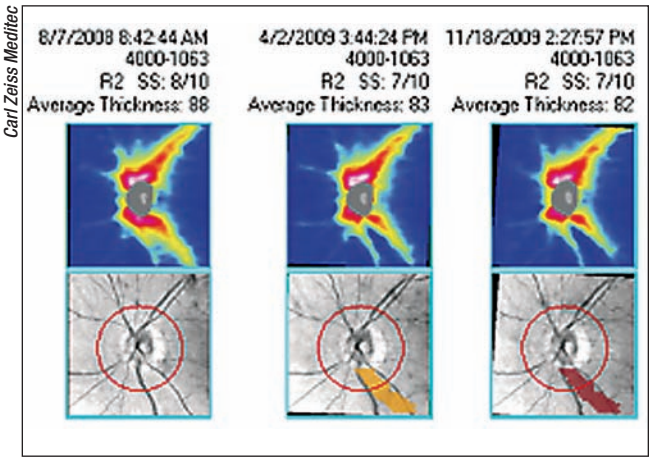
The Optovue Avanti combines nerve fiber layer and ganglion cell complex measurements to highlight changes over time.

Jean-Claude Mwanza, MD, research assistant professor at the University of North Carolina School of Medicine, says that numbers are crucial, but so is looking at the OCT's map of the RNFL thickness. "When you're looking at the RNFL thickness map, it's the best way to see where the progression has occurred within a defect that you noted previously," says Dr. Mwanza, who has experience with several OCT devices. "You can tell if the same defect has expanded and/or deepened, or if you have new defects occurring in other places."

• ***Macular thickness.*** Though the RNFL thickness is a key factor in tracking progression, physicians say it's often helpful to look at multiple structures, including macular thickness, especially in cases where the RNFL thickness may be indeterminate. "Because any structure is subject to artifacts, it's better to have at least two structures to measure with," says Dr. Asrani. "It's uncommon for an artifact to affect both the RNFL and the total retinal thickness measurements. So, we like to look at the macular thickness along with the RNFL thickness. When both show corresponding change, we consider that a change that we will give more weight to. It's important to note that the macular thickness change is typically arcuate in shape. In fact, when total macular thickness changes in other diseases, it's usually not arcuate; it's only in glaucoma that the macular thickness changes in an arcuate shape." Dr. Asrani says you can notice if the change is arcuate in shape by looking at a subtraction map that subtracts the current macular thickness from the previous measurement. "If you have an arcuate-shaped loss of macular thickness superiorly, and there's a loss of greater than 10 µm of thickness in the corresponding superotemporal quadrant compared to the previous visit, then you know the change is most likely real."

When bringing patients in for OCT exams, surgeons generally agree that once every six months is a useful timetable, and they like to have about five measurements before making a decision on progression. "The rule-of-thumb is that it depends on how your device does its statistical progression analysis," says Dr. Budenz. "If a methodology like linear regression is performed, typically you have to have five measurements. However, the more different the measurements are, the fewer you may need. Just like visual fields, you need a good baseline and good reproducibility with whatever test you're using. Ideally, these tests should be six months apart, but

some clinicians are running into reimbursement roadblocks with that, and may end up doing it once a year instead."



Carl Zeiss Meditec

The Cirrus OCT's Guided Progression Analysis feature attempts to highlight significant variances in key structures over time in an effort to detect glaucomatous damage.

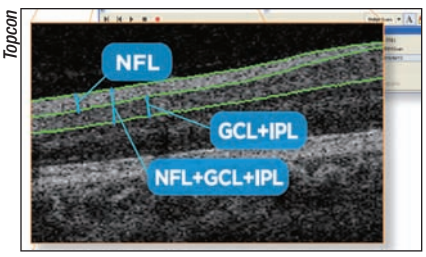
Confounding Factors

Surgeons say that precisely imaging a complex tissue such as the retina can sometimes be compromised by variables such as co-existing ocular disease.

"One of the biggest caveats that a reader of OCT images has to accept is that you have to rule out artifacts before you can accept an apparent change as real," says Dr. Asrani. "You have to be able to look at the raw image to confirm that the software has identified the top and the bottom of the RNFL properly. Sometimes the software may skip over one part or may include, for example, the edge of an epiretinal membrane or the posterior edge of the vitreous, leading to the RNFL appearing to be thicker.[3]

"There are two other big artifacts that cause difficulty in monitoring progression with OCT," Dr. Asrani continues. "One is the evolution of a posterior vitreous detachment. As the vitreous pulls away from the retina, it can cause the RNFL to appear thicker by traction. Then, when it detaches, the RNFL may suddenly appear thinner since the traction has been released and the RNFL has gone back to its normal thickness, and this might appear to be progression. So, one has to be able to see the vitreous interface with the RNFL in the raw scan before one accepts this change as progression. The second artifact that really causes difficulties is the presence of inflammation, namely uveitis. In patients with uveitis, the RNFL can appear normal due to the swelling. Therefore, when the uveitis is controlled, the RNFL that had appeared normal because of swelling now looks much thinner because the swelling has gone away. The tie-breaker in these cases is to look at the macula. Note, however, that just like the RNFL, the macular thickness is also subject to problems such as artifacts and the software not identifying the correct layers. Again, you have to look at the raw images, rule out the artifacts, and then accept the images before you can accept the results. In looking at the macular thickness, the subtraction maps come stratified as to whether the change is 10, 20 or 30 µm; if it's 10 µm or greater, only then will I give weight to it, so I'm going two standard deviations or greater."

Howard Barnebey, MD, clinical assistant professor of ophthalmology at the University of Washington in Seattle, says diabetic retinopathy, in addition to ERM, can skew the results. "If there are measurements of other things, such as diabetic macular edema, occupying the retinal space, then that data isn't going to be useful to you for tracking glaucoma progression," he says. "If the patient has DME or exudative age-related macular degeneration, you can't look in the macular area with OCT, but the RNFL should be OK. You could say the same thing about BRVO or artery occlusion. The OCT scan is a very useful metric to help quantify tissue heights that we couldn't do before, but it's an adjunct to the clinical exam—it doesn't replace the clinical exam. You still have to look at the optic disk, the macula and the vessels. There will even be times when your clinical exam will be superior to looking at an OCT: For instance, if someone has a flame-shaped hemorrhage adjacent to the optic disk, it's not uncommon for an OCT to miss that."



Topcon

Segmenting the retina into the nerve fiber layer, the ganglion cell layer and the inner plexiform layer may help detect change.

OCT and Perimetry

As tests for progression, experts say that OCT and visual fields often share the top spot, with one surpassing the other in specific patient presentations.

"In many cases, structure changes before function in glaucoma," says Dr. Asrani. "So, we don't see such changes in the visual fields as early as we see them on the OCT, and that has been a constant conundrum for a lot of us because by the time the visual field changes occur, irreversible structural changes have already taken place. So if you only wait for visual fields to change, then you are waiting until it's a little too late. On the other hand, if you're not 100-percent sure of changes on the OCT and you're taking action before seeing the visual field changes, you may be overtreating. Considering

the number of artifacts that can affect OCT, we don't want to pull the trigger on an escalation of glaucoma management—such as increased medication or surgery—unless we have another proven technology to confirm that the changes we see are real. That technology is the perimeter.

"However, even though I've used OCT for many years and know its major pitfalls when it's used alone for progression tracking, I will use it solely for monitoring patients above the age of 80," Dr. Asrani continues. "A majority of these patients are unable to perform a reliable visual field due to physical changes such as arthritis in the hands. Sitting in front of a perimeter for at least three to five minutes isn't easy for them. So, I tend to use OCT for this age group without having to have the corresponding change necessarily in the visual field."

The Floor Effect

Despite OCT's increasing accuracy, clinicians say there will come a time when the RNFL is too thin to be used as a reliable indicator of progression, a situation they call the floor effect.

"The floor effect is a real phenomenon," says Dr. Mwanza. "In short, the RNFL isn't only made of retinal ganglion cell axons, but also contains the vessels and support cells such as glial and Müller cells. So, when glaucoma is advancing and even when a patient becomes completely blind there will still be something remaining in that layer of the retina, something not related to glaucoma, such as the glial cells, so the layer will not disappear completely and you can still measure it. That's the floor. Studies with time-domain OCT, the Stratus, found the floor was an average RNFL thickness of 45 µm. So, if you're following someone with glaucoma and the RNFL reaches 45 µm, even though the patient can still see, this means the average RNFL measurement is no longer useful. You should use something else, maybe visual fields, or you could still follow the sectors of the RNFL but just not the average thickness anymore."

Dr. Budenz says the floor he's measured with the Cirrus is 55 µm, thicker than time-domain because spectral-domain doesn't smooth over vessels. "Since the test/retest variability is about 5 µm, this means you'll have about nine opportunities to detect change from normal to the floor," he says.

Though tracking progression still involves a number of tests and a good clinical exam, Dr. Barnebey says that clinicians are becoming more comfortable using OCT "Right now, progression is, and has always been, defined by visual field change," says Dr. Barnebey who notes that, ironically, the definition of glaucoma doesn't include visual fields. "We recognize that, by the time you see visual field change, you've lost a fair amount of nerve fibers. So the appeal of OCT is detecting pre-perimetric glaucoma, or the search for those patients who have structural damage but don't have reproducible visual field defects. I think more clinicians are depending on the use of the OCT to help them establish an earlier diagnosis." REVIEW

Aids for Progression Tracking

Many optical coherence tomographers have features for tracking progression or ensuring accurate imaging at each visit. Here's a rundown of what they offer:

- ***Cirrus (Carl Zeiss Meditec).*** The Cirrus' FastTrac allows the scan to be in the same area for each visit, which is key to monitoring progression over time. It also has Macular Change Analysis to show the difference between visits and Guided Progression Analysis that compares retinal nerve fiber layer thickness and optic nerve measurements over time to determine if statistically significant change has occurred. Areas of significant change will be colored yellow for the initial change and then red if the change remains at later visits. GPA also provides numerical trend analysis and confidence intervals are shaded when the rate of change is statistically significant.
- ***Spectralis (Heidelberg Engineering).*** The Spectralis uses custom TruTrack technology to acquire images. The company says that tracking the eye with simultaneous dual-beam imaging minimizes motion artifact, enables noise reduction and allows the instrument to track change over time. The device also provides retinal thickness and asymmetry analysis. AutoRescan lets the device place follow-up scans in the same place.
- ***XR Avanti (Optovue).*** In addition to measuring the RNFL and optic disk, the Avanti measures the ganglion cell complex, and can provide data on loss of volume in the GCC. It also provides combined RNFL/GCC change reports to highlight significant change over time. Trend analysis will highlight change that's borderline in light purple with black numbers, and change that's significant in dark purple with white numbers.
- ***3D-OCT 2000 (Topcon).*** The 3D-OCT 2000 provides trend analysis comparing disc topography and RNFL thickness from a minimum of two visits. For the disc, it provides cup/disc ratio, cup volume and cup area. For the RNFL, it gives the average thickness of inferior RNFL, superior RNFL and the average of the total RNFL.
- ***RS-3000 (Nidek).*** An available tracking HD plus function tracks involuntary eye movements to maintain the same scan location. There's also an available torsion eye tracker to ensure accurate image capture and eliminate cyclotorsion even if the patient tilts his head.

1. Ghasia FF, El-Dairi M, Freedman SF, Rajani A, Asrani S. Reproducibility of spectral domain optical coherence tomography measurements in adult and pediatric glaucoma. J Glaucoma 2013 May 29. [Epub ahead of print]
2. Mwanza JC, Chang RT, Budenz DL, Durbin MK. Reproducibility of peripapillary retinal nerve fiber layer thickness and optic nerve head parameters measured with cirrus HD-OCT in glaucomatous eyes. Invest Ophthalmol Vis Sci 2010;51:11:5724-30.
3. Asrani S, Essaid L, Alder BD, Santiago-Turla C. Artifacts in spectral-domain optical coherence tomography measurements in glaucoma. JAMA Ophthalmol 2014;132:4:396-402.

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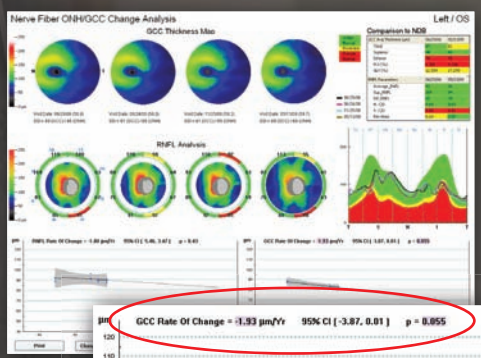

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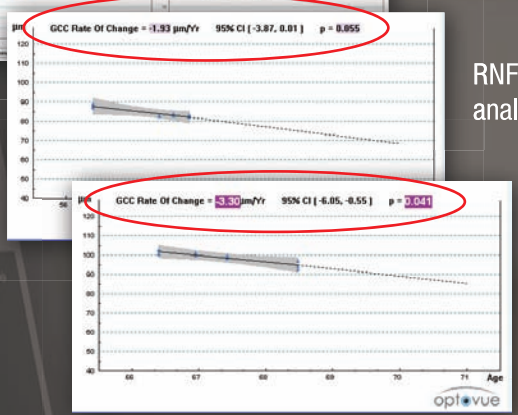

RNFL & GCC Trend plot gives a statistical analysis of the patient's complete history.

Avg Thickness	OD	OS	Inter Eye (OD-OS)
Total	87.46	97.49	-10.03
Superior	78.25	98.95	-20.70
Inferior	96.70	96.04	0.66
Inter Eye (S-I)	-18.45	2.91	N/A
FLV (%)	5.398	0.288	5.110
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Glaucoma Medications: It's All in the Delivery

Michelle Stephenson, Contributing Editor

New classes of drugs and new delivery systems will change the way glaucoma is managed.

First-line glaucoma treatment in the United States has long meant topical medications. Unfortunately, all of these drugs require at least daily dosing, and most are commonly administered two or three times daily.

"The biggest issue in medical therapy is compliance," says Michael Stiles, MD, in private practice in Overland Park, Kan. And, the need for frequent dosing with the currently available medications makes compliance challenging.

Some newer preservative-free and combination medications are already addressing the issues of compliance and safety, and some new drug delivery systems are in the pipeline that will hopefully take medication compliance completely out of patients' hands.

Zioptan

Two concerns with glaucoma medications are their safety and tolerability, because patients will typically have to take them for the rest of their lives. Zioptan (tafluprost, Merck) was the first preservative-free prostaglandin approved by the Food and Drug Administration. It has been on the market for just over two years, and it has been shown to be as effective as the preserved prostaglandins.

A recent study found that treatment with once-daily preservative-free tafluprost was effective, well-tolerated and safe in treatment-naïve patients.[1] The study included 579 treatment-naïve patients: 349 had primary open-angle glaucoma; 105 had ocular hypertension; 71 had normal-tension glaucoma; 27 had exfoliative glaucoma; and 27 had other glaucomas. At month three, significant reductions in mean IOP were seen in all patients. Preservative-free tafluprost lowered mean IOP significantly in patients with primary open-angle glaucoma and ocular hypertension who had IOP levels of 20 to 23 mmHg or higher from 21.9 ±1.1 mmHg at baseline to 16.5 ±2.2 mmHg. Overall, patients with higher baseline IOP values showed a better response than patients with lower baseline IOP levels. At three months, 97.9 percent of all patients remained on therapy.

Mildred Olivier, MD, in private practice in Hoffman Estates, Ill., notes that preservative-free prostaglandins are especially "great for younger people who will perhaps be on drops for a longer period of time, because preservatives can have damaging effects to the conjunctiva."

Simbrinza

In April 2013, Simbrinza (Alcon), which is a beta-blocker-free, fixed-combination therapy for glaucoma patients, was approved by the FDA. It combines brinzolamide 0.1% and brimonidine tartrate 0.2% into one multi-dose bottle. Studies have found that it provides sustained control and a 21 percent to 35-percent reduction in intraocular pressure.

The FDA approval is based on data from two pivotal Phase III trials that included approximately 1,300 patients.[2,3] The studies evaluated the safety and efficacy of Simbrinza administered three times daily, compared to separate three-times-per-day dosing of one or the other component. Both studies met their primary endpoints and demonstrated that Simbrinza is statistically superior compared to either component regarding mean IOP at month three for all times points. In both studies, Simbrinza achieved a 5-mmHg to 9-mmHg reduction from baseline to month three. Patients' mean IOP at baseline was 22 mmHg to 36 mmHg.

In the two, three-month clinical trials, the most frequently reported adverse reactions in patients treated with Simbrinza (occurring in approximately 3 to 5 percent of patients) were blurred vision, eye irritation, dysgeusia, dry mouth and eye allergy. Discontinuation of Simbrinza treatment (mainly due to adverse reaction) was reported in 11 percent of patients. The safety profile of the combination agent is comparable to each of the individual components.

"So far, my experience with Simbrinza has been very positive. I have had good results, and patients seem to tolerate it well. However, I have had difficulty with some insurance companies, because it is not always a well-covered medication," says Richard Lehrer, MD, in private practice in Alliance, Ohio.

According to Dr. Olivier, compliance is much better with combination drugs. "However, my concern with any combination drug is that you'd like to know that each one of them works well for a patient before you commit her to two drugs. Additionally, combination drugs can be more costly to the patient. Our goal is to make the medications easier to take," she says.

Rescula

Rescula (unoprostone isopropyl, CIBA) was first approved in 2000. While unoprostone was developed from a prostaglandin metabolite, it is considered to be a docosanoid, with different properties from those of prostaglandin analogs. The labeled dosing frequency was twice daily.

As once-daily true prostaglandin analogs entered the marketplace, Rescula disappeared from the U.S. market. In December 2012, the FDA approved a new drug application for Rescula, and it re-entered the market. It is now considered a docosanoid in the prostone family rather than a prostaglandin analog.

"I have found it to be effective in some patients," Dr. Olivier says. "In fact, some patients have a surprising decrease in pressure. I like it because it doesn't have many side effects. You do have to dose it twice a day, but just this week I had a patient whose pressure was the same after trying three different medications. They were just not working. I put her on Rescula, and it's the only drop that reduced her pressure. I typically use it in people who have earlier forms of glaucoma, like ocular hypertensives. However, in these patients, I will typically try a once-a-day medication first. Then, if I have to go to a second drop and I already have to do twice a day, then Rescula is a drop that I will try. Or if I haven't had any success with the prostaglandins as a first line, then I will try Rescula because the side effects are still fewer than the side effects of brimonidine, a topical beta-blocker, or a carbonic anhydrase inhibitor," Dr. Olivier says.

New Classes & Delivery Systems

None of the currently available medications are ideal, so researchers are continuing to investigate new classes of drugs that look promising. For example, "A couple of companies are working on rho-kinase inhibitors, and results seem to be very positive," Dr. Lehrer says. "Hopefully, they will be available very shortly and will be beneficial for our patients to improve outflow and lower pressures."

Dr. Olivier agrees, noting that "Rho-kinase inhibitors offer new mechanisms of action with equivalent IOP reduction with a unique ability to lower pressures in the normal range."

A Phase II study is currently underway to evaluate the ocular hypotensive efficacy of rho-kinase inhibitor (AR-12286 0.5% and 0.7%) ophthalmic solutions in patients diagnosed with exfoliation syndrome and ocular hypertension or open-angle glaucoma treated for six months.[4] Primary data is scheduled to be available in September 2014.

The newest area of interest is evaluating new delivery systems that would take the responsibility for medication compliance away from patients. "The delivery systems are a very hot topic right now. There is quite a bit of research going on as far as drug delivery systems, such as subconjunctival injections and punctal

(continued on page 53)

HZO Warrants Quick Recognition & Action

Samuel Yun, MD, Ryan Wong, MD, Ajay Malholtra, MBBS, John Huang, MD, and Flora Levin, MD, New Haven, Conn.

A rare combination of ophthalmoplegia, panuveitis and optic neuritis from herpes zoster emphasizes the need for prompt diagnosis and action.

Herpes zoster ophthalmicus is a relatively common disease that often affects elderly population with rare, but devastating intraocular, neuro-ophthalmic complications if not recognized promptly and treated appropriately. To re-emphasize the importance of prompt diagnosis and treatment, we share this brief review and a case report of what clincians may encounter in practice.

Background

The lifetime risk of having herpes zoster is 20 to 30 percent, with 10 to 20 percent of the patients developing herpes zoster ophthalmicus.[1] HZO may present with diverse ocular and central nervous system symptoms with 50 percent of patients having ophthalmic manifestations.[1] HZO has caused extraocular muscle palsies of the third, fourth and sixth cranial nerves in 7 to 31 percent of patients and is usually a self-limiting condition.[2] Optic neuritis and orbital involvement from HZO has been described.[3-6] However, panuveitis and orbital disease in one patient is rare.

Diagnosis and Treatment

As initially described in 1965, HZO reactivation is largely dependent on depressed cellular immunity as is often the case in patients on immunosuppression therapy.[1,7] Various ocular complications of the HZO may include inflammation in any part of the eye including blepharitis; keratoconjunctivitis; iritis; and scleritis as well as intraocular involvement of anterior uveitis and posterior uveitis involving the retina.[8] Optic neuritis has been documented as well and may be bilateral even in unilateral HZO.[5]

Several cases of orbital apex syndrome in HZO have been reported.[9] There is one case report of an immunocompromised patient with anterior uveitis, optic neuritis, complete ptosis and ophthalmoplegia due to myositis.[10] Our case is unique in that it involves panuveitis, orbital apex syndrome and optic neuritis. Although the pathophysiology of cranial nerve involvement is not yet clear, it is suggested to be due to either direct viral invasion or a combination of inflammation and occlusive vasculitis.[11-13]

Treatment of HZO is mainly antivirals. Combination of IV acyclovir as initial therapy in the acute phase and valacyclovir as an outpatient regimen can be often utilized. Tapering doses of oral prednisone in 60, 30

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Sympathetic stimulation may be essential to support the circulation in patients with diminished myocardial contractility and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure. In patients with no history of cardiac failure, continued depression of the myocardium with beta-blocking agents over time can lead to cardiac failure. Discontinue COMBIGAN® at the first sign or symptom of cardiac failure.

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IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS: (continued)

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

Although rare, timolol can increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

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Ocular hypersensitivity has occurred with brimonidine tartrate ophthalmic solutions 0.2% (eg, increase in IOP).

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

[a]Includes preferred, approved, and tiers 1-4, with and without step-edits, and also includes prior authorization, based on 203,671,234 total lives.

1. Managed Markets Insight & Technology, LLC, database as of December 2013.

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Please see the **COMBIGAN®** package insert for full prescribing information.

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

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

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

Clinical Studies Experience: Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. **COMBIGAN®:** In clinical trials of 12 months duration with **COMBIGAN®**, the most frequent reactions associated with its use occurring in approximately 5% to 15% of the patients included: allergic conjunctivitis, conjunctival folliculosis, conjunctival hyperemia, eye pruritus, ocular burning, and stinging. The following adverse reactions were reported in 1% to 5% of patients: asthenia, blepharitis, corneal erosion, depression, epiphora, eye discharge, eye dryness, eye irritation, eye pain, eyelid edema, eyelid erythema, eyelid pruritus, foreign body sensation, headache, hypertension, oral dryness, somnolence, superficial punctate keratitis, and visual disturbance.

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

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

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

OVERDOSAGE

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

Rx Only

Based on package insert 72060US13 revised 10/2012.
Patented. See: www.allergan.com/products/patent_notices

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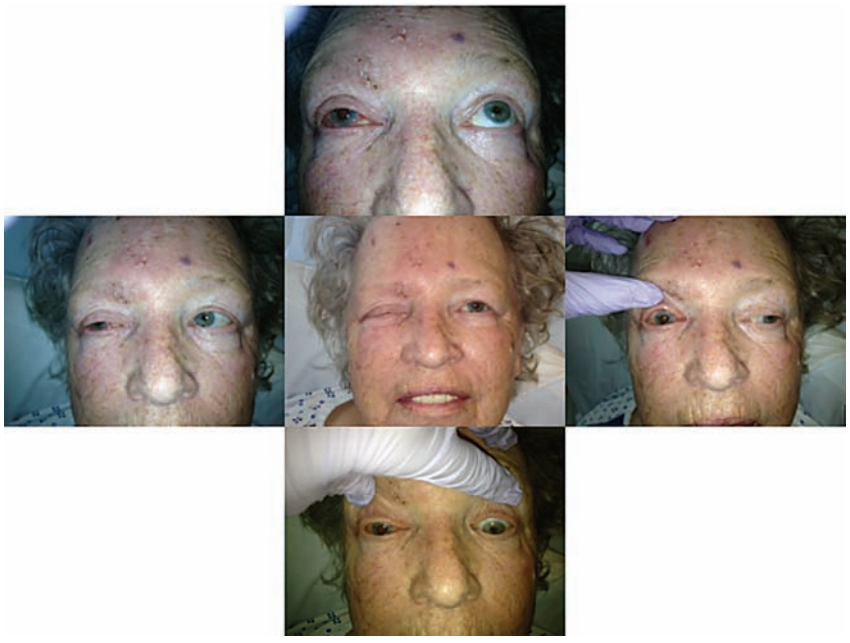

Figure 1. External photography of eye positions in four directions

and 15 mg/day per week may be used as well in cases of severe pain, severe rash and cranial polyneuritis.[14,15] Our patient's condition significantly improved with oral antiviral alone in terms of visual acuity, motility and inflammation.

Without increased awareness of the disease, herpes virus often has protean presentations that may be misdiagnosed initially, as it was in this case.

Case Report

An 82-year-old retired nun with a history of dementia was referred for evaluation of right visual loss and ophthalmoplegia. The patient initially presented to an outside emergency department for altered mental status and was discharged to a short-term rehabilitation facility with a diagnosis of worsened depression. During the admission, she was treated with topical and oral antibiotics for presumed right conjunctivitis. Two weeks later she was seen by an outside ophthalmologist and found to have right vision loss and ophthalmoplegia. She was referred to neuro-ophthalmology for further evaluation.

The patient complained of a gradual decrease in vision, redness and swelling of the right eye over one month. She also described a non-painful rash over her right eye, which preceded all other symptoms. Her systemic review of systems was otherwise negative. Pertinent medical history includes history of herpes zoster over the abdomen 10 years previously.

On examination, the patient was awake and alert. Best-corrected visual acuity was count finger at 3 feet in the right eye, and 20/30 in the left. Pupillary exam showed a dilated, poorly reactive right pupil with a relative afferent defect. Intraocular pressure was 24 mmHg in the right eye and 12 mmHg in the left. There was ophthalmoplegia with -3 restriction of supraduction, -2 abduction, -2 infraduction, and -4 adduction *(See Figure 1)*.

External exam revealed near complete ptosis of the right eye with eyelid swelling and a scattered vesicular rash with crusts in the V1 and 2 distributions. There was right corneal hypoesthesia. Slit-lamp exam showed right conjunctival injection, corneal edema and a hyphema with neovascularization of the iris. There was dense nuclear sclerosis and vitritis that precluded fundoscopic examination. Right B-scan ultrasonography showed dense vitreous debris without retinal detachment.

The patient was admitted to the hospital and started on IV acyclovir (10 mg/kg), and topical prednisolone and cyclopentolate eye drops.

Laboratory evaluations for other infectious and inflammatory etiologies were negative. HIV status was not documented. A contrast-enhanced MRI of the brain and orbit showed right optic nerve sheath enhancement with intraconal inflammation and right trigeminal nerve enhancement of V1 and V2 distribution *(See Figure 2)*.

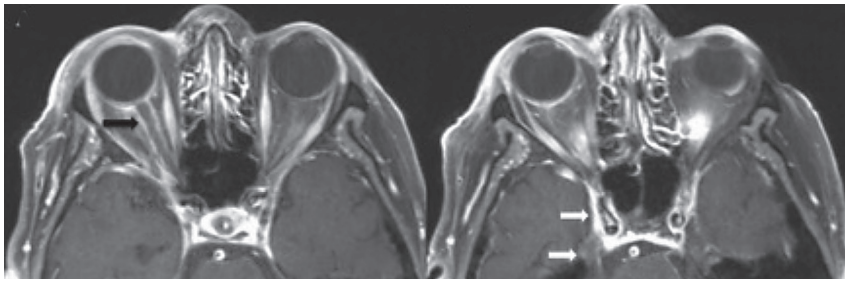

Figure 2. Axial post-contrast, fat suppressed T1-weighted MRI images showing the right optic sheath enhancement (black arrow) with orbital apex involvement (white arrow); asymmetric enhancement in the right superior orbital fissure extending along the right cavernous sinus, right Meckel's cave and cisternal segment of the right trigeminal nerve.

(continued on page 79)

Physician, Prep Thyself (For Personal Finances)

Chandak Ghosh, MD, MPH, New York City

Many newly practicing surgeons are woefully unprepared to handle finances. Here's help.

Having supervised residents for more than a decade, I see most start their professional lives with a major mistake: being complacent about personal finances. Consequently, along with teaching the art of ophthalmology, I discuss how saving and spending properly early in a career will support a comfortable future and retirement. Investment advisors and insurance agents are well-aware that many doctors are financially illiterate. To guard against grave fiscal mistakes, I offer these general guidelines. The tips are not to make you rich but to help you lead a secure financial life.

Your Current Life

- ***Stop fearing money.*** Finances, budgets, debt, loans and investments require only basic arithmetic.
- ***Stop overspending.*** Focus on buying what you need, not everything you want. While you may think random strangers are impressed by your fancy car and clothes, truthfully, they don't care what you drive or wear.
- ***Pay off credit cards monthly.*** Carrying a balance on your credit cards indicates overspending. The interest on credit cards means those shoes you bought at a bargain price will actually cost much more.
- ***Live like a student.*** At least for a few years after you start earning a professional's income. This will allow you to pay off student loans, amass savings and decide what you want money to do for you in life.
- ***Start paying student loans.*** If rates are low (1 to 3 percent), there is not much hurry to pay them off. If interest is 5 percent and above, concentrate on paying them off as early as you are able. If you take the full 10 years, you will pay far more than what you originally borrowed because of accruing interest. As you start your first job, set aside money to pay some of the interest and capital each month. One of the best days of your life will be the day you make your final payment.
- ***Know your FICO score.*** Comparing your debt to credit ratio, this score summarizes your credit worthiness and determines what interest rate you will get for a mortgage, car loan, etc. Canceling a credit card will reduce the amount of credit you have, lowering your FICO score. Unless you pay an annual fee, keep all your credit cards open even if you never use them. Go to myfico.com to buy your FICO report. Work to push your score into at least the upper 700s. Also, check your personal credit reports from the three credit reporting agencies—Equifax, Experian and TransUnion— for accuracy. You may check all three free

annually at annualcreditreport.com.

Your Future

Looking a bit farther over the horizon, here are a few important considerations regarding needs that may not seem apparent at present, but require thoughtful planning.

Emergencies

• ***Save an emergency fund.*** Determine how much money you and your family need to live every month—rent, food, diapers, restaurants, movies, etc. Keep six to eight month's worth in an accessible savings account. If someone in your family gets sick, this fund will allow you to decrease your workload to help.

• ***Buy disability insurance.*** You have spent so much time and money training for this career that, if you become disabled, you should still be able to live securely. Find what is referred to as "own occupation" disability insurance, which give you payments if you cannot perform your own occupation but may be able to do another.

• ***Buy life insurance only if someone else depends on your income.*** Buy insurance to cover five to seven times your annual income. Avoid the combination life insurance and investment policy known as whole, variable or permanent life insurance. Insurance agents aggressively push these because of large commissions. Keep life insurance and investments separate. Buy term life for a fixed term of 20 or 30 years. This is much cheaper and pays out if you die while your kids are still young. By the time they are 20 or 30, they will no longer be dependent on your salary.

Retirement

• ***Save for 25 to 30 retirement years.*** With lifespans rising, expect to live 90 years or more. Assuming you retire near 65, you will need money to live an additional 25 to 30 years but without income from work.

The following rules are supported by solid financial research:

Save 15 to 20 percent of your income yearly in a combination of retirement investment vehicles, personal investment accounts and saving accounts.

Take no more than 4 percent of your savings out per year when you retire. For example, save $1 million for every $40,000 you need yearly—achievable if you save as recommended.

Most will need 70 to 80 percent of their current income to maintain living standards after retirement.

Pay off your house, car and any other large expenses before retirement.

When investing, most will buy mutual funds and hold for decades until retirement. Over the long term, assume an 8 percent return yearly on average. The compounding of this interest over many years causes your money to double and triple. The earlier you start investing, the larger that final number will be, by a significant amount. For example, starting at age 30 instead of 20 could cost you over $1 million in the long run.

Retirement Investment Vehicles

Over decades, if invested wisely, your money compounds so you will have enough at retirement. Once you put money in, do not touch it until retirement. Legally, you are allowed to borrow money, but doing so will incur fines, fees and taxes. There are four main stock investment vehicles.

401(k)/403(b). Provided by your employer, 401(k) is in for-profit companies and 403(b), in non-profits. In 2014, you can contribute up to $17,500 per year pre-tax. You pay taxes only when you withdraw the money at retirement.

Roth 401(k)/403(b). Same as the regular 401(k)/403(b) but you pay with after-tax money. The money grows over many years. When you withdraw, you owe no extra taxes.

Traditional IRA. You open your own IRA at a financial institution. In 2014, you can contribute up to $5,500 pre-tax per year. Those with incomes below $129,000, if single, or $191,000, if married, qualify for a tax deduction. Pay taxes only upon withdrawal of funds.

Roth IRA. Same as traditional IRA except contributions are post-tax so you are not taxed when you withdraw at retirement. No one receives a tax-deduction on contributions.

If your employer offers a regular 401(k)/403(b) and matches your contributions (usually 1 to 5 percent), contribute only up to the match.

If your employer offers a Roth 401(k)/403(b), contribute the full $17,500/year.

If your income is within the limit, contribute the full $5,500/year to a Roth IRA.

If your income is above the limit, contribute the full $5,500/year to a traditional IRA, but do it with post-tax money. Decline the tax deduction. "Roll over" the money to a Roth IRA. This process is termed a "Backdoor Roth IRA" and can be executed at any income level.

Invest the rest in a personal investment account.

Contribute money to all of these consistently throughout the year until you reach the contribution limits and have reached your target of 15 to 20 percent of annual income. Called "dollar cost averaging," this method of regularly buying funds, whether the market is up or down, will cause returns to even out in the long run.

Investing Your Contributions

Contributions to your 401(k)/403(b), IRA and personal investment account must be invested in the stock market if you hope to benefit from strong gains. Never invest in individual stocks. Instead, invest in mutual funds, most of which contain a large, diverse group-

ing of stocks. Particularly good are Index Mutual Funds, which contain the same stocks as a particular stock market index. Stock-market indices are used to judge market performance on a daily basis. Examples of such Index Mutual Funds are any S&P 500 fund, Wilshire 5000 Fund, Russell 3000 Fund, Total Market Fund, Small Cap Fund, Large Cap Fund and Total International Stock Market Fund. (The various investment firms have different names for their index mutual funds, so look closely at their descriptions.) S&P 500 Mutual Fund, for example, has historically bested "actively managed" funds 80 percent of the time. Actively managed funds are those with a management team that buys and sells stocks often, changing the fund over time.

Choose mutual funds listed as "no-load" (costing nothing to buy or sell) and have an expense ratio of less than 1 percent. The expense ratio signifies the cost to run that fund. Taking out more than 1 percent per year for administration will reduce what you receive at the end dramatically. Actively managed funds, for example, tend to have higher costs. To keep your finances simple, choose no more than three index mutual funds per account.

Employers usually limit investment choices for their 401(k)/403(b)s. To open your personal IRA account, go online to a discount brokerage like Fidelity, Schwab or Vanguard. These offer a vast array of choices.

When building your investment portfolio, choose mutual funds that reflect various areas of the market, so if there is a big loss in one area , it will not affect your entire account. An example portfolio at Vanguard could be 35 percent Total Stock Market Index Fund, 35 percent Total International Stock Index Fund, 30 percent Bond Market Index Fund. Some experts dislike bond funds. Instead they like individual bonds, especially municipal bonds. Buying the best MUNIs, however, usually requires the guidance of a financial advisor.

An alternative to different Index Mutual Funds is a target fund. You choose the fund based on the year you plan to retire (e.g., 2055 Target Fund). Target funds move your money from stocks toward the more stable bonds as you age closer to retirement. Some experts dislike target funds because these funds do not respond to the current market. For example, if interest rates go up just as you retire, those bonds will produce nothing, while stocks will produce great dividends. These target funds, however, remain simple, effective tools for those who want to invest and forget until retirement.

When you leave your job, you may either keep your funds in the old 401(k) or send them to a rollover IRA, a much better vehicle because you will gain a larger choice of funds. Go online to a discount brokerage like Fidelity, Vanguard or Schwab, create a rollover IRA, and take advantage of better investment options.

After saving 15 to 20 percent, the rest of the money is yours to spend as you want or save for large purchases like a house.

Finances, in a Nutshell

- In a savings account, create an emergency fund to last six to eight months.
- Save 15 to 20 percent of your income each month in the following order: If offered a regular 401(k)/403(b), only contribute to the employer match, or, if offered a Roth 401(k)/403(b), contribute full $17,500. Then, contribute the maximum to a Roth IRA. Then, deposit in a personal investment account at a discount brokerage.
- In 401(k)/403(b), Roth IRA and personal investment accounts, invest in each up to three no-load index mutual funds, all with Expense Ratios of less than 1 percent. Keep 30 percent of your portfolio for bonds and bond funds to protect you in case of stock value drop. Dollar cost average your contributions so market highs cancel market lows.
- Always pay off credit cards in full.
- Never borrow from 401(k)/403(b) or IRA.
- Create a will, powers of attorney for health-care and finance, and a living revocable trust.
- Buy life insurance only if you have dependents, and buy disability insurance.
- Only spend 4 percent of your savings each year in retirement.
- Pay off all large life expenses like house and car prior to retirement.
- Live long and prosper.

—CG

Important Financial Rules

- ***Buying a car.*** Financially speaking, leasing a car is a terrible idea. Plan to pay it off in three years. If you need longer, you are paying far more than the car is worth.
- ***Buying a house.*** Save at least 20 percent for a down payment on your house. If too difficult to save 20 percent, you cannot afford the house. Choose a 15 or 30-year fixed-rate mortgage. The mortgage payment should be no more than 30 percent of your income.
- ***Vital legal documents.*** Everyone should have a will, health-care power of attorney, financial power of attorney and living revocable trust. The will is for property transference on death. A health-care power of attorney allows another person to make health-care decisions on your behalf when you cannot. A financial power of attorney allows another person to make financial decisions on your behalf when you cannot. A living revocable trust allows property ownership to transfer from one person to another if the owner becomes incapacitated. Unlike a will, when a person dies, a trust prevents having to endure the expensive, time-consum-

ing probate process during which a judge must first declare the will valid. In that trust, place your house, bank accounts and life insurances. The will and powers of attorney can be drawn up cheaply without legal help using any online kits. Drawing up a reliable living revocable trust, however, requires a trust lawyer. The cost ranges from $2,000 to $4,000.

• ***Funding college for kids.*** State 529 Plans are the best vehicles for college tuition savings. Like a Roth IRA, money is contributed post-tax and withdrawn without any taxes when your child enters college. While you may contribute in any state's 529, your own may offer tax breaks for contributing. Saving at least $6,000 a year and investing in stock mutual funds will allow most to fund a state-school tuition bill completely.

• ***Prenuptial agreements.*** Before you marry is when you and you partner are most likely to be generous to one another. This is the best time to create a prenuptial agreement. Whatever you bring to the marriage (property or family heirlooms) can remain in your ownership alone as long as they are not paid for from a joint account, and the owner's name is not changed on the documents. In community property states, everything earned during the marriage is divided 50-50 unless you have a prenuptial agreement that says otherwise. Most marital arguments are about finances, so always be honest about money to each other. Budget, pay bills and do taxes together. Divorce will wreak havoc on both your finances.

• ***Paying bills with a spouse/live-in partner.*** If you both work, bills should be paid based on percentage of total income brought to the partnership. So if you earn $100,000 and your partner $50,000, you pay two-thirds of each bill, and your partner one-third. Keep separate bank accounts for yourselves and one joint account for common bills. Again, be very honest about what you have in your accounts.

The most disconcerting part of personal financial planning is the cacophony of contradictory advice from friends, relatives, salespeople and the media. Many have a financial stake in the products they advise you to buy. Instead, follow these tried-and-true steps, all backed by reliable research and experience, to become confident and calm about your financial future. REVIEW

Dr. Ghosh is an ophthalmologist who teaches residents in New York City. Contact him at Chandak.Ghosh@gmail.com. He reports no financial interests in any products or services discussed.

(continued from page 45)

plugs containing medication. These options would prevent patients from having to take their medications every day. There are quite a few companies developing these technologies, and they are currently in Phase II and III studies," Dr. Lehrer says.

Dr. Stiles agrees, noting that researchers are also looking at medications that can be placed in a slow-release material that can be inserted in the fornix of the conjunctiva on the outside of the eye, or that's implantable and can release medication in the sub-Tenon's space. "There has been a lot of research done on those types of medications. This is medical therapy's answer to try to maintain medical therapy as an effective way of treating glaucoma by eliminating the compliance issue," he adds.

Drug delivery systems currently in clinical development include conjunctival, subconjunctival and intravitreal inserts, punctal plugs, and drug depots.

One example is a hybrid dendrimer hydrogel/poly(lactic-co-glycolic acid) nanoparticle platform that is being developed to deliver glaucoma therapeutics topically.[5] It is designed to release the drug slowly, and it is compatible with many of the currently used glaucoma drugs.

Another example is a timolol maleate-loaded chitosan film that was recently found to be safe and efficient as an ocular drug delivery system in the treatment and prevention of glaucoma.[6] Chitosan is a cationic polysaccharide biopolymer with mucoadhesive properties, and this study compared the efficacy and safety of chitosan-coated timolol maleate mucoadhesive film with the use of a 0.5% timolol maleate commercial ophthalmic solution in a rabbit model. Twice a day for 15 days, 0.5% timolol maleate commercial ophthalmic solution was administered in five eyes and was compared to chitosan-coated timolol maleate in five eyes. In the control group of five eyes, saline was used twice a day. The maximum timolol maleate release times from chitosan films were also recorded. The animals were sacrificed, and the right eyes of the rabbits in all three groups were removed for histologic analyses.

Timolol maleate was released from the film for four weeks, with 85 percent of the drug being released during the first two weeks. However, *in vivo* IOP levels were lowered over a 10-week period. No significant difference with regard to lowering IOP was seen between the eyes that received the commercial ophthalmic solution and the eyes that received the films. Additionally, no signs of ocular discomfort or irritation were seen on ophthalmic examination by slit-lamp biomicroscopy. No alterations in ophthalmic structures that came in direct contact with the films were observed in histopathological studies, and the rabbits showed

(continued on page 79)

Resistance Fighters: An Antibiotics Update

Antibiotic innovation has slowed, allowing drug resistance to catch up, but there is still hope for the future of anti-infectives.

Mark B. Abelson, MD, CM, FRCSC, FARVO, Aron Shapiro, and James McLaughlin, PhD, Andover, Mass.

Antibiotics are the compounds we think of when we hear the term "wonder drug"; no other class of therapeutic agents can claim to match their impact on medicine and medical practice. Alas, they have also become the poster child for the concept of too much of a good thing. Their indiscriminant use and misuse has hastened the evolutionary counterattack, selecting and promoting bacterial strains with significantly reduced sensitivity to antibiotic control. In recent years we have seen reports of growing numbers of bacterial isolates that can thrive despite exposure to multiple, high-dose antibiotic treatments. Despite this threat, progress in development of new ocular anti-infectives has slowed to a trickle in the past decade. Fortunately, we see this trend beginning to shift as the battle for septic superiority begins to heat up. This month we examine the forces acting on new antibiotic drug discovery and take a look at what the future may hold for the prevention and treatment of infectious conditions of the eye.

It's hard to overestimate the problem of drug-resistant pathogens. In the United States alone, microorganisms live with a constant pressure to respond to more than 15 million kg of antibiotic introduced into the environment annually.[1] Recent Centers for Disease Control and Prevention estimates suggest that somewhere between 20,000 to 40,000 people (old and young) die in the United States annually from bacterial infections resistant to antibiotic therapy. While ocular infections rarely lead to death, there is significant morbidity associated with infectious keratitis, uveitis and endophthalmitis due to resistant strains of microbes.

A number of studies have established that antibiotic therapy leads to dramatic changes in both the relative populations of commensal species and the frequency of antibiotic resistance.[2,3] Data from the human biome project has established a basic paradigm that with antibiotic therapy comes a decrease in the diversity of commensal species, as well as a trend toward increased pathogenicity of bacteria that are normally innocuous.[4] Based on the 2009 ARMOR study,there is an increasing incidence of resistant pathogens taken from bacterial eye infections in the United States, including methicillin-resistant coagulase-negative *Staphylococcus* strains and methicillin-resistant *Staphylococcus aureus*.[5] Additionally, a 2008 New York Eye and Ear Infirmary study demonstrated that the incidence of both *S. aureus* and MRSA increased dramatically in bacterial conjunctivitis patients from 1998 to 2008.[6] Moreover, gram negatives such as *Acinetobacter* or *Pseudomonas* are now typically resistant to multiple antibiotics, and have expanded their range such that they are no longer considered primarily nosocomial pathogens.[7]

Antimicrobial Development

What's clear is that combating the problem of antibiotic resistance requires a combination of three elements: infection control; antibiotic stewardship; and development of new compounds.[1] Infection control and stewardship are the public-health policies and procedures implemented at hospitals and other health-care facilities that will combine the strictest hygiene protocols with spare, judicious use of the most potent antibiotics only

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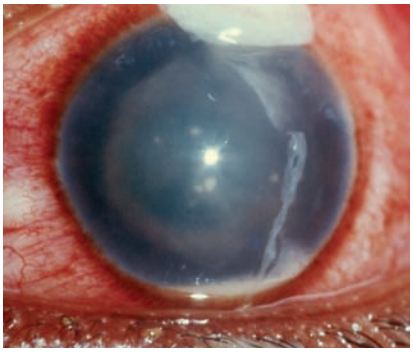
in those cases where infection by a resistant microbial strain is established. There is also a need for new therapeutics, including the next generation of existing drug classes, as well as agents with new mechanisms of action.

It may seem surprising that as we watched the issue of antibiotic resistance grow ever more problematic, progress in development of new anti-infectives ground to a halt. This reflects a mixed bag of forces acting on this therapeutic space. In ophthalmology, the dearth of new products is due in part to the high efficacy of fourth-generation fluoroquinolones that have occupied the largest segment of the market since their introduction in 2003. At the same time, many pharmaceutical companies exited the antibiotic development arena, preferring to focus on other therapeutic areas. A number of advocacy groups and governmental agencies have voiced their concerns about this therapeutic innovation vacuum. The Infectious Disease Society of America proposed a response to the need in 2010, with the "10 x '20 Initiative," a global commitment to develop 10 new antibacterial agents by 2020.[8] In 2012, the U.S. Congress passed the Generating Antibiotic Incentives Now Act, a program that provides for extended patent exclusivity and accelerated review for new antibiotics targeted toward serious and life-threatening infectious diseases.[9] This is a key step, since the biggest impediment to new antibacterial drug development is the lack of an economic incentive: Regardless of demand, it's not feasible to bring a new drug to market with no possibility of recouping the costs of clinical development. The jury is out on whether these initiatives will lead to improved tools to combat ocular infections.

Assessing the Need

Ocular indications for anti-infective therapy include bacterial conjunctivitis, blepharitis, bacterial keratitis and endophthalmitis. Each of these conditions is most commonly associated with a handful of causative bacterial agents, and while the strains remain the same, rates of resistance are on the rise across the board. For example, while *S. aureus* is the most common culprit in bacterial conjunctivitis, the strains of *S. aureus* cultured from conjunctiva between 1994 and 2003 showed a threefold increase in ciprofloxacin resistance, and an almost tenfold increase in MRSA (4.4 percent to 42.6 percent).[7] While most acute infections involve *S. aureus* or *S. pneumoniae*, gram negative pathogens such as *H. influenzae* are also seen, particularly in the pediatric population. It's important to note that while external infections such as bacterial conjunctivitis are generally self-limiting, there remains a sound rationale for the use of topical antibiotics to shorten both the duration and the severity of the infections.[10,11]



Rates of resistance for organisms that cause infections such as endophthalmitis are on the rise.

Resistance to virtually all classes of antibiotics has been documented for each of the bacterial species commonly associated with ocular infection, leading to a progression from first-line agents such as a macrolide (e.g., erythromycin) to aminoglycosides (e.g., tobramycin) and finally to a fluoroquinolone such as moxifloxacin.[3] Fluoroquinolones are Food and Drug Administration-approved for treatment of ocular infections such as bacterial conjunctivitis, but they are also currently used as a prophylactic treatment after surgical procedures. The desire for prophylaxis is certainly understandable given the consequences of infection and current standard of care. It's important to note, however, that studies designed to support such use have been equivocal. In addition, ophthalmologists' preference for later-generation flurorquinolones because of their high potency, though well-intentioned, may not represent the ideal in antibiotic stewardship. A study published in 2013 found that nearly half of endophthalmitis-cultured bacteria were resistant to fluoroquinolones, while no such resistance was found in a similar study conducted 10 years earlier.[12] Use of prophylactic antibiotics is an important issue, and while the likelihood of a patient developing endophthalmitis following these procedures is low (0.02 to 0.7 percent),[7] the aging population and exponential growth of intravitreal injection as a treatment paradigm has dramatically increased the numbers of at-risk patients. Even a low risk of this type of infection becomes problematic when it's caused by a treatment-resistant strain.

Pipeline Perspective

With the slowdown in development, the ophthalmic medicine cabinet for bacterial infections hasn't changed much in the past decade. Thankfully, there are encouraging signs of activity, an array of new compounds in the development pipeline, and the hope that some of these will be formulated and tested for ocular indications. Newer classes of compounds include antimicrobial peptides, bacterial biosynthetic inhibitors, biologicals and a host of next-generation compounds.[13,14] A number of glycopeptide compounds such as Oritavancin (The Medicines Company) that act by inhibiting cell

An Alternative Approach to Infection Control

In a recent perspective piece, noted infectious disease expert Brad Spellberg, MD, suggested that an alternative solution to the problem of antibiotic resistance is to develop therapies that "do not drive resistance."[1] The clinical outcomes of infection derive from host response as well as microbial growth, he says, so if our goal is to prevent the sequela of the infection-inflammation tête-à-tête, perhaps we should rethink our entire strategy. As an example, he cited the action of lipopolysaccharide inhibitors that prevent gram negatives such as Acinetobacter from synthesizing the LPS that initiates the inflammatory response. The bacteria are rendered harmless and their growth is minimized by enhanced phagocytosis. Because the inhibitor is not harmful to the bacteria, it creates much less selective pressure, and a lower risk of resistance. *—MBA*

wall biosynthesis have shown promise against gram positive organisms, including MRSA. While similar in action to vancomycin, compounds such as Oritavancin are active against most vancomycin-resistant strains. A related compound, Telavancin (Theravance), was approved for IV use against MRSA infections in 2009, but has seen limited use due to production issues.

Carbapenems are the most recently developed family of beta-lactam antibiotics and, like penicillins and cephalosporins, they exhibit broad-spectrum activity against gram positive and gram negative bacteria. None of the currently approved compounds have ocular indications, but several are in development. Another next-generation candidate is Plazomicin (Achaogen), a new aminoglycoside which, like its predecessors tobramycin and gentamycin, acts by inhibiting bacterial protein synthesis. Early studies suggest it's more potent than others in this class, but a final verdict will come from ongoing studies.

As the most powerful group in the ocular antibiotic arsenal, improving on the existing fluoroquinolones is a logical place for enhancing therapeutic efficacy. A number of next-generation fluoroquinolones are in development, including delafloxacin (Melinta Therapeutics), JnJ-Q2 (Furiex Pharma) and ACH-702 (Achillion Pharma). All fluoroquinolones target some combination of topoisomerase IV and DNA gyrase, two bacterial enzymes that are paramount to DNA replication and thus the proliferation of invading bacteria. While the various fluoroquinolones differ in their specificity for each enzyme, these two shared mechanisms have led to the emergence of pathogens that show varying degrees of resistance to all fluoroquinolones. Widespread usage of the latest generation of fluoroquinolones makes the potential for this "cross-resistance" among ocular pathogens a real concern for public-health officials and ophthalmologists. Based on the emergence of resistant pathogens and the potential for cross-resistance, there is a need for a novel antibiotic that avoids the common mechanism of resistance.

ACH-702 has demonstrated the ability to kill fluoroquinolone-resistant *S. aureus*. Unlike the first generation of this drug class, ACH-702 has the ability to inhibit topoisomerase and DNA gyrase in resistant bacterial strains, and also demonstrated a 128-fold increase in the minimal inhibitory concentrations compared to moxifloxacin in resistant *S. aureus* clinical isolates.[15] It's thought that this new fluoroquinolone also exhibits a unique enzyme inhibitory activity against bacterial DNA primase, a novel bacterial target. This action is important for two reasons: it provides an MOA distinct from topoisomerase and DNA gyrase inhibition; and it allows the compound to target and kill metabolically active bacteria even in a non-dividing state. The unique features of ACH-702 represent the types of molecular strategies necessary to defeat the process of antibiotic resistance.

As with other candidate therapeutics, new antimicrobials will still require testing in an ocular setting before they can be brought to market for ophthalmic indications. Despite these hurdles, there does seem to be a renewed effort to identify and develop compounds that can address the problem of antibiotic resistance. For those whose sight is threatened by multidrug-resistant bacteria, these compounds will definitely qualify as wonder drugs. REVIEW

Dr. Abelson is a clinical professor of ophthalmology at Harvard Medical School. Mr. Shapiro is vice president for anti-infectives at Ora Inc, where Dr. McLaughlin is a medical writer.

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Stem Cells for Corneal Disease: A Primer

A look at the various types of stem cell therapies that are already or may soon be available to improve our patients' vision.

Thomas John, MD, Chicago

Stem cells are undifferentiated, non-specialized, precursor cells that are present in all multicellular organisms and are capable of self-proliferation, migration and differentiation. It was Alexander Maksimov, a Russian histologist who first coined the term "stem cells" in 1908 at the Congress of the Hematologic Society in Berlin.

Types of Stem Cells

Mammalian stem cells may be A) embryonic stem cells, B) adult stem cells or C) cord blood stem cells. The inner cell mass of blastocysts contains the embryonic stem cells, while the adult stem cells are housed in various tissues of the body, where they (adult stem cells and progenitor cells) replace adult tissues as a reparative process of the body. Unlike the adult scene, in the developing embryo, these stem cells are pluripotent and can differentiate into ectoderm, mesoderm and endoderm, thus covering all the bodily specialized cells.

• ***Stem cell origin.*** Adult, autologous stem cells can originate from the bone marrow, blood and fat or adipose tissue. For bone-marrow-derived stem cells, drilling is carried out at the iliac crest or the femur, while blood-derived-stem cells can be obtained by apheresis harvest of stem cells from donor blood. On the other hand, stem cells from adipose tissue are obtained by liposuction. Yet another source of stem cells can be the umbilical cord blood immediately after birth.

• ***Stem cell features.*** To qualify as a stem cell, cells have to self-renew with potency to differentiate into specialized cells. Self-renewal refers to the ability of the cells to undergo multiple cell division cycles while at the same time maintaining their undifferentiated cell state. From a potency standpoint, the stem cells have to be pluripotent or totipotent to be able to form any mature cell type. The various types of stem cell potency are described below:

Pluripotent: These stem cells are derived from totipotent stem cells and can differentiate into any of the three germ layers.[1]

Totipotent or omnipotent: These are stem cells with the maximum potential, namely they can differentiate into both embryonic and extra-embryonic cell types. Biologically, they can build a complete organism that is viable. These totipotent stem cells are produced as a result of the fusion between an egg and sperm cell and also from the initial few divisions of the fertilized egg.[2]

Multi-potent: These stem cells can differentiate into a number of different cells that are closely related to a family of cells and they are also in the amniotic fluid.[3]

Oligo-potent: These stem cells have limited potential and can differentiate into a few cells, for example, myeloid or lymphoid stem cells.[3]

Uni-potent: These stem cells can produce only their own type of cells (one cell type).[3] The property of self-renewal differentiates these cells from non-stem cells.

Induced pluripotent: These are different from all the stem cells described above. These are adult cells such as epithelial cells that are then reprogrammed to acquire pluripotent potential. These often involve genetic reprogramming using protein transcription factors.

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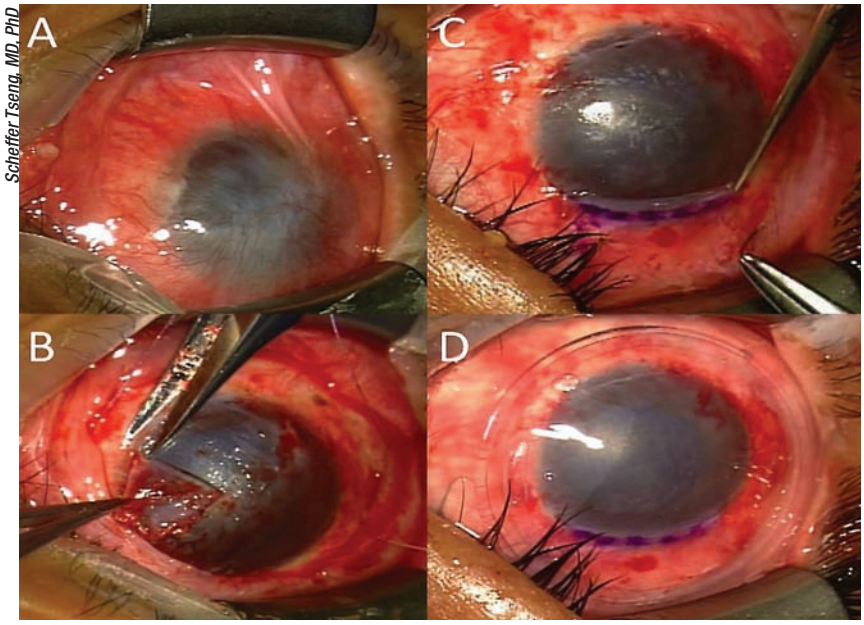

Scheffer Tseng, MD, PhD

Conjunctival-limbal autologous transplant for A) total limbal stem cell deficiency in a case of total LSCD OD due to chemical burn injury. B) Superficial keratectomy was performed to remove the pannus. C) Autologous transplant was secured over an amniotic membrane permanent graft. D) Prokera (BioTissue Inc.) was then applied as a temporary patch graft to enhance the healing.

Ocular Stem Cells

Treating ocular diseases utilizing stem cells is of significant interest to both clinicians and researchers. Currently, there is no treatment to fully cure ocular surface stem cell deficiency states and ocular neurodegenerative diseases. Ocular location of stem cells is primarily in the front regions of the globe, namely, at the limbus, conjunctiva and retinal-ciliary margin. Limbal stem cells are sandwiched between conjunctival epithelium on the outside and corneal epithelium on the inside. Among all adult somatic stem cells, those of the corneal epithelium have a unique location in a specific limbal structure called the Palisades of Vogt.[4] The understanding that corneal epithelial stem cells are located in the limbal area sheds light on multiple observations including the mature-looking basal cells, the preponderance of tumor formation in the limbal zone, and the centripetal cellular migration.[5]

Limbal stem cells play an important role in corneal homeostasis. This garland-like pattern of the limbal, corneal epithelial stem cells on the ocular surface, encircling the limbus, also plays a role in policing the area, thus, preventing the conjunctival epithelium from encroaching onto the clear cornea, which can result in corneal neovascularization, corneal clouding and blurred vision or even total vision loss. Human limbal stem cells detection is possible both *in vivo* and *in vitro* by their expression of p63 transcription factor. Protein p63 retains the proliferative potential of limbal stem cells. Additionally, extraocular stem cells, namely, adult stem cells, embryonic stem cells and induced pluripotent stem cells seem to be promising in restoring vision loss as well.

Bilateral blindness worldwide is estimated to be around 45 million as per the World Health Organization, and more than 20 percent (10 million) is secondary to corneal diseases. Of the corneal disorders, limbal stem cell deficiency may be considered as one of the most severe and difficult-to-manage clinical entity. On the ocular surface, autologous limbal stem cells clearly have the potential to regenerate and reproduce damaged corneal tissue secondary to stem cell deficiency. For instance, in cases of severe ocular burn with damaged limbal stem cells, surgical engraftment of limbal epithelial cells, with or without *ex vivo* expansion often improves eyesight in patients afflicted with limbal stem cell deficiency.[4]

Moving to the back of the eye, in the retinal arena, there is heightened interest in the potential for stem cell treatment in retinal degenerative diseases such as age-related macular degeneration, Stargardt's disease and retinitis pigmentosa, which lack curative treatment at the present time. Many of the outer retinal diseases seem to be linked to the degeneration of the epithelial monolayer, namely, the retinal pigment epithelium, which is essential for supporting tissue involved in retinol cycling, nutrient transport, growth factor production and phagocytosis of the photoreceptor outer segments.[6]

Management

It is conceivable that the treatment of human diseases can be revolutionized by stem cell therapy. Although there are various treatment strategies, one widely known approach is cell replacement therapy, in which stem cells that are differentiated into the desired cell type are then delivered to the damaged tissue in order to integrate and restore function.[6] An alternative modality is via a paracrine effect, in which the transplanted stem cells secrete trophic factors that help the resident tissue to self-restore and proliferate.[6,7] Further, there is some evidence that stem cells may fuse with existing cells in order to restore function.[6,8]

The risk with the use of stem cells

is decreased when we use autologous harvesting, obtaining the stem cells from one's own body. The various choices of limbal stem cell restoration include 1) keratolimbal allograft from a donor cornea; 2) conjunctival allograft from a living relative; 3) patient's conjunctival limbal autograft; and 4) autologous culture of limbal cells used as a route of transplant tissue. However, the culture techniques are currently not FDA-approved; hence the other options may be considered based on unilateral or bilateral ocular involvement, and the severity of the limbal stem cell deficiency. Following limbal stem cell stabilization, any corneal opacity that is interfering with vision may be addressed by partial thickness, anterior, lamellar keratoplasty, penetrating keratoplasty or a keratoprosthesis (artificial cornea) such as the Boston keratoprosthesis.

Stem cell-based treatment for retinal disease states bifurcates into regenerative and trophic approaches, both of which comprise the implantation of cells into the subretinal space. In the regenerative strategy, a human embryonic stem cell (hESC) line that has differentiated into retinal pigment epithelial cells is used to replace the disease-related, RPE cell loss. In the trophic approach, undifferentiated human umbilical, tissue-derived cells (hUTC) are used to support degenerating cells via the release of different mediators including neurotrophic factors, interleukins, etc.

Complete success in the arena of human stem cell replacement would result in a paramount effect on anatomic and functional tissue restoration, with relief of stem cell deficiency related ocular symptoms and regaining vision. REVIEW

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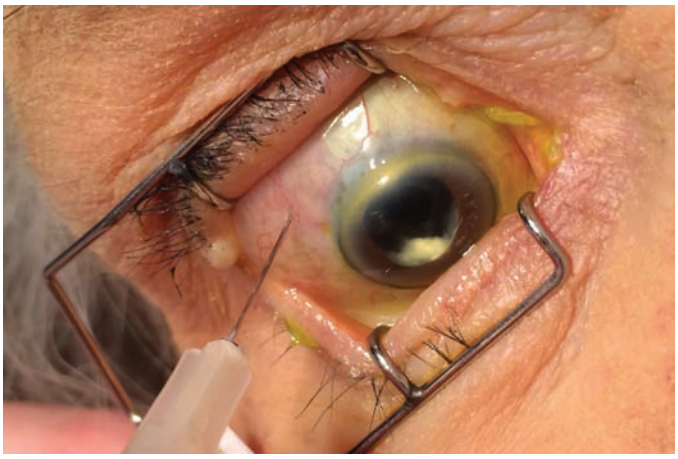
IVT Injections: Health Policy Implications

This therapeutic revolution has important implications for health policy, for physicians and most importantly, for patients.

George A. Williams, MD, Royal Oak, Mich.

The advent of intravitreal drug therapy for retinal vascular disease over the past decade constitutes a therapeutic revolution of unprecedented scale in the history of ophthalmology. The ability to minimize loss of vision in more than 90 percent of patients with new-onset neovascular age-related macular degeneration and to improve vision in approximately 40 percent of patients over a period of years has resulted in untold clinical benefit.[1] More recently, a similar treatment benefit has been demonstrated in retinal venous occlusive disease and diabetic macular edema.[2-4] This report will discuss the epidemiology of intravitreal injections—examining the past growth, estimating the current number, and speculating on the future growth of intravitreal injections with a consideration of potential health policy implications.



The Numbers

The best available data on the epidemiology of intravitreal injections comes from the AMA/Specialty Society RVS Update Committee Database.[5] However, this database is limited to a 5-percent sample of the Medicare Physician Fee for Service schedule. It does not include Medicare Advantage or non-Medicare utilization and therefore is not a comprehensive source.

Prior to 2001, the number of intravitreal injections (CPT code 67028) in the RUC database was relatively stable at approximately 4,500 per year, primarily for the treatment of endophthalmitis. In 2002, the number of injections tripled to 15,000 (largely triamcinolone) and by 2004 it was 83,000. The breakthrough year was 2005 with growth to 252,000 following the first reports on pegaptanib, bevacizumab and ranibizumab. By 2008, more than 1,000,000 injections were performed. In 2011, aflibercept became available and total intravitreal injections topped 2,000,000. In 2012, 2,354,753 were reported in the RUC database.

Although precise numbers are not available for total 2013 utilization, a reasonable estimate can be calculated by using a conservative growth rate of 10 percent (substantially less than the growth rates of 14 to 27 percent over the period 2008 to 2012), resulting in approximately 2.4 million injections. A total number of injections for Medicare can be estimated by including Medicare Advantage beneficiaries at ~30 percent of the Medicare population for an approximate 3.1 million injections in the total Medicare program. Although Medicare-eligible

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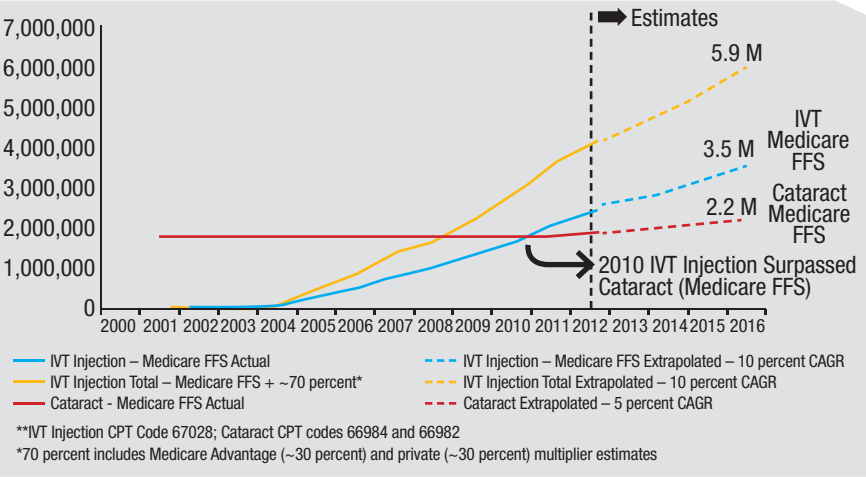
patients continue to constitute the majority of individuals treated with intravitreal injections, an increasing number of younger patients are being treated for diabetic macular edema and retinal venous occlusions. Based on utilization data from my group, I estimate that approximately 30 percent of patients receiving intravitreal injections are not in Medicare. This results in an estimated total of 4.1 million injections in 2013.

Table 1. Intravitreal Injection and Cataract Procedures in the United States by Year**



**IVT Injection CPT Code 67028; Cataract CPT codes 66984 and 66982
*70 percent includes Medicare Advantage (~30 percent) and private (~30 percent) multiplier estimates

Tough to Predict

Now that we have established a baseline, what can we predict about future growth? Although I am a big fan of the Yogi Berra aphorism that, "Its hard to make predictions, especially about the future," I think we can use our knowledge of demographics and the likely timeline for future disruptive technologies to estimate what to expect over the next three years. Using a conservative yearly growth rate of 10 percent suggests approximately 5.9 million injections in 2016. If we assume a less conservative, but still realistic growth rate of 20 percent the estimate is 7.9 million. The logistics of delivering these numbers of injections will be challenging.

The RUC database reveals interesting demographics about Medicare beneficiaries receiving intravitreal injections. As expected, there is substantial racial disparity: 93.9 percent white, 2.5 percent black, 1.2 percent Hispanic and 2.4 percent other. A gender disparity also exists, with 67 percent female and 33 percent male. A remarkable 34 percent are greater than 85 years of age and 77 percent are greater than 75 years of age. More than 97 percent are age-eligible for Medicare, with 2 percent disabled and 1 percent with end-stage renal disease.

An analysis of the indications for intravitreal injections based on ICD-9 coding reveals that 96.5 percent are in the ICD 362 family that includes most retinal vascular diseases. Unfortunately, the database does not have granularity within the ICD 362 family to determine the relative proportion of neovascular AMD, diabetic retinopathy or retinal vascular occlusions. Diabetes, coded as ICD 250, occurs in 2.5 percent with glaucoma (ICD 365) at 0.2 percent and other CPT diagnoses at 0.4 percent constituting the remainder.

New Scrutiny

The logarithmic growth of intravitreal injections is attracting increasing health policy scrutiny. Despite consensus on the clinical efficacy and safety of intravitreal injections, the rapidly expanding costs are a concern. These costs include the examinations and retinal imaging associated with intravitreal injections, and of course the cost of the drugs. The reimbursement for the intravitreal injection procedure was substantially decreased by Medicare in 2010 due to a shortened procedure time. Although the continuing volume growth may result in additional review, I do not see how ophthalmologists can further significantly cut the time necessary to deliver this essential treatment. Furthermore, cuts in physician reimbursement will have minimal effect on overall costs.

In June of 2013, the General Accounting Office released a report on Part B drug costs for 2010.[6] In this report, ranibizumab was the third highest-expenditure Part B drug for Medicare beneficiaries at $1.18 billion. In 2010, Medicare expenditure for intravitreal injections was approximately $200 million. Even with the addition of other related physician services such as ocular examinations and imaging, the primary driver of expenditures associated with intravitreal injections is the cost of the drugs. New indications such as diabetic macular edema, central vein occlusion and branch vein occlusion as well as the advent of aflibercept and ranibizumab for DME have substantially further increased drug expenditures. In 2013, U.S. sales of ranibizumab and aflibercept were approximately $1.73 billion and $1.35 billion respectively, according to available financial reports. Therefore, in composite, drugs for intravitreal injections are now likely the highest expenditures for Part B drugs.

The health policy implications of

the increasing cost of intravitreal therapies are becoming apparent. Some payers are now requiring step therapy protocols that mandate the initial use of bevacizumab. Ranibizumab or aflibercept may only be used in cases of treatment failure. The criteria for treatment failure are often poorly defined. The mandated use of bevacizumab has been complicated by the recent Drug Quality and Security Act that has created access and logistical issues for use of off-label bevacizumab in several parts of the country.

The ACA Impact

The Affordable Care Act is also likely to impact intravitreal injections, particularly the choice of drug. Starting in 2015, a value-based modifier will be a factor in Medicare physician payment. The details of VBM are uncertain, but it is likely that the use of expensive drugs, regardless of clinical indication, will be associated with a financial penalty as part of a quality and cost assessment. This penalty will be a 2-percent cut on all Medicare physician payments. Considering the limited margin on Part B drugs, some ophthalmologists may be unable to continue using expensive drugs. (And as noted above, federal and state compounding regulations may make it increasingly unattractive to use less-expensive drugs).

Patients will also be affected. The new health exchange plans and many commercial health insurance plans are characterized by high deductible expenses that may preclude the use of expensive drugs. The exploding cost of intravitreal therapy will present increasingly complex challenges to ophthalmologists, payers and most importantly, patients. REVIEW

Dr. Williams practices at Associated Retinal Consultants, William Beaumont Hospital, 3535 West 13 Mile Rd. #344, Royal Oak, MI 48073. Contact him at GWilliams@beaumont.edu.

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Root Out Multifocal Lens Problems

Just because a patient is unhappy with her multifocal lens doesn't necessarily mean she needs a surgical solution.

Surendra Basti, MD, Chicago

When a patient presents with vision complaints after having received a multifocal lens, you essentially have a problem to solve, and, as Albert Einstein said, "The framing of a problem is often far more essential than its solution." The reason that framing the problem is so crucial in these patients is that their complaints can stem from any number of factors: There can be problems that appear early in their postop course or late, or that are caused by refractive error, pupil issues or even retinal conditions. With Einstein's dictum in mind, here is a stepwise approach to these patients that's helped me root out their problems and define the best solutions.

The Nature of the Problem

After determining basic facts such as the type of multifocal lens the patient has and specifically the reading add power, I ask several key questions:

• ***Is the complaint a lack of visual clarity or is it a specific type of visual disturbance such as glare, halo or starbursts?*** Making this differentiation is important since the former symptom is multifactorial but many causes are treatable.

• ***If it's a lack of clarity, is the problem specific to one viewing distance or is it present at all distances?*** The thought process here is that, if the patient's problem is specifically related to one particular viewing distance, the etiology of the problem is usually a refractive error such as residual myopia or hypermetropia. Once this is identified, it is important to determine if the patient's lack of clarity is much improved by placing a refractive correction. Ensuring this suggests that surgical correction of the refractive error is likely to help.

The other aspect of problems along these lines is that, sometimes, a patient will have a multifocal lens and will discover that it isn't easy to see at the intermediate distance. This issue is particularly common with the Tecnis multifocal lens, which only has a strong +4 add in the United States. With that lens, intermediate vision tasks are sometimes only clear if the patient moves closer to the object of regard, such as the computer screen or other intermediate target. Because of this, it's important to determine if the difficulty a patient is having is related to the distance he needs to be from the target. For instance, say a patient has a Tecnis multifocal intraocular lens and is having a problem with the computer. If, in trying to characterize the problem, you find out that the patient is actually saying he can't see the screen from the usual distance but can see it when he moves closer, that's something that you know is simply a function of how the lens operates. Knowing this, you can explain the situation to the patient and then design a pair of eyeglasses that can counteract the problem.

A lack of clarity at all distances could be the result of various other factors, some of which are further elaborated below.

• ***How long has the patient had the symptoms or lack of clarity?*** If the patient's problems started literally from the get-go after cataract surgery, that's an important fact to know. This is because the reasons why such instant problems could be occurring are slightly different from those behind problems that occur after a few months or years of having the lens. The latter case is suggestive of an

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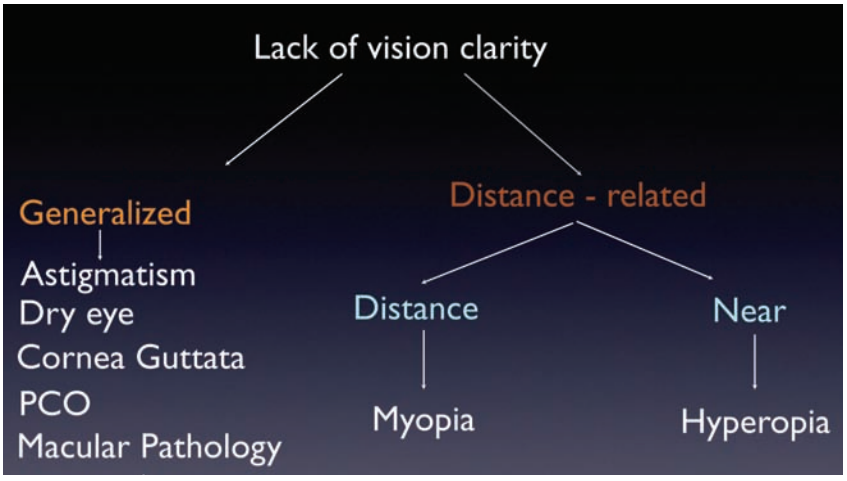


When formulating a treatment plan for an unhappy presbyopic intraocular lens patient who complains of a lack of visual clarity, dividing complaints into generalized vision problems or those dependent on distance can help formulate a solution.

acquired cause for the unhappiness and, in many cases, an acquired cause is treatable.

I recall one case in particular in which a patient who had received a multifocal lens was referred to me complaining of poor vision. The referring surgeon concluded that the IOL was decentered. When I asked the patient if she had been having this vision problem all along since her surgery, she replied that she hadn't. In fact, she told me that she had loved her vision for the first few months, but then, for the past six months, didn't like it. So, even though the referring surgeon was convinced that a decentered lens was causing the problem, the fact that she had loved her vision immediately after the cataract surgery made me look deeper for other causes. Eventually, I found that posterior capsular opacification had occurred, and that the decentration was minimal if it was there at all, and not the cause of the problem.

• ***Is the lack of functionality or clarity dependent on the amount of light available?*** Most of the currently available multifocal lenses are dependent on pupil size and the amount of light available for reading. So, when the light is good and the pupil is small, that facilitates reading with some of the multifocal lenses. Knowing this can help you differentiate between problems that you can actually solve and those that are simply endemic to using a particular lens. For example, if a patient with a ReSTOR lens complains that he can't read in a dim light situation such as in a restaurant, you can't change or help that situation. That is simply the nature of how the refraction works with such lenses.

Exam Notes

In addition to a careful history, here are ways to approach the physical exam that can yield helpful diagnostic information.

• ***Refraction.*** In a patient with a multifocal lens, the retinoscopic reflex can be confusing, because you have different reflexes coming from different areas of the lens. When performing a refraction then, focus right in the center of the lens where there is a small area with no multifocal rings. Doing that will provide a clue to the real refractive error in these patients.

I like to test the vision at all distances. This helps me understand straightaway what the patient can and can't do easily. For instance, if he can read 20/20 at distance but doesn't do well at intermediate or near, I then suspect that he may have a small amount of hypermetropia that he's able to counter well at a far distance but not at the other distances.

• ***Slit lamp exam.*** At the slit lamp, I like to focus on four things. First, I assess the status of the tear film and the ocular surface. Are there dry spots on the cornea? What is the quality (assessed by tear-film breakup time) and the quantity (assessed via Schirmer's) of the tears? If one or both of these tests is sub-optimal, you can get dry-eye-related vision difficulty. A low Schirmer's test and dry spots on the corneal surface tell you that the patient's volume of tears is low. A very rapid tear-film breakup could be due to a low tear volume, but it could also be due to meibomian gland dysfunction. So, if you see a very rapid breakup, look at the Schirmer's result. If the Schirmer's was normal then home in on the meibomian gland, focusing on the gland secretions. If the meibomian gland secretions are very thick, they could cause a rapid breakup, which could result in suboptimal vision.

The second structure to focus on is the endothelium. If there are guttata, that can be an important cause of poor visual quality.

The third important consideration is the position and centration of the IOL, for obvious reasons. If the lens isn't well-centered, the patient won't be able to get the best vision from it.

Finally, check the status of the posterior capsule, which really needs to be clear in order to get good quality from these multifocal lenses.

• ***Pupil examination.*** Of the three aspects of the pupil exam—size, centration and angle kappa—pupil size is the most important in the unhappy multifocal lens patient. This is because most surgeons know that if the pupil is grossly decentered the multi-

focal patient obviously is not going to be happy. More to the point, most surgeons wouldn't have implanted one of these lenses in that kind of patient in the first place. The impact of pupil size, though, is very easy to miss if you didn't specifically look for it preoperatively.

For multifocal IOL patients, in order to see well at distance, especially in dim light while driving, for example, the pupil needs to get to its normal physiologic size in dim light, which is 5 to 6 mm. However, in order for a multifocal lens to allow a patient to read, the photopic pupil size should be close to 3 mm. From time to time, though, we will encounter a patient whose pupil doesn't come down that much and, because of this, you can expect that the reading ability won't be as good in that patient if he has a multifocal lens. On the other hand, some elderly patients will have pupils that don't dilate as widely as they should, and they may be unhappy with their nighttime driving vision due to decreased clarity. Therefore, you will be able to surmise that the patient's problem isn't a visual disturbance but is instead a pupil-related difficulty with distance vision in dim light, which may be helped with a dilute mydriatic.

• ***Corneal topography.*** Pay attention to indices that are available on many topographers such as the surface regularity index and the surface asymmetry index. In some cases, you may see some dry eye or basement membrane dystrophy, but the impact of these is more obvious when you use one of these indices. Topography is also very useful for getting a sense of the astigmatism, since the most common cause of unhappiness in premium lens patients is some sort of residual refractive error, including cylinder.

• ***Macula exam.*** I have a low threshold for doing optical coherence tomography in these patients, and will do OCT on anyone who's unhappy, because macular changes are a critically important cause of poor vision after a premium IOL. It's not uncommon to miss a subtle epiretinal membrane on ophthalmoscopy but then find the wrinkling caused by the ERM to be obvious on OCT.

Though patients' complaints following multifocal IOL implantation can be caused by a number of factors, if you take a logical, stepwise approach, you're likely to frame the problem properly and take the right steps toward a solution. There is clearly a small subset of patients who will need IOL exchange, but by taking a systematic approach you can identify and correct those that can be treated without intraocular surgery. REVIEW

Dr. Basti is a fellowship-trained specialist in refractive, corneal and cataract surgery and is an associate professor of ophthalmology at Northwestern University's Feinberg School of Medicine.


Goniosynechialysis: Beyond Angle Opening

If peripheral anterior synechiae are present, simply opening a narrow angle may not restore trabecular outflow. GSL can help.

Robert Ritch, MD, New York City

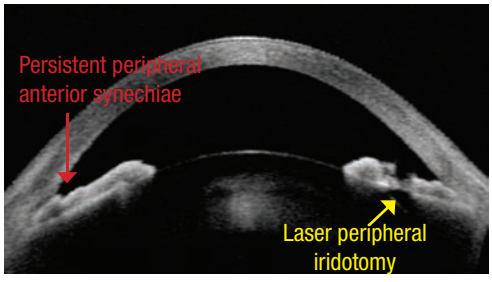
A significant number of the glaucoma patients and suspects encountered in clinical practice have narrow angles. Although this is most common in Eastern Asia, particularly among the Chinese population, it is common worldwide, and was long underdiagnosed. Fortunately, that problem has improved significantly in recent years.

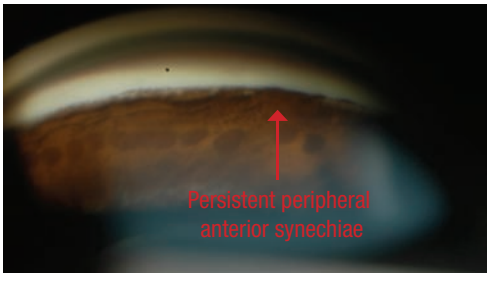
These patients may have narrow angles, intermittent angle closure, appositional closure, or closure with the development of peripheral anterior synechiae (PAS), termed chronic angle closure. If glaucomatous damage is present, then angle-closure glaucoma becomes the appropriate term. Angle closure can be caused by abnormalities in the relative or absolute sizes or positions of anterior segment structures, or by abnormal forces in the posterior segment that alter the anatomy of the anterior segment.

Our group has divided angle-closure mechanisms into four categories, depending on the site of the "force" causing iris apposition to the angle wall:[1]

- relative pupillary block (note that absolute pupillary block, where the iris is completely bound down to the lens by posterior synechiae, is rare);
- plateau iris, in which the ciliary body is large and/or anteriorly positioned and holds the iris against the trabecular meshwork (termed plateau iris syndrome when it is the cause of persistent appositional closure after the elimination of pupillary block by iridotomy);
- lens-induced or lens-related angle closure, in which the lens pushes the ciliary body and iris against the meshwork; and
- forces posterior to the lens.

Primary angle closure comprises angle closure due to relative pupillary block and plateau iris. It responds to pilocarpine with constriction of the pupil and opening of the angle. Lens-related glaucoma and malignant glaucoma are paradoxically worsened by pilocarpine, causing the lens to move forward. Laser iridotomy provides the definitive treatment in eyes with pupillary block and should be used in the treatment of all angle-closure mechanisms, on the presumption that





Chronic apposition of the peripheral iris to the angle leads to synechial formation. Treatment of this condition should not be limited to eliminating the mechanisms of angle closure using laser iridotomy and iridoplasty, but also to restoring trabecular outflow. Laser treatments can eliminate pupillary block and residual appositional angle closure, but they do not affect peripheral anterior synechiae, despite some reports to the contrary in the literature.

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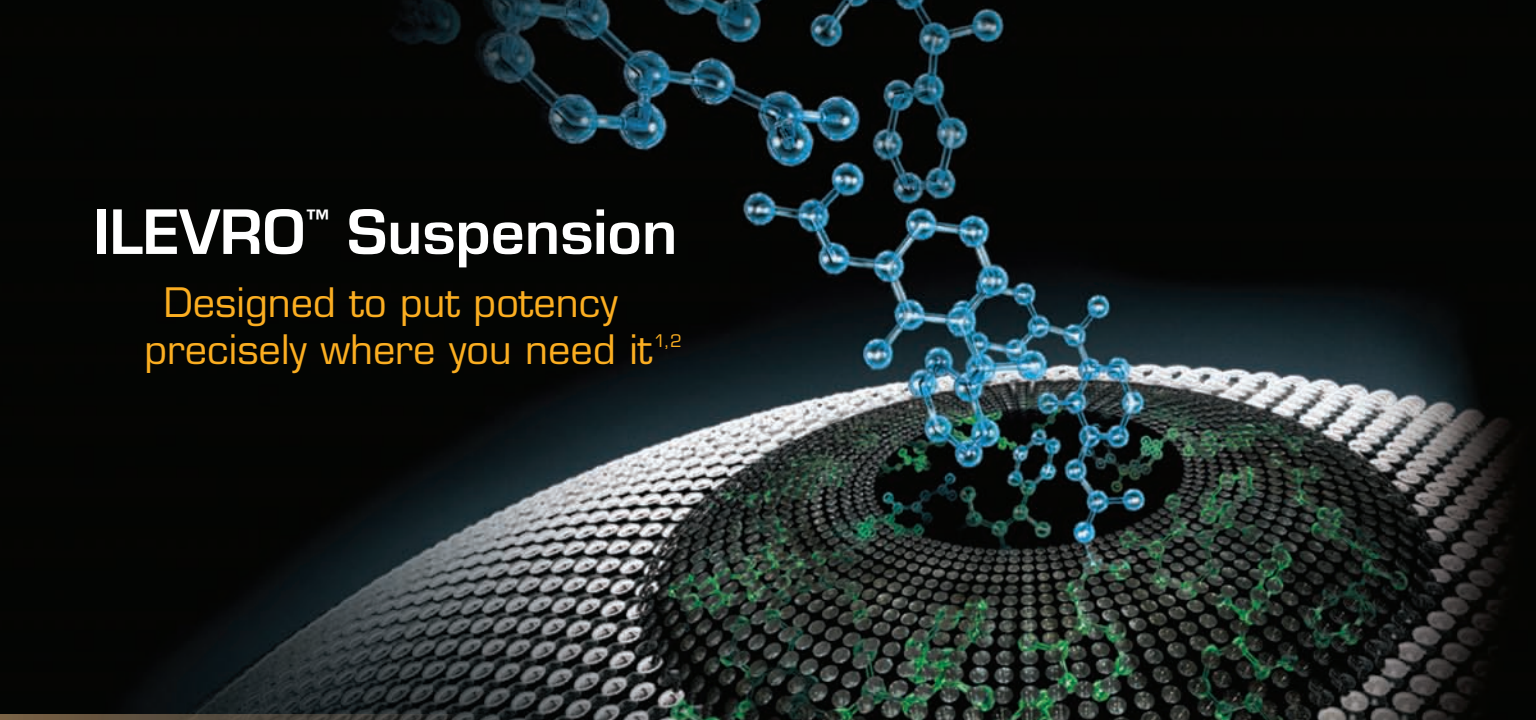

ILEVRO™ Suspension

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

ONCE-DAILY POST-OP

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

Use of ILEVRO™ Suspension more than 1 day prior to surgery or use beyond 14 days post-surgery may increase patient risk and severity of corneal adverse events[3]

INDICATIONS AND USAGE

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

Dosage and Administration

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

IMPORTANT SAFETY INFORMATION

Contraindications

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

Warnings and Precautions

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

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

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

Adverse Reactions

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

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

References: 1. Ke T-L, Graff G, Spellman JM, Yanni JM. Nepafenac, a unique nonsteroidal prodrug with potential utility in the treatment of trauma-induced ocular inflammation, II: In vitro bioactivation and permeation of external ocular barriers. *Inflammation*. 2000;24(4):371-384. **2.** Data on file. **3.** ILEVRO™ Suspension package insert.

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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 post-implantation loss, reduced fetal weights and growth, and reduced fetal survival.

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

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

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

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

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

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

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

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

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

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

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

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

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

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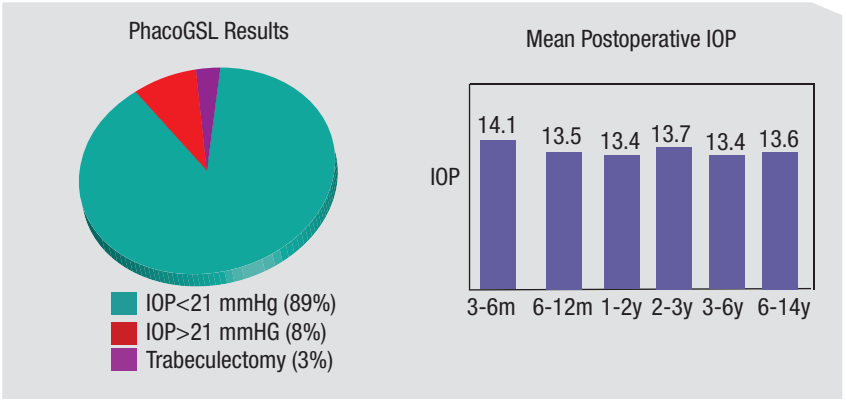
Results of Phaco Combined with Goniosynechialysis



Our group performed combined phacoemulsification and goniosnyechialysis in 81 patients who had had primary angle closure for less than six months, with peripheral anterior synchiae over more than 180 degrees of the angle and uncontrolled IOP despite laser surgeries. Eighty-nine percent of patients had a significant reduction of the synechiae and controlled IOP without medications; only 3 percent required subsequent trabeculectomy. Postoperative IOP was reduced to the low or mid-teens, regardless of the preoperative level. The success rate did not change after the third postoperative month, and pressures have been stable for up to 14 years. This suggests that long-lasting control is possible.

any case of angle closure has some element of pupillary block.

If angle closure persists after iridotomy, argon laser peripheral iridoplasty is the next step, especially if a double-hump sign characteristic of plateau iris is present. ALPI may also be used as a primary procedure to break an attack of acute angle closure, almost always successfully, and to treat persistent angle closure in cases of lens-related and malignant glaucoma.[2]

Early opening of the angle can restore aqueous outflow. If the angle is not opened, the chronic apposition will lead to increased pigmentation of the trabecular meshwork and eventually to the development of PAS—permanent adhesions between the iris and the meshwork. Performing laser iridotomy—and, if indicated by continued angle closure, ALPI—may not be the end of the story, however. If PAS are present (and these cannot be broken by ALPI, despite two reports in the literature claiming this) they may pose a threat even after the angle is opened. If PAS are extensive and uncontrolled glaucoma is present, surgical intervention becomes necessary.

Here, I'd like to share some of what we've learned about the surgical management of PAS, and the indications and use of goniosynechialysis to help patients who have developed this problem.

Angle Closure and Outflow

Initially, PAS form on the inner surface of the meshwork, but prolonged obstruction eventually leads to irreversible changes inside the meshwork, seen ultrastructurally, permanently blocking the outflow pathway at the site of the PAS. Unfortunately, cataract surgery alone does not eliminate PAS. Research has shown that up to 32 percent of patients with uncontrolled angle closure who underwent phacoemulsification alone still had persistent synechiae and uncontrolled pressure postoperatively.[3]

Goniosynechialysis was first described by David G. Campbell and Angela Vela in 1984. It is designed to strip PAS from the angle wall and restore trabecular function. The procedure consists of using a cyclodialysis spatula, an iris spatula, a bent 25-ga. needle or an Ahmed micrograsper to manually break the PAS. (I prefer to flatten PAS with a spatula under direct visualization to ensure that I don't tear the iris with a forceps.)

When performing the procedure, the surgeon creates a paracentesis and allows the anterior chamber to shallow. In phakic eyes, massaging the eye will help to move aqueous from the posterior chamber to the anterior chamber. Once the anterior chamber has been filled with viscoelastic and the surgeon achieves clear, direct visualization of the angle, the synechiae are stripped one small segment at a time. The eye is rotated to reach as much of the angle as possible; if necessary, a second incision can be made. Following surgery, the patient should undergo a course of steroids (plus NSAIDs if the surgery was combined with cataract surgery), with pilocarpine used to help prevent reclosure of the angle.

In Dr. Campbell's study, GSL was successful in 80 percent of eyes, with minimal complications, as long as the synechiae had been present in the angle for less than one year. However, the authors also noted that the synechiae could recur in eyes that continued to have crowding of the anterior chamber.

Back in 1999 I published a paper with Chaiwat Teekhasaenee, MD, in which we described the results of a large series of GSL procedures.[4] We performed combined phacoemulsification and GSL in 81 patients who had had primary angle closure for less than six months and had uncontrolled IOP following laser surgeries. They also had synechiae in more than 180 degrees of the angle. *(See chart, above.)*

Potential Complications: GSL vs. Trabeculectomy

Complications	Goniosynechialysis	Trabeculectomy
Postop IOP spike	can occur	unlikely to occur
Iridodialysis	can occur	unlikely to occur
Flat AC	unlikely to occur	can occur
Hypotony	unlikely to occur	can occur
Malignant glaucoma	unlikely to occur	can occur
Bleb-related problems	unlikely to occur	can occur
Late endophthalmitis	unlikely to occur	can occur

A comparison of the potential complications of GSL and trabeculectomy shows the comparative safety of GSL.

Postoperative IOP was reduced to the low or mid-teens, regardless of the preoperative IOP. Eighty-nine percent of the subjects had a significant reduction of the synechiae, and their IOP was controlled without any medications; only 3 percent required subsequent trabeculectomy. The success rate did not change after the third postoperative month, and intraocular pressures were stable for up to 14 years, suggesting that long-lasting control is possible.

That series also demonstrated that if you do GSL, it is very important to remove the lens. Again, most of these eyes have angle closure, so they have a shallower anterior chamber and a steeper lens vault. Replacement of the natural lens with a thinner IOL creates space in the anterior chamber, discouraging PAS reformation. However, the iris has "memory," so if the lens remains and the angle is not grade 4, the iris creeps back up and undoes the GSL. We found this to be true even when we put patients on pilocarpine after the procedure. For that reason, our highest success rate was with the patients in whom we removed the lens, did the GSL simultaneously and then kept the patients on pilocarpine for a while afterwards to keep the angle open and prevent the iris from creeping back up.

Other studies have confirmed the efficacy of this combination procedure.[5-7]

Surgical Considerations

When deciding whether GSL is necessary, there are a number of factors to consider. Good candidates for this procedure include eyes with a previously normal trabecular meshwork that now have chronic angle closure—eyes that have undergone iridotomy and possibly iridoplasty, with 50 percent or more of the angle sealed by PAS and an elevated IOP. Recent synechial closure is usually associated with better results.

There are few contraindications. Generally, GSL is a safe procedure. However, patients who might be considered less-ideal candidates would include patients with neovascular glaucoma, in whom extensive bleeding might be encountered; eyes with significant visual field loss or cupping, which would be more effectively treated with filtration surgery; and eyes that have had PAS for more than one year.

Other factors to consider:

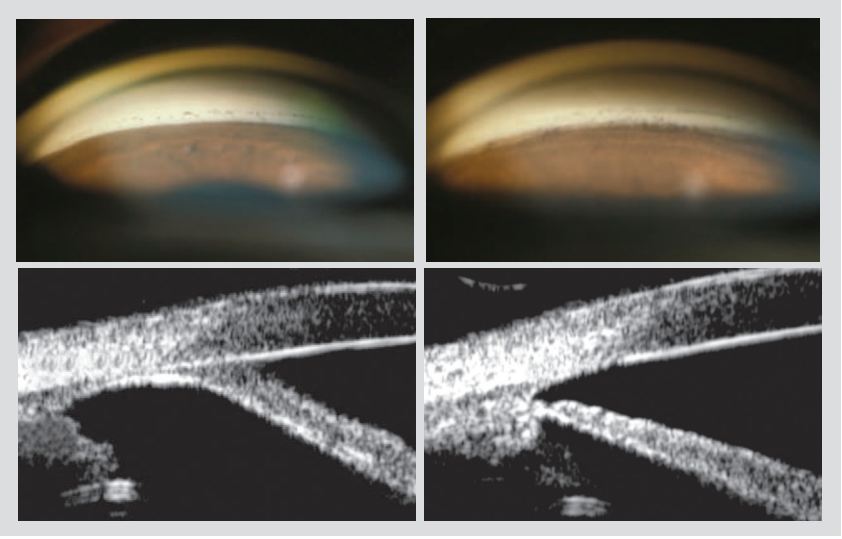
• ***You don't always need to perform GSL.*** If the patient has 20/25 vision and you do an iridotomy and only half the angle opens up, you probably wouldn't want to perform GSL as long as the pressure is 16 mmHg. Why do surgery if the pressure is normal? Maybe it will stay normal until the patient is 90 years old. Similarly, if you put the patient on a couple of drops, the pressure is well-controlled and any PAS seem to be unchanging, I'd observe the patient, rather than performing GSL.

• ***When possible, combine GSL with cataract surgery.*** If the patient was having a cataract removed, even if the IOP was controlled on several medications, I would combine GSL with the cataract surgery. And, I would not postpone cataract surgery if a patient receiving GSL was a candidate for cataract removal. Our research found that the results of performing GSL were significantly better when the lens was removed.

• ***A limited GSL may be better than none at all.*** There are conditions under which it may be acceptable (or necessary) to perform a limited GSL procedure. (If the patient only has 180 degrees of PAS, you only need to address that part of the angle.) In some situations, it may be difficult or impossible to treat 360 degrees. Maybe you can't make a second incision; maybe you can't get your microscope positioned appropriately; maybe you can't see the entire angle. When this occurs, it's worth doing as much of the angle as you can; even half might be sufficient to get the pressure down and preserve the patient's vision.

For example, one published study involved a series of five patients with chronic angle-closure glaucoma and total synechial angle closure whose intraocular pressures were >21 mmHg on maximally tolerated medications. They received 180 degrees of inferior GSL followed by argon laser peripheral iridotomy.[8] Mean IOP dropped from 33.8 mmHg preoperatively to 15.8 mmHg postoperatively. The success rate was 80 percent.

• ***It may be worth following up with other surgeries, if necessary.***



Before and after phaco-goniosynechialysis. Irregular pigmentation on the re-exposed trabecular meshwork is a common postoperative gonioscopic finding. UBM in this patient also confirmed the reopening of the angle.

If the PAS have been present for more than a year and GSL is expected to have limited effect, it's possible to try other follow-up options. I've tried performing goniotomy, just as I might for congenital glaucoma. This creates a slit in the trabecular meshwork, allowing aqueous access to the outer meshwork, even if the inner meshwork is blocked by ingrown iris tissue. In theory, another possibility would be using the Trabectome, although this approach has not been described in the literature.

It might also be reasonable to perform selective laser trabeculoplasty on the newly opened angle, even if there is iris tissue within the meshwork. I have done this in a couple of instances and it did result in pressure lowering. Whether this affected the synechiae is not clear; because I perform GSL on any eye with 50 percent or more of the angle displaying PAS, it's possible that the SLT worked because I hit parts of the meshwork that were clear of PAS.

The only way to prove that SLT actually reduces the impact of the synechiae themselves would be to try it in a series of cases in which the trabecular meshwork was totally sealed by PAS when the GSL was performed. (Fortunately, I don't see many patients with angles totally sealed by PAS—unlike 30 years ago, when angle closure was chronically misdiagnosed. Ninety percent of the patients who came to see me with angle closure back then came in misdiagnosed with POAG.)

Following GSL with argon laser trabeculoplasty would be another possibility.

• ***Complications are relatively rare.*** Of course, complications are always possible in this type of surgery; you can tear the iris and cause iridodialysis, hyphema or bleeding, and you have to be on the lookout for inflammation and IOP spikes. The most common complication is hyphema, because you're tearing into tissue. Careful treatment of the delicate iris tissue and a good gonioscopic view are important.

A Valuable Procedure

It's difficult to know how often GSL is not done when it would benefit the patient, but my guess is that it is probably underperformed. (The procedure is more popular in Asia than in the United States or Europe.) If it is underutilized, it's unlikely to be the result of overlooking the presence of PAS; the only reason a clinician would overlook the presence of PAS is lack of experience with gonioscopy. (Although there is no substitute for gonioscopy, perhaps the availability of anterior segment optical coherence tomography will improve the ability of clinicians to diagnose synechial angle closure.)

A more likely reason that GSL might be underutilized would be a reflexive reliance on other procedures to lower pressure, such as trabeculectomy. If GSL can relieve elevated IOP, it is a far safer way to reduce IOP than more extensive surgery; it utilizes the natural outflow pathway, and it doesn't have the kind of long-term risks seen with filtration procedures. It's certainly an option to consider when managing a patient with angle-closure issues. REVIEW

Dr. Ritch is surgeon director and chief of glaucoma services at the New York Eye and Ear Infirmary, New York City, professor of clinical ophthalmology at The New York Medical College in Valhalla, N.Y., and medical director of The Glaucoma Foundation.

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Diagnosing Glaucoma With TC-OCT Variables

Data from the Advanced Imaging for Glaucoma Study suggests that the diagnosis of glaucoma can be improved with time-domain optic coherence tomography measurements of the optical disc and circumpapillary retinal nerve fiber layer variables, which had better diagnostic accuracy than macular retinal variables. Combining the top RNFL and optic disc variables significantly improved diagnostic performance. Clinically, or-logic classification was the most practical analytical tool with sufficient accuracy to diagnose early glaucoma.

Ninety-six age-matched normal and 96 perimetric glaucoma participants were included in this observational, cross-sectional study. Support vector machine, or-logic, relevance vector machine and linear description function were used to analyze the performances of combined TD-OCT diagnostic variables.

The area under the receiver-operating curve (AROC) was used to evaluate the diagnostic accuracy and to compare the diagnostic performance of single and combined anatomic variables. The best RNFL thickness variables were the inferior (AROC=0.900), overall (AROC=0.892) and superior quadrants (AROC=0.850). The best optic disc variables were horizontal integrated rim width (AROC=0.909), vertical integrated rim area (AROC =0.908) and cup/disc vertical ratio (AROC=0.890). All macular retinal thickness variables had AROCs of 0.829 or less. Combining the top three RNFL and optic disc variables in optimizing glaucoma diagnosis, the support vector machine had the highest AROC, 0.954, followed by or-logic (AROC=0.946), linear discrimination function (AROC=0.946) and relevance vector machine (AROC=0.943). All combination diagnostic variables had significantly larger AROCs than any single diagnostic variable. There were no significant differences among the combination diagnostic indices.

J Glaucoma 2014;23:129-135.
Wang M, Lu A, Varma R, Schuman J, et al.

Cosmetic Facial Fillers and Severe Vision Loss

California physicians have observed vision loss from central retinal artery occlusion occurring after cosmetic facial enhancement, with a result of irreversible blindness in three patients, and a small amount of recovery in a fourth patient who received aggressive therapy. This is an adverse effect of off-label use of cosmetic facial fillers in the forehead that is not typically mentioned to patients. The filler presumably enters the central retinal artery via the external-internal carotid anastomoses, and becomes embedded in the retinal tissues. Physicians performing cosmetic enhancement surgery involving facial fillers need to be aware of this and should include significant vision loss as a possible rare complication of off-label use.

JAMA Ophthalmol 2014;132: 637-639.
Carle M, Roe R, Novack R, Boyer D.

A Mediterranean Diet, Vitamin D And Dry-Eye Syndrome

Researchers evaluating the association between a Mediterranean dietary pattern (MeDi) and vitamin D levels on dry-eye syndrome have found no association between adherence to the MeDi and a beneficial effect on DES. Higher vitamin D levels had a small, favorable, but likely statistically insignificant effect on DES symptoms.

Male patients (n=247) seen at the Miami Veterans Affairs eye clinic with normal eyelid, corneal and conjunctival anatomy were recruited to participate in this cross-sectional study. Patients filled out the 2005 Block Food Frequency Questionnaire and the Dry Eye Questionnaire 5, and underwent measurement of tear film parameters. The serum level of 25-hydroxy vitamin D was also measured. The main outcome measures included the association among MeDi, vitamin D levels and DES.

Mean patient age was 69 years (r: 55 to 95). Using latent class analysis to categorize the presence or absence

of disease and quantify its severity, researchers found that adherence to the MeDi was positively associated with the risk of having DES (r: 1.25; 95 percent confidence interval, 1.06 to 1.47; p=0.007) and with increasing disease severity. Vitamin D levels were not significantly associated with the presence or severity of disease. However, higher levels of vitamin D were associated with decreased DES symptoms, with a -1.24 decrease in median Dry Eye Questionnaire score for every 10-U increase in vitamin D levels (p=0.01).

Cornea 2014;33:437-441.
Galor A, Gardener G, Pouyeh B, Feuer W, Florez H.

Lutein: A New Dye for Chromovitrectomy

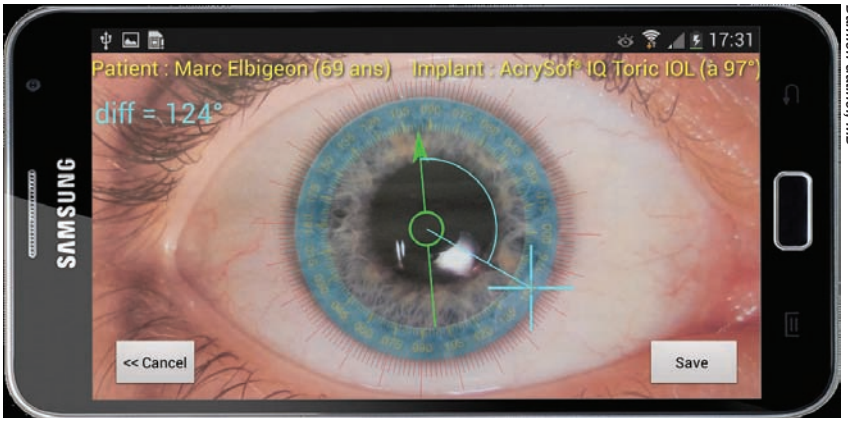
Brazilian researchers evaluating the feasibility, advantages and safety of a novel, lutein-based dye for improving identification and removal of the vitreous, internal limiting membrane and epiretinal membrane during chromovitrectomy found that the new dye improved intraoperative identification of the internal limiting membrane and posterior hyaloid/vitreous.

The researchers prospectively evaluated 12 eyes that underwent pars plana vitrectomy using the novel dye in patients with macular hole, epiretinal membrane or proliferative diabetic retinopathy/tractional diabetic macular edema. One surgeon performed standard chromovitrectomy and completed a postoperative questionnaire to compare the novel dye staining with that of the available dyes. The peeled membranes were evaluated histologically, and follow-up examinations were performed on postop days one, seven, 30, 90 and 180; best-corrected visual acuity, optical coherence tomography, fluorescein angiography, autofluorescence and visual fields were performed.

The green dye was deposited on the posterior pole because of its higher density than the balanced saline solution; vigorous dye flushing into the vitreous cavity was unnecessary. The dye stained the posterior hyaloid/vitreous base by deposition onto the vitreous; brilliant blue stained the internal limiting membrane. The epiretinal membrane was poorly stained. Postop, the BCVA improved in all eyes, without clinical toxicity or toxicity on images/visual fields. Histology showed effective removal of the internal limiting membrane and the epiretinal membrane in all eyes.

Retina 2014;34:262-272.
Mala M, Furlani B, Souza-Lima A, Martina D, et al.

(continued from page 22)



Damien Gatinel, MD

Once the surgeon captures the eye image with Toreasy, he can then use the application's reticle to mark the location of a prominent ocular landmark. Knowing the meridian of the landmark lets him find the toric lens axis later in the operating room.

finger farther out into the periphery and then select the degree location, you'll get extra precision," he says. "You can make more precise, fine adjustments."

In terms of centering the Toreasy gauge on the image of the eye, Dr. Gatinel recommends using the patient's limbus rather than the center of the pupil. "We recommend using the limbus because the IOL won't be centered if you center the axis measurement on an eccentric pupil," he says. "The intraocular lens centers in the capsular bag, which is probably more aligned with the limbus than with the pupil, the latter of which tends to sometimes move in a non-concentric way."

Toreasy is available for Android-based devices at the Google Store for $200 (https://play.google.com/store). It's also available pre-loaded on a new Samsung S4 Zoom smartphone for $2,500. Dr. Gatinel says it will work on Apple iOS devices but isn't yet available at the Apple App Store.

Since a lot of the accuracy of the digital marking process with Toreasy relies on the smartphone's camera, Dr. Gatinel recommends using the application on a device with a high-resolution camera, such as the latest generation of Samsung devices (S4, S4 Zoom and S5, for example). He says a good zoom feature that maintains a sharp image is helpful also, since it makes it easier to locate ocular features. For more information on Toreasy, visit toreasy.com. REVIEW

All of the surgeons interviewed have a financial interest in their respective apps or devices.

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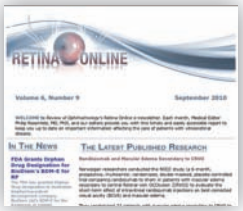

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(continued from page 53)

no signs of ocular discomfort during the experimental assays.

Other alternatives used for extended drug release include particulate drug delivery systems or injectable formulations such as microspheres, liposomes and nanospheres/nanoparticles.[7] The delivery includes trapping the drug in the nanocarrier matrix and delivering it into the eye. After administration, the bioactive agent is released in a controlled fashion by diffusion through the matrix or by degradation of the polymer matrix. Additionally, once the nanomicrocarriers are injected, they can act as a reservoir system for drug release for a prolonged time period.

Researchers have evaluated the release of timolol maleate from biodegradable microspheres. They are administered by subconjunctival injection, which is less invasive than intravitreal injection, and drug release has been sustained for more than three months.[8]

Liposomes are another polymeric particulate delivery system being studied for ocular drug delivery. For example, investigators have developed and studied brimonidine tartrate liposomes for their IOP-lowering effects in glaucoma. There was a constant delivery of therapeutics with a linear release profile.[9] Additionally, after topical application, the IOP-lowering effect of the drug was sustained.

Recently, the IOP-lowering ability of a latanoprost-loaded liposome injected subconjunctivally in rabbit eyes was compared with conventional daily administration of latanoprost eye drops.[10] The liposomes were well-tolerated, and sustained delivery was achieved for approximately 50 days. No adverse effects in ocular tissue were seen with subconjunctival injection, and the IOP-lowering effect was superior to latanoprost eye drop administration.

Other potential drug delivery systems include nonbiodegradable ocular devices that are already approved for intravitreal drug delivery in other ocular diseases and could be adapted for glaucoma management. Examples include Vitrasert, Retisert and Iluvien.

However, even with these new medications and delivery systems, surgical alternatives will still have a role. "There will be patients who fail medical therapy or don't tolerate medical therapy and need to go on to surgery," Dr. Lehrer says. "Every time a new drug gets approved, it bumps down our surgery practice because we try the new drug to see if it can keep patients out of surgery for a while. Sometimes this works, and sometimes it doesn't. Right now, I don't think there is a medication that will keep everyone out of surgery."

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(continued from page 49)

After 48 hours of systemic therapy with acyclovir, the patient's vision and orbital findings began to improve. On one week follow-up after discharge with oral acyclovir, the patient's right visual acuity improved to 20/60 and intraocular pressure decreased to 18 mmHg without any ocular hypotensive therapy. Motility improved in all directions. Vitritis subsided to allow dilated fundus exam, which showed vitreous debris. The optic nerve appeared sharp and pink with no retinal involvement. REVIEW

The authors are at the Yale School of Medicine. Drs. Yun, Wong, Huang and Levin are in the Department of Ophthalmology and Visual Sciences; Dr. Malhotra is in the Department of Neuroradiology.

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Not long after an uncomplicated delivery, a young mother experiences a sudden onset of blurry vision in both eyes.

Neil Vadhar and Alice Williams, MD

Presentation

A 23-year-old female presented to the Wills Eye emergency department with a chief complaint of sudden onset blurry vision in both eyes. It began in her right eye approximately 15 hours prior to presentation and in her left eye 10 hours later. She also had many floaters and flashing lights in both eyes. She denied any headaches, double vision, transient obscurations of vision, dizziness, numbness or weakness.

Medical History

The patient was 10 days post-partum from an uncomplicated spontaneous vaginal delivery. Past medical history and ocular history were otherwise unremarkable. Prenatal vitamins were her only medication.

Examination

Ocular examination revealed a visual acuity without correction of 20/60 in the right eye and 20/70 in the left eye. There was minimal improvement with pinhole to 20/50 in both eyes. Her pupils were equal, round and reactive to light with no afferent pupillary defect. Her intraocular pressures were 16 mmHg in both eyes. Motility was full and visual fields were full to confrontation. Color plates were 3/8 in the right eye and 6/8 in the left eye.

Slit lamp examination of the anterior segment was unremarkable, and Shafer's sign was negative in both eyes. Fundus examination revealed serous retinal detachments over the macula extending to the periphery in both eyes *(See Figure 1)*. The vitreous, optic nerve, and vessels were otherwise normal.

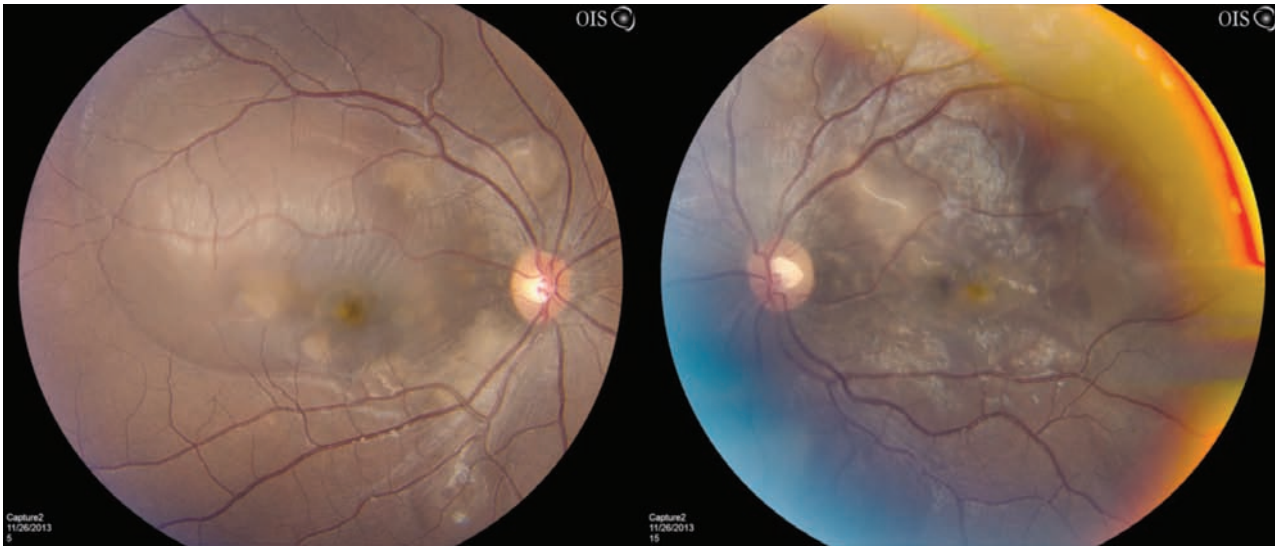

Figure 1. Fundus photos reveal bilateral subretinal fluid.

What is your differential diagnosis? What further workup would you pursue? Please turn to p. 84

Diagnosis, Workup and Treatment

The differential diagnosis for bilateral serous retinal detachment is broad. It includes neoplastic, inflammatory, vascular, congenital and idiopathic disorders such as central serous chorioretinopathy. Given the patient's post-partum status, the most likely etiologies were those associated with pregnancy, including pre-eclampsia, eclampsia, HELLP syndrome, disseminated intravascular coagulation (DIC), and thrombotic thrombocytopenic purpura (TTP).

Her blood pressure was checked immediately and was normal. Optical coherence tomography demonstrated outer retinal edema and subretinal fluid in both eyes *(See Figure 2)*. A systemic workup including a CBC, CMP and coagulation studies was also obtained. It was remarkable for renal failure (creatinine 1.5), anemia (hemoglobin 8.1), and thrombocytopenia (platelets 8,000).

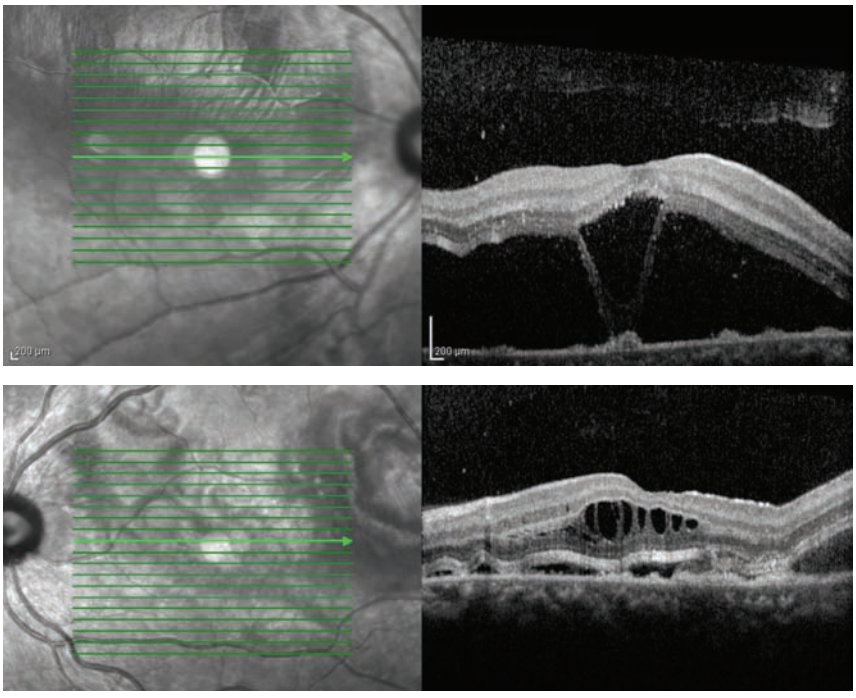

Figure 2. Optical coherence tomography of the right (upper) and left (lower) eyes, showing outer retinal edema and subretinal fluid.

The patient was admitted to the medical service at Thomas Jefferson University Hospital for further management. Additional bloodwork demonstrated an elevated LDH (883), low haptoglobin (<10), and an elevated total bilirubin (1.6). All of these results indicated an ongoing hemolytic process, which was confirmed by the presence of schistocytes on the peripheral blood smear. Coagulation studies were normal, making a consumptive coagulopathy such as DIC less likely, and the presumptive diagnosis of TTP was made. Treatment with plasmapheresis and steroids was initiated and the diagnosis of TTP was later confirmed with an ADAMTS13 activity level, which was less than 1 percent.

The patient's hospital course was complicated by two anaphylactic reactions to plasmapheresis, as well as an episode of atrial fibrillation with rapid ventricular response requiring intensive care management. Despite these setbacks, the patient made a full recovery and was eventually discharged in stable condition. Her subretinal fluid resorbed as her systemic abnormalities resolved, and within two weeks of presentation she had regained 20/20 vision in both eyes. Fundus examination at that time revealed flat retinae with sharp foveal reflexes in both eyes.

Discussion

TTP is an acute syndrome that manifests as microangiopathic hemolytic anemia, thrombocytopenia, acute renal insufficiency, neurologic abnormalities and fever. With advancements in medical treatment, the above pentad is rarely seen in a single patient. It is caused by low levels of ADAMTS13, a metalloprotease involved in hemostasis. With decreased ADAMTS13 activity, platelets aggregate and form complexes that lead to microthrombosis and hemolysis.[1] Before the 1970s, TTP was almost universally fatal. Since that time, improvements in diagnosis and management have reduced the mortality rate to 40 percent.[2] First-line treatments include steroid therapy and plasmapheresis. IVIG and other immunomodulatory therapies are second-line options.

The incidence of TTP in pregnancy is only one in 25,000, but 10 to 25 percent of all patients diagnosed with TTP are pregnant or recently post-partum.[3,4] As a result, these pa-

tients may be initially misdiagnosed with an obstetric complication, such as pre-eclampsia or HELLP syndrome.[5] Pregnancy has been shown to decrease the levels of ADAMTS13, precipitating TTP in patients who have below-normal levels of this enzyme.[1,6]

Ocular involvement is seen in 14 to 20 percent of all patients with TTP.[7,8] Although our patient presented with visual complaints, they usually develop in the later stages of the disease.[6] These complications may vary widely. Serous retinal detachments are the most common manifestation of TTP, but choroidal bleeding, macular infarction, occlusions of the central retinal artery and vein, Purtscher-like retinopathy, and cortical infarcts resulting in visual field defects, diplopia and cortical blindness have also been reported.[9] Although the exact pathophysiology is unknown, serous retinal detachments are thought to be related to the formation of microthrombi in the choroidal vasculature. Ischemic injury to the retinal pigment epithelium leads to a breakdown of the blood-retinal barrier, reduced resorption of subretinal fluid and subsequent serous retinal detachments.[9] Hypertension, if present, may also contribute to choroidal vascular damage and retinal pigment epithelial tears.[7] Most case reports have shown that plasmapheresis will result in complete resolution of the retinal detachment and any visual deficits, usually in days, demonstrating excellent prognosis with prompt treatment.[8,10,11] REVIEW

The authors would like to thank Bill Benson, MD, of the Wills Eye Hospital Retina Service, for his time and assistance in preparing this case report.

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REVIEW Advertising Index

LUMIGAN® 0.01% AND 0.03%
(bimatoprost ophthalmic solution)

Brief Summary—Please see the LUMIGAN® 0.01% and 0.03% package insert for full Prescribing Information.

INDICATIONS AND USAGE

LUMIGAN® 0.01% and 0.03% (bimatoprost ophthalmic solution) is indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

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

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with **LUMIGAN®** 0.01% and 0.03% (bimatoprost ophthalmic solution) can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Eyelash Changes: LUMIGAN® 0.01% and 0.03% may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation: LUMIGAN® 0.01% and 0.03% should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

Macular Edema: Macular edema, including cystoid macular edema, has been reported during treatment with bimatoprost ophthalmic solution. **LUMIGAN®** 0.01% and 0.03% should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Angle-closure, Inflammatory, or Neovascular Glaucoma: LUMIGAN® 0.01% and 0.03% has not been evaluated for the treatment of angle-closure, inflammatory or neovascular glaucoma.

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

Use With Contact Lenses: Contact lenses should be removed prior to instillation of **LUMIGAN®** 0.01% and 0.03% and may be reinserted 15 minutes following its administration.

ADVERSE REACTIONS

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

In clinical studies with bimatoprost ophthalmic solutions (0.01% or 0.03%) the most common adverse reaction was conjunctival hyperemia (range 25%–45%). Approximately 0.5% to 3% of patients discontinued therapy due to conjunctival hyperemia with 0.01% or 0.03% bimatoprost ophthalmic solutions. Other common reactions (>10%) included growth of eyelashes, and ocular pruritus.

Additional ocular adverse reactions (reported in 1 to 10% of patients) with bimatoprost ophthalmic solutions included ocular dryness, visual disturbance, ocular burning, foreign body sensation, eye pain, pigmentation of the periocular skin, blepharitis, cataract, superficial punctate keratitis, periorbital erythema, ocular irritation, eyelash darkening, eye discharge, tearing, photophobia, allergic conjunctivitis, asthenopia, increases in iris pigmentation, conjunctival edema, conjunctival hemorrhage, and abnormal hair growth. Intraocular inflammation, reported as iritis, was reported in less than 1% of patients.

Systemic adverse reactions reported in approximately 10% of patients with bimatoprost ophthalmic solutions were infections (primarily colds and upper respiratory tract infections). Other systemic adverse reactions (reported in 1 to 5% of patients) included headaches, abnormal liver function tests, and asthenia.

Postmarketing Experience: The following reactions have been identified during postmarketing use of **LUMIGAN®** 0.01% and 0.03% in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to **LUMIGAN®**, or a combination of these factors, include: dizziness, eyelid edema, hypertension, nausea, and periorbital and lid changes associated with a deepening of the eyelid sulcus.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C

Teratogenic effects: In embryo/fetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost which achieved at least 33 or 97 times, respectively, the maximum intended human exposure based on blood AUC levels.

At doses at least 41 times the maximum intended human exposure based on blood AUC levels, the gestation length was reduced in the dams, the incidence of dead fetuses, late resorptions, peri- and postnatal pup mortality was increased, and pup body weights were reduced.

There are no adequate and well-controlled studies of **LUMIGAN®** 0.01% and 0.03% (bimatoprost ophthalmic solution) administration in pregnant women. Because animal reproductive studies are not always predictive of human response **LUMIGAN®** should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether **LUMIGAN®** 0.01% and 0.03% is excreted in human milk, although in animal studies, bimatoprost has been shown to be excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when **LUMIGAN®** is administered to a nursing woman.

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

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

Hepatic Impairment: In patients with a history of liver disease or abnormal ALT, AST and/or bilirubin at baseline, bimatoprost 0.03% had no adverse effect on liver function over 48 months.

OVERDOSAGE

No information is available on overdosage in humans. If overdose with **LUMIGAN®** 0.01% and 0.03% (bimatoprost ophthalmic solution) occurs, treatment should be symptomatic.

In oral (by gavage) mouse and rat studies, doses up to 100 mg/kg/day did not produce any toxicity. This dose expressed as mg/m2 is at least 70 times higher than the accidental dose of one bottle of **LUMIGAN®** 0.03% for a 10 kg child.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility: Bimatoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 2 mg/kg/day and 1 mg/kg/day respectively (at least 192 and 291 times the recommended human exposure based on blood AUC levels respectively) for 104 weeks.

Bimatoprost was not mutagenic or clastogenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* mouse micronucleus tests.

Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (at least 103 times the recommended human exposure based on blood AUC levels).

PATIENT COUNSELING INFORMATION

Potential for Pigmentation: Patients should be advised about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of **LUMIGAN®** 0.01% and 0.03% (bimatoprost ophthalmic solution).

Potential for Eyelash Changes: Patients should also be informed of the possibility of eyelash and vellus hair changes in the treated eye during treatment with **LUMIGAN®** 0.01% and 0.03%. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

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

When to Seek Physician Advice: Patients should also be advised that if they develop an intercurrent ocular condition (e.g., trauma or infection), have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of **LUMIGAN®** 0.01% and 0.03%.

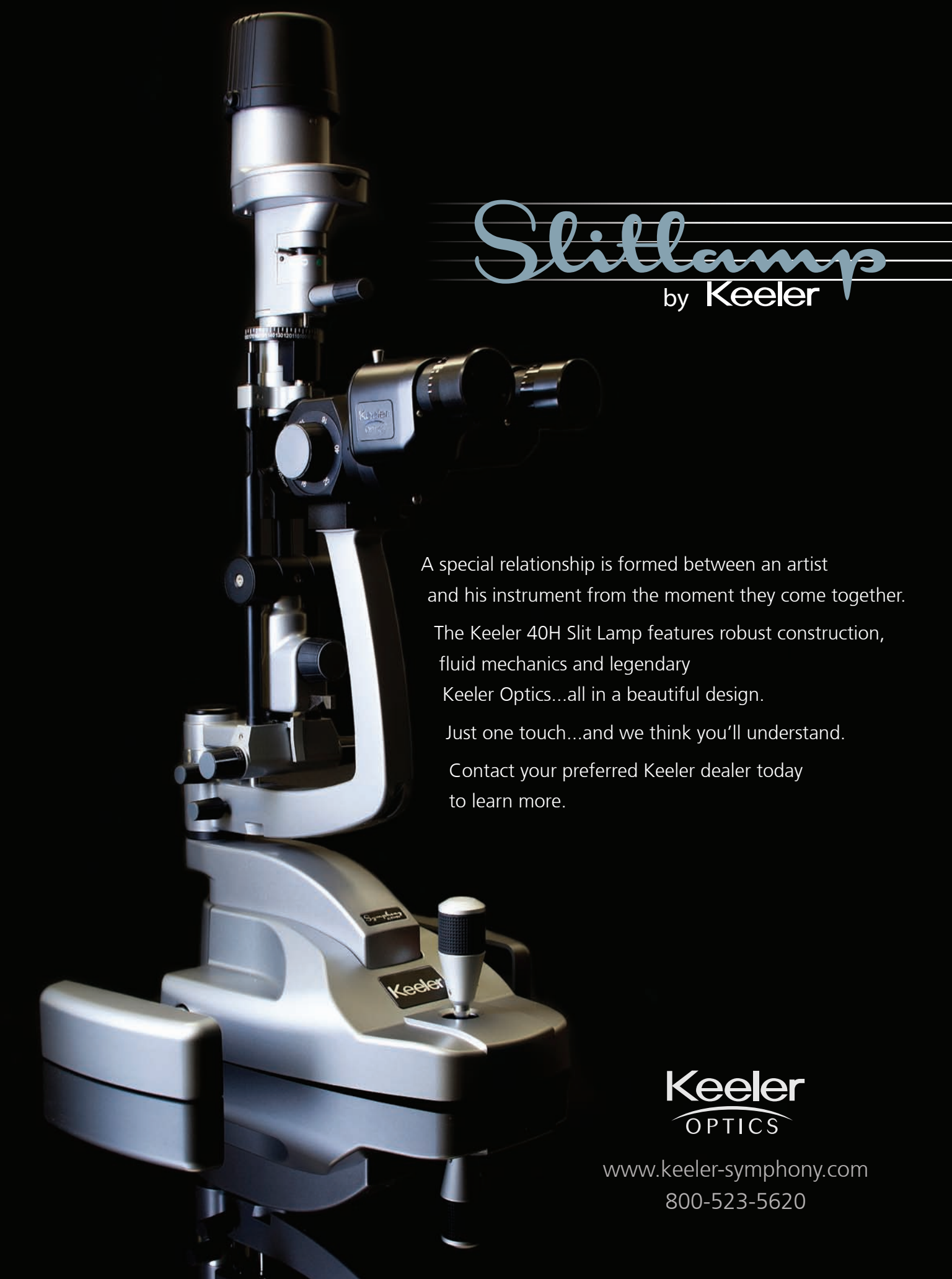
Use with Contact Lenses: Patients should be advised that **LUMIGAN®** 0.01% and 0.03% contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of **LUMIGAN®** and may be reinserted 15 minutes following its administration.

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

APC70EN12 based on 71807US13.

Rx only

ALLERGAN®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Broad preferred coverage[3]

•

Comprehensive patient support

Indication: LUMIGAN® (bimatoprost ophthalmic solution) 0.01% is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

Important Safety Information

Warnings and Precautions: LUMIGAN® 0.01% causes changes to pigmented tissues, mostly increased pigmentation of the iris, eyelid, and eyelashes as long as LUMIGAN® 0.01% is administered. Iris color change may not be noticeable for several months to years. After discontinuation of bimatoprost, iris pigmentation is likely to be permanent, while eyelid and eyelash changes have been reported to be reversible in some patients. Patients should be informed of the possibility of increased pigmentation. The long-term effects of increased pigmentation are not known.

LUMIGAN® 0.01% should be used with caution in patients with active intraocular inflammation (eg, uveitis) because the inflammation may be exacerbated. Macular edema, including cystoid macular edema, has been reported with LUMIGAN® 0.01%. LUMIGAN® 0.01% should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema. LUMIGAN® 0.01% has not been studied to treat types of glaucoma other than open-angle glaucoma. Remove contact lenses prior to instillation of LUMIGAN® 0.01% and reinsert after 15 minutes.

Adverse Reactions: The most common (25%-45%) adverse event with LUMIGAN® 0.01% was conjunctival hyperemia. Approximately 0.5% to 3% of patients discontinued therapy due to conjunctival hyperemia. Other common events (> 10%) included growth of eyelashes and ocular pruritus.

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

1. LUMIGAN® Prescribing Information. **2.** Katz LJ, Cohen JS, Batoosingh AL, Felix C, Shu V, Schiffman RM. Twelve-month, randomized, controlled trial of bimatoprost 0.01%, 0.0125%, and 0.03% in patients with glaucoma or ocular hypertension. *Am J Ophthalmol*. 2010;149(4):661-671. **3.** Managed Markets Insight & Technology, LLC, database, as of November 2013.

LUMIGAN® 0.01%
(bimatoprost ophthalmic solution) 0.01%

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