REVIEW® of Ophthalmology

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Cataract Issue

Dealing *with* Complications

P. 32

Smarter. Better. Faster.
LenSx® Laser. There's only one.

Delivering uncompromised precision and consistency, the LenSx® Laser has maintained its global leadership through continuous innovation in laser refractive cataract surgery. The LenSx® Laser leverages the power of The Cataract Refractive Suite by Alcon with tools designed to further streamline and improve the entire procedure. **LenSxLasers.com**

SMARTER
- Pre-population of patient and incision data
- Advanced pre-positioning of incisions and capsulotomy
- Platform design enables continued innovation and rapid enhancements

BETTER
- Customizable lens fragmentation for easy lens removal[2]
- SoftFit™ Patient Interface for easy docking, secure fixation and lower IOP[3]
- Compatible with the VERION™ Digital Marker for surgical planning and execution[1]

FASTER[2]
- Laser procedure efficiency with reduced programming and suction time
- Designed for maximum procedural flexibility and ease of patient flow and transfer
- Simpler, easier patient docking

1. Multicenter prospective clinical study. Alcon data on file.
2. Using current LenSx® Laser systems
3. Alcon data on file.

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For important safety information, please see adjacent page.

LenSx® LASER
Designed for Growth™

THE CATARACT REFRACTIVE SUITE BY ALCON

LenSx® LASER

Designed for Growth™

VERION™

IMAGE GUIDED SYSTEM

IMPORTANT SAFETY INFORMATION

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

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

RESTRICTIONS:

- Patients must be able to lie flat and motionless in a supine position.
- Patient must be able to understand and give an informed consent.
- Patients must be able to tolerate local or topical anesthesia.
- Patients with elevated IOP should use topical steroids only under close medical supervision.

Contraindications:

- Corneal disease that precludes applanation of the cornea or transmission of laser light at 1030 nm wavelength
- Descemetocele with impending corneal rupture
- Presence of blood or other material in the anterior chamber
- Poorly dilating pupil, such that the iris is not peripheral to the intended diameter for the capsulotomy
- Conditions which would cause inadequate clearance between the intended capsulotomy depth and the endothelium (applicable to capsulotomy only)
- Previous corneal incisions that might provide a potential space into which the gas produced by the procedure can escape
- Corneal thickness requirements that are beyond the range of the system
- Corneal opacity that would interfere with the laser beam
- Hypotony or the presence of a corneal implant
- Residual, recurrent, active ocular or eyelid disease, including any corneal abnormality (for example, recurrent corneal erosion, severe basement membrane disease)
- History of lens or zonular instability
- Any contraindication to cataract or keratoplasty
- This device is not intended for use in pediatric surgery.

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

PRECAUTIONS:

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

AES/COMPLICATIONS:

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

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

IMPORTANT SAFETY INFORMATION FOR THE VERION™ REFERENCE UNIT AND VERION™ DIGITAL MARKER

CAUTION: Federal (USA) law restricts this device to sale by, or on the order of, a physician.

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

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

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

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

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

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

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

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

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

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

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

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REVIEW NEWS
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Potential Drug Targets Found For Early-Onset Glaucoma

Using a novel high-throughput screening process, scientists have for the first time identified molecules with the potential to block the accumulation of a toxic eye protein that can lead to early onset of glaucoma.

The researchers have implicated a mutant form of the protein myocilin as a possible root cause of increased eye pressure. Mutant myocilin is toxic to the cells in the part of the eye that regulates pressure. These genetically inherited mutants of myocilin clump together in the front of the eye, preventing fluid flow out of the eye, which then raises eye pressure. This cascade of events can lead to early-onset glaucoma, which affects several million people from childhood to age 35.

To find molecules that bind to mutant myocilin and block its aggregation, the researchers designed a simple, high-throughput assay and then screened a library of compounds. They identified two molecules with potential for future drug development to treat early-onset glaucoma.

"These are really the first potential drug targets for glaucoma," said Raquel Lieberman, PhD, an associate professor in the School of Chemistry and Biochemistry at the Georgia Institute of Technology in Atlanta, whose lab led the research.

Dr. Lieberman presented her findings on January 20 at the Society for Laboratory Automation and Screening conference in San Diego, Calif. The study was published on Nov. 26, 2013, in the journal *ACS Chemical Biology*.

At the heart of the study was an assay that Dr. Lieberman's lab created to take advantage of the fundamental principles of ligand binding. In their assay, mutant myocilin is mixed with a fluorescent compound that emits more light when the protein is unwound. When a molecule from the library screen binds to myocilin, the pair becomes highly stable—tightly wound—and the fluorescent light emitted decreases. By measuring fluorescence, researchers were able to identify molecules that bound tightly

Exercise May Slow Retinal Degeneration

Moderate aerobic exercise helps to preserve the structure and function of nerve cells in the retina after damage, researchers at the Emory Eye Center and the Atlanta VA Medical Center have found.

The findings, from a study of an animal model of age-related macular degeneration, are the first to suggest that aerobic exercise can have a direct effect on retinal health and vision. The results were scheduled for publication Feb. 12 in the *Journal of Neuroscience*.

"This research may lead to tailored exercise regimens or combination therapies in treatments of retinal degenerative diseases," said Machelle Pardue, PhD, one of the senior authors. "Possibly in the near future, ophthalmologists could be prescribing exercise as a low-cost intervention to delay vision loss."

Although several studies in animals and humans point to the protective effects of exercise in neurodegenerative diseases or injury, less was known about how exercise affects vision.

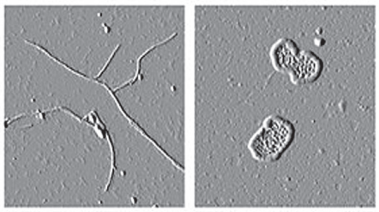
The researchers ran mice on a treadmill for two weeks before and after exposing the animals to bright light that causes retinal degeneration. They found that treadmill training preserved photoreceptors and retinal cell function in the mice.

They trained mice to run on a treadmill for one hour per day, five days per week, for two weeks. After the animals were exposed to toxic bright light—a commonly used model of retinal degeneration—they exercised for two more weeks. The exercised animals had nearly twice the number of photoreceptor cells of animals that spent the equivalent amount of time on a stationary treadmill, and their retinal cells were more responsive to light.

"One point to emphasize is that the exercise the animals engaged in is really comparable to a brisk walk," Dr. Pardue said. "One previous study that examined the effects of exercise on vision in humans had examined a select group of long distance runners. Our results suggest it's possible to attain these effects with more moderate exercise."

The researchers were able to show that the effects of exercise come partly from a growth factor called BDNF, which was thought to be involved in the beneficial effects of exercise in other studies. Exercised mice had higher levels of BDNF in the blood, brain and retina, while chemically blocking BDNF receptors effectively eliminated the protective effects of aerobic exercise, they demonstrated.

The group is testing whether other exercise regimens are even more protective and whether exercise is beneficial in models of other retinal diseases such as glaucoma and diabetic retinopathy.



The glaucoma-associated olfactomedin domain of myocilin in straight fibrils common to many amyloids (left) and a disease-causing variant forming large circular fibrils (right).

to mutant myocilin.

The researchers then added these molecules to cultured human cells that were making the toxic aggregating myocilin. Treating the cells with the newly identified molecules blocked the aggregation and caused the mutated version of myocilin to be released from the cells, reducing toxicity.

"We found two molecules from that initial screen that bound to our protein and also inhibited the aggregation," Dr. Lieberman said. "When we saw that these compounds inhibited aggregation then we knew we were onto something good because aggregation underlies the pathogenesis of this form of glaucoma."

In a separate study, the same lab characterized the toxic myocilin aggregates. The study found that myocilin aggregates are similar to the protein deposits called amyloid, which are responsible for Alzheimer's disease and other neurodegenerative diseases.

"In Alzheimer's disease, the deposits are extracellular and kill neurons. In glaucoma the aggregates are not directly killing neurons in the retina to cause vision loss, but they are cytotoxic in the pressure-regulating region of the eye," Dr. Lieberman said. "It's parallel to all these other amyloids that are out there in neurodegenerative disease."

(continued on page 7)

Ophthalmic Product Development Insights

Matthew Chapin and Van Sandwick • Ora Inc., Andover, Mass.

The Eyes: The Window to the Soul of R&D

Last year, we instituted a quarterly column that addressed some of the considerations of ophthalmic product development: securing the appropriate patents, planning regulatory meetings, calculating business plans to secure financing, and concepts for crafting the Target Product Profile. We invite you to join us as we continue to peel back the curtain to reveal how ophthalmic innovators are identifying and capitalizing on the current trends while advancing novel technologies to treat patients. In this issue, we will explore a couple of key elements around how entrepreneurs with broad platforms may choose to lead with an ocular indication. We will use a current case study of a start-up company that is tying together many of the elements we have been discussing. We feel it provides a great example of using the eye as a proof of concept for an exciting platform delivery technology.

Novel Science for Ocular Indications

As stated with the old proverb that "the eyes are the window to the soul," innovative science has a habit of flowing through the eye. Pursuing ophthalmic indications can help novel technology platforms "move the ball down the field" for the following reasons.

• ***Attenuating toxicity and delivery issues.*** While most therapies in development have been optimized to target their respective receptors, enzyme binding sites and/or substrates, failing to achieve sufficient bioavailability can derail even the most promising clinical candidate. Whether one is trying to treat a disease of the anterior or posterior segment, topical and intravitreal administration typically deliver clinically meaningful dosages of the therapeutic to the tissue where it is supposed to produce a treatment effect. Achieving sufficient bioavailability in the vitreous or retina can be more challenging due to the restricted injection volume, degradative enzymes, and the expedient elimination of small molecules, certainly if one is trying to deliver a drug topically to the back of the eye with sustained release. However, it is possible to optimize formulations or utilize sustained-release implants to deliver clinically significant amounts of therapy to the target tissue in the eye. In the same vein, local ocular dosing dramatically reduces the systemic absorption of therapies compared to other routes of administration, limiting the potential for untoward systemic consequences that can impact your development program. Ergo, there is significant potential to repurpose therapies for ophthalmic indications based on demonstrated clinical efficacy in other indications that show effect with the mechanism of action, but were halted because the active pharmaceutical ingredient did not go or reside where it was supposed to, or faced systemic safety issues.

• ***Time and cost-to-value inflection.*** As stated in our previous article, Developing a Business Plan to Secure Funding (September 2013), venture capital firms or pharmaceutical partners may prefer to see data from clinical trials before investing in young companies. Therefore, it can be difficult to raise money around novel technology platforms that are yet to be validated. Luckily, the path to an Investigational New Drug, and ultimately the clinic, can be relatively straightforward (fast and inexpensive) for ophthalmic indications where the intervention is dosed locally.

No Adverse Effect Level (NOAEL) doses that arise from systemic toxicology studies are typically many multiples of the doses tested in Good Laboratory Practice ocular toxicology studies, and of the anticipated clinical dosage. Clean toxicology studies usually translate to IND acceptance, which allows for progress to the clinical proof-of-concept study and for the therapeutic to reach value inflection, increasing the potential for additional external investment. Investment from alternative sources, other than VCs, can be covered by translational science grants, friends and family, strategic partners and angels and should be pursued if the desire or ability to raise venture dollars doesn't materialize. Strategic partners can become invaluable based on their ability to help shape the Target Product Profile, critical study elements and designs that will help drive decisions within organizations (which may be different across companies) in addition to their stated interest aiding in fundraising/business development. With this in mind, designing creative deal structures by engaging strategic and exit partners as early as possible can help ensure appropriate focus.

Many ophthalmic indications can serve as the lead, as proof-of-concept and to build value for other diseases in the areas of inflammation, allergy (specifically leveraging the unique clinical-regulatory allergen challenge pathway available for the eye), neuroprotection, infection, vascular disease and others.

Pursuing orphan diseases is a strategy to potentially significantly lower the cost of development, while attempting to serve patients who have large unmet needs. *EvaluatePharma's 2013 Orphan Drug Report* estimates that pivotal studies cost about $186M per drug (across all pharma) and that huge cost savings are possible by pursing orphan indications, where pivotals cost are between $43 and $85 million if the 50-percent U.S. tax credit available via the Orphan Drug Act is factored into the equation. That said, assets targeting orphan diseases do not usually have an expedited pathway to the clinic and typically still require the standard IND enabling safety studies.

Indications with High Unmet Need

Programs that focus on an indication with high unmet need may be able to leverage a regulation that provides several incentives for development in indications that

have fewer than 200,000 patients in the United States, or affects more than 200,000 patients but are not expected to recover the costs of developing and marketing a treatment drug in the United States (*21 USC 360bb*). The Orphan designation provides for:

- Seven years' marketing exclusivity from the date of marketing approval;
- Tax credit of up to 50 percent for qualified expenses for clinical research to support approval of an orphan drug;
- Grants to support clinical development of products for use in rare diseases;
- Exemption from certain user fees that are normally charged sponsors; and
- Other special consideration from the Food and Drug Administration for accelerated development, review by the FDA and approval, on a case-by-case basis.

This can have significant implications in some programs where a streamlined clinical program can be used. In ophthalmology, this includes indications such as, but not limited to, posterior uveitis; vernal keratoconjunctivitis; pterygium; ocular melanoma; endothelial dystrophies; inherited retinal diseases (retinitis pigmentosa, Stargardts; Leber's congenital amaurosis; Leber's hereditary optic neuropathy), corneal ectasia; and others.

AURA Biosciences

Started in Cambridge in 2009 by CEO Elisabet de los Pinos, PhD, Aura Biosciences is developing its novel tumor-targeting pseudovirion technology discovered at the National Cancer Institute, with the lead indication for ocular melanoma. To date, Aura has been funded mainly through angel funding, including convertible debt instruments as well as government grants.

Pseudovirions are made up of the protein coat of a virus, conferring tumor specificity, but without infectious potential. Aura's lead drug, AU011, features virion capsules conjugated to a photoreactive dye. The capsule selectively binds to cancer cells, and then the associated photoreactive dye is activated with infrared energy, free radicals are released that efficiently kill the cancer cells without damaging surrounding tissue. Each pseudovirion particle is able to deliver up to 1,000 of the photoreactive dye molecules without compromising its tumor-targeting capabilities, thus serving as an efficient delivery mechanism.

AU011 can be leveraged for indications such as head and neck, lung and prostate cancer. The pseudovirion technology can also be combined with other drug payloads, beyond the photoreactive dye from the ocular project, unlocking the potential of a transformative technology platform. Despite a wide range of uses to address high unmet medical needs and generate value, the company decided to develop its lead product, AU011, in a rare cancer indication (ocular melanoma) to speed the path to clinical proof of concept, and obtain registration in approximately four years. But, this is certainly a strategy that reduces the risk for further development across other indications.

Ocular melanoma is a highly unmet medical need. There are currently no targeted therapies available to treat primary tumors, and all current treatment options like surgery (enucleation) and radiotherapy (plaque radiotherapy) are highly invasive and have major side effects for these patients. There is a high interest in treating smaller tumors with therapies other than surgery and brachytherapy alone. In fact, a trend in diagnosing a greater proportion of small melanomas and a shift toward eye-sparing treatment of smaller tumors was reported from the Collaborative Ocular Melanoma Study (COMS) centers. Aura expects that ocular melanoma will be granted orphan status by the FDA, and if successful, will provide the first tumor-targeted therapy for these patients.

In focusing on optimizing the initial Target Product Profile to make the clinical program as efficient as possible, the program is able to leverage: a) local delivery via intraocular injection, reducing the risk of systemic toxicity; b) direct visualization of the tumor area to monitor efficacy in a short period of time; and c) clear clinical endpoints to evaluate safety. These elements provide a clear path to proof-of-concept for the lead indication in ocular melanoma and opens the future possibility to expand the product to treat other non-ocular cancers. This is a clear example of how a company can be financed through different sources, and focus on building value for its platform, leading with an identified unmet need in the eye.

Mr. Chapin and Mr. Sandwick are with the Corporate Development Group at Ora Inc. Ora provides a comprehensive range of product development services in ophthalmology. Ora is providing clinical-regulatory and development services to Aura Biosciences. They welcome comments or questions related to this or other development topics. Please send correspondence to: mchapin@oraclinical.com

The researchers are now focusing on mapping the structure of myocilin to learn more about what myocilin does and why it is in the eye in the first place.

"The underlying problem with myocilin is that for 14 years it has been studied and still nobody really knows what its biological role is inside the eye," Dr. Lieberman said.

Chemical Restores Light Perception To Blind Mice

Progressive degeneration of photoreceptors—the rods and cones of the eyes—causes blinding diseases such as retinitis pigmentosa and age-related macular degeneration. While there are currently no available treatments to reverse this degeneration, a newly developed compound allows other cells in the eye to act like photoreceptors. As described in a study appearing in the February 19 issue of the journal *Neuron*, the compound may be a potential drug candidate for treating patients suffering from degenerative retinal disorders.

The retina has three layers of nerve cells, but only the outer layer contains the rod and cone cells that respond to light. When the rods and cones die during the course of degenerative blinding diseases, the rest of the retina remains intact but unable to respond to light. Even though the innermost layer's nerve cells, called ganglion cells, remain connected to the brain, they no longer transmit information useful for vision.

Professor Richard Kramer, of the University of California, Berkeley, and his colleagues have invented "photoswitch" chemicals that confer light sensitivity on these normally light-insensitive ganglion cells, restoring light

(continued on page 10)

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(continued from page 7)

perception in blind mice. An earlier photoswitch required very bright ultraviolet light, making it unsuitable for medical use. However, a new chemical, named DENAQ, responds to ordinary daylight. Just one injection of DENAQ into the eye confers light sensitivity for several days.

Experiments on mice with functional, nonfunctional or degenerated rods and cones showed that DENAQ only impacts ganglion cells if the rods and cones have already died. It appears that degeneration in the outer retina leads to changes in the electrophysiology in the inner retina that enables DENAQ photosensitization, while the presence of intact photoreceptors prevents DENAQ action.

The selective action of DENAQ on diseased tissue may reduce side effects on healthy retina, exactly what is desired from a vision-restoring drug. "Further testing on larger mammals is needed to assess the short- and long-term safety of DENAQ and related chemicals," says Dr. Kramer. "It will take several more years, but if safety can be established, these compounds might ultimately be useful for restoring light sensitivity to blind humans. How close they can come to re-establishing normal vision remains to be seen." REVIEW

MIT Researchers Devise Hand-Held OCT

Researchers at the Massachusetts Institute of Technology have devised a new ophthalmic-screening instrument that could enable widespread use of a hand-held optical coherence tomographer to screen for retinal disease. The paper describing their device was published in the open-access journal *Biomedical Optics Express*.

The developers say the new design is the first to combine cutting-edge technologies such as ultrahigh-speed 3-D imaging, a tiny micro-electro-mechanical systems mirror for scanning and a technique to correct for unintentional movement by the patient. These innovations, they say, should allow clinicians to collect comprehensive data with just one measurement.

"Hand-held instruments can enable screening a wider population outside the traditional points of care," such as a primary-care physician's office, a pediatrician's office or even in the developing world, said author and researcher James Fujimoto, PhD, of MIT.

Tabletop OCT imagers have become a standard of care in ophthalmology. The researchers were able to shrink what has been typically a large instrument into a portable size by using a MEMS mirror to scan the OCT imaging beam. They tested two designs, one of which is similar to a handheld video camera with a flat-screen display. In their tests, the researchers found that their device can acquire images comparable in quality to conventional table-top OCT instruments.

To deal with the motion instability of a hand-held device, the instrument takes multiple 3-D images at high speeds, scanning a particular volume of the eye many times but with different scanning directions. By using multiple 3-D images of the same part of the retina, it is possible to correct for distortions due to motion of the operator's hand or the subject's own eye. The next step, Dr. Fujimoto said, is to evaluate the technology in a clinical setting. But the device is still relatively expensive, he added, and before this technology finds its way into doctors' offices or in the field, manufacturers will have to find a way to support or lower its cost.

In the future, Dr. Fujimoto envisions that hand-held OCT technology can be used in many other medical specialties beyond ophthalmology, for example, in applications ranging from surgical guidance to military medicine.

"The hand-held platform allows the diagnosis or screening to be performed in a much wider range of settings," he said. "Developing screening methods that are accessible to the larger population could significantly reduce unnecessary vision loss."

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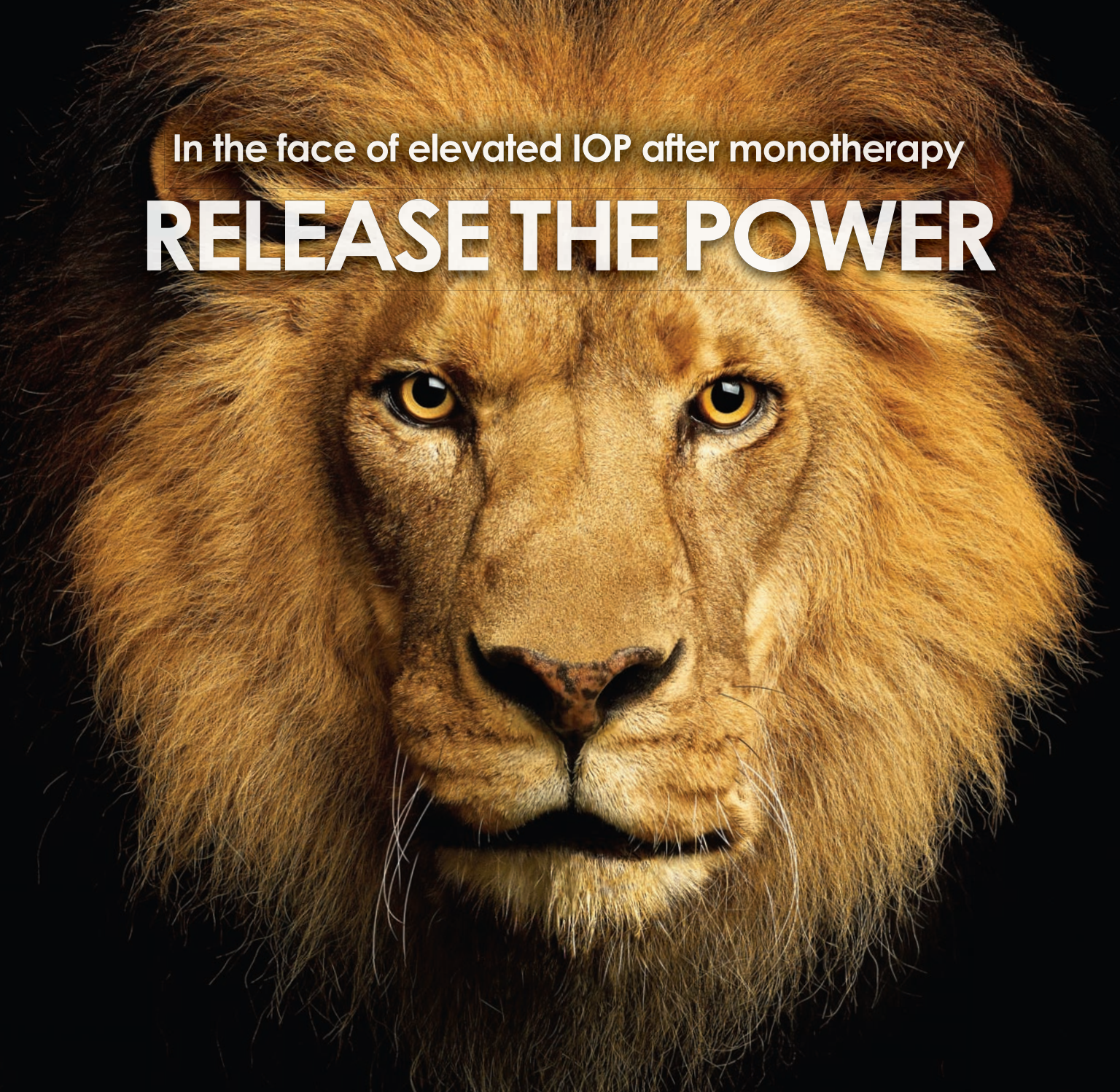

INDICATIONS AND USAGE: COMBIGAN® (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5% is an alpha-adrenergic receptor agonist with a beta-adrenergic receptor inhibitor indicated for the reduction of elevated intraocular pressure (IOP) in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP; the IOP-lowering of COMBIGAN® dosed twice a day was slightly less than that seen with the concomitant administration of 0.5% timolol maleate ophthalmic solution dosed twice a day and 0.2% brimonidine tartrate ophthalmic solution dosed three times per day.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS: COMBIGAN® (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5% is contraindicated in patients with bronchial asthma; a history of bronchial asthma; severe chronic obstructive pulmonary disease; in patients with sinus bradycardia; second or third degree atrioventricular block; overt cardiac failure; cardiogenic shock; in neonates and infants (under the age of 2 years); in patients with a hypersensitivity reaction to any component of COMBIGAN® in the past.

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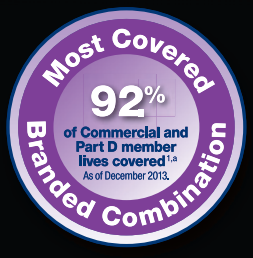

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS: COMBIGAN® (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5% contains timolol maleate; while administered topically, it can be absorbed systemically and systemic adverse reactions to beta-blockers may occur (eg, severe respiratory reactions including death due to bronchospasm in patients with asthma have been reported).

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.

Patients with chronic obstructive pulmonary disease (eg, chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease should not receive COMBIGAN®.

COMBIGAN® may potentiate syndromes associated with vascular insufficiency. Use caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans.

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.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS: (continued)

Beta-blockers may mask the signs and symptoms of acute hypoglycemia and clinical signs (eg, tachycardia) of hyperthyroidism. Use caution in patients subject to spontaneous hypoglycemia or diabetics (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Carefully manage patients who may develop thyrotoxicosis to avoid abrupt withdrawal of beta-blockers that might precipitate a thyroid storm.

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

Some authorities recommend gradual withdrawal of beta-blockers due to impairment of beta-adrenergically mediated reflexes during surgery. If necessary during surgery, the effects of beta-blockers may be reversed by sufficient doses of adrenergic agonists.

ADVERSE REACTIONS: The most frequent reactions with COMBIGAN® (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5% in about 5% to 15% of patients included: allergic conjunctivitis, conjunctival folliculosis, conjunctival hyperemia, eye pruritus, ocular burning, and stinging.

DRUG INTERACTIONS: Use caution in the co-administration of COMBIGAN® with: antihypertensives or cardiac glycosides; beta-blockers (concomitant use of two topical beta-blockers is not recommended); calcium antagonists (avoid co-administration in patients with impaired cardiac function); catecholamine-depleting drugs; CNS depressants/anesthetics; digitalis and calcium antagonists; CYP2D6 inhibitors; tricyclic antidepressants; and monoamine oxidase inhibitors.

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.

Combigan®

(brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5%

COMBIGAN®

(brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5%

BRIEF SUMMARY

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

INDICATIONS AND USAGE

COMBIGAN® (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5% is an alpha adrenergic receptor agonist with a beta adrenergic receptor inhibitor indicated for the reduction of elevated intraocular pressure (IOP) in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP; the IOP-lowering of **COMBIGAN®** dosed twice a day was slightly less than that seen with the concomitant administration of 0.5% timolol maleate ophthalmic solution dosed twice a day and 0.2% brimonidine tartrate ophthalmic solution dosed three times per day.

CONTRAINDICATIONS

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

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

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

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

OVERDOSAGE

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

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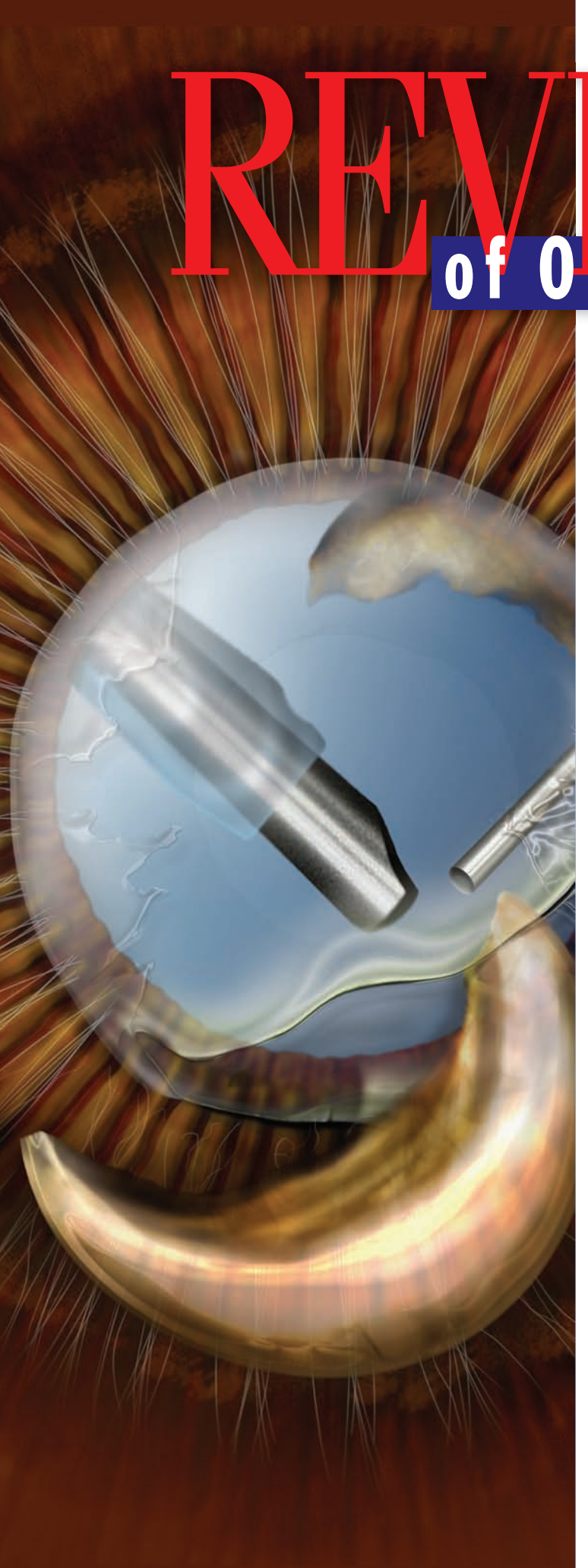

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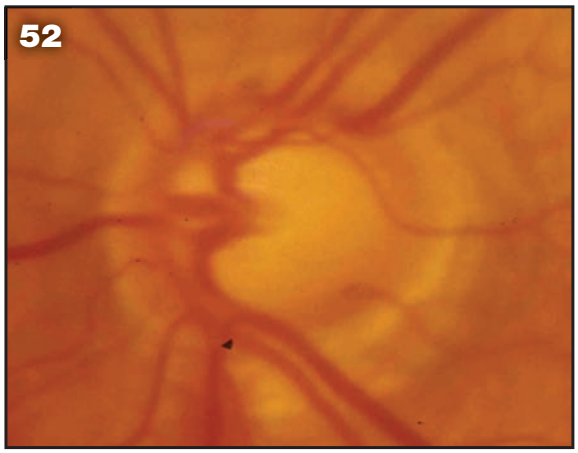
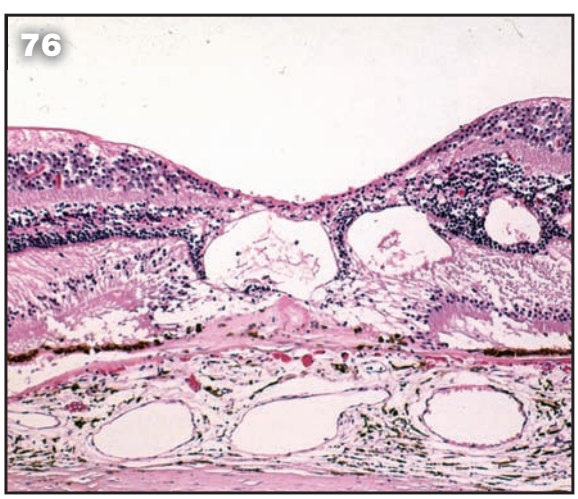
Cover Focus

Feature Article

Cover illustration by Mark Erickson, jirehdesign.com

Departments





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

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REVIEW of Ophthalmology

REVIEW Editor's Page

Christopher Glenn, Editor in Chief

Compounding Interest in Pharmacy

While the issue has receded somewhat from the national headlines, our article on drug compounding (p. 49) shows that concerns over the safety and continued availability of compounded ophthalmic drugs are still very much alive and well-warranted.

Highly publicized cases in recent years of tainted products, including Avastin and trypan blue as well other compounds not related to ophthalmic use, culminated in federal legislation last fall designed to tighten controls on compounding. So far the impact, apparently, has been underwhelming. The message that emerges from the experts we spoke to is clear: If you're using a compounding pharmacy, you better get to know your pharmacist and his processes real well.

That turns out not to be bad advice even for those who don't use compounders. The pharmacist, thanks to a host of converging influences, is poised to take a far bigger part in patient care than his traditional role of dispensing pills.

The Affordable Care Act, for one, is expected to bring a huge influx of new patients, straining the capacity of already-overloaded primary-care practices. Beyond the emergence of minute-clinic models in pharmacies and other retail locations, legislation is being considered and in some cases has already been enacted that allows appropriately licensed pharmacists to provide immunizations and in some cases even write prescriptions after a physician's diagnosis. A California law that took effect in January enables licensed pharmacists to independently furnish routine vaccinations, hormonal contraception, nicotine replacement medications and certain prescription drugs for travelers. The law also creates a new designation of "advanced practice pharmacist," which would enable designated pharmacists (after receiving additional training and experience) to assess and refer patients; start, stop and adjust drug therapies; order and interpret drug therapy-related tests; and "participate in the evaluation and management of diseases and health conditions." The law states that "pharmacists are health care providers who have the authority to provide health care services." Such provider status legislation could allow more pharmacists to practice "at the top of their license," that is, to the full extent of their training and education.

While the immediate impact of such changes is more likely to be felt in primary care, ophthalmologists need to be aware that the pharmacist is emerging as a potentially valuable and increasingly involved member of the health-care team.


Alternate Uses for Corneal Cross-linking

This long-awaited procedure may be able to do more than just treat keratoconus and ectasia.

Christopher Kent, Senior Editor

American ophthalmologists are eagerly awaiting the long-delayed Food and Drug Administration decision on corneal cross-linking to treat keratoconus and manage ectasia. However, CXL may have potential uses in other areas as well.

Treating Resistant Ulcers

CXL is showing benefit as a means to prevent complications and promote healing when corneal ulcers are otherwise non-responsive to standard antibiotic or fungal treatment. This use of CXL technology is called PACK-CXL (Photo-Activated Chromophore for infectious Keratitis cross-linking).

Farhad Hafezi, MD, PhD, chair and professor of ophthalmology at the University of Geneva, Switzerland, and clinical professor of ophthalmology at the Doheny Eye Institute at the University of Southern California, Los Angeles, has been using this approach since 2007. His group published the first paper on this procedure in 2008.[1]

Recently, Dr. Hafezi and colleagues conducted a randomized, prospective clinical trial involving 40 patients at clinics in Egypt, the UK and Switzerland with advanced infectious keratitis and corneal melting (*Ophthalmology* 2014, in press). Twenty-one eyes were treated with both antimicrobial therapy and PACK-CXL; 19 control eyes received only antimicrobial therapy. The size of the corneal ulcers was significantly larger in the PACK-CXL group: 5.62 ±1.88 x 6.22 ±1.98 mm, vs. 3.97 ±2.5 x 4.22 ±2.18 mm.

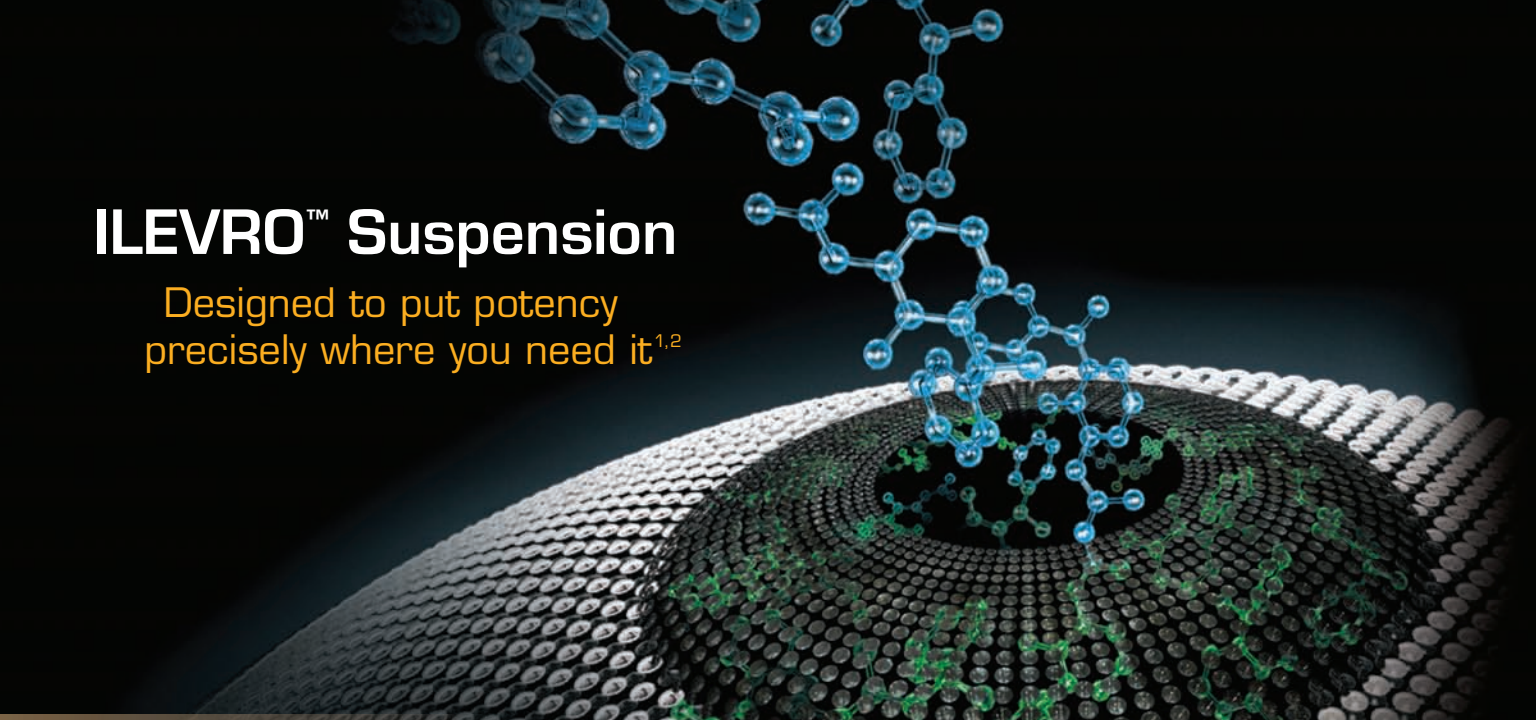
Mean duration to complete healing was 39.76 ±18.22 days for the PACK-CXL group and 46.05 ±27.44 days in the control group (not significant: p=0.68). Three patients in the control group (21 percent) developed perforation; one had an infection recurrence. In contrast, there were no complications in the PACK-CXL group. There was very little difference in CDVA after treatment. Dr. Hafezi notes that in theory, at least, the PACK-CXL group might have been expected to do worse, given that their ulcers were significantly larger at the outset. (That did not happen.)

Possible Mechanisms

Dr. Hafezi explains there are three possible mechanisms that might account for the benefits seen when using PACK-CXL. "The first possibility is direct intercalation of the chromophore to the DNA of the pathogen, causing irreversible binding and suppression of replication," he says. "A second possibility is that generation of reactive oxygen species during the process destroys the cell walls of the pathogens. A third possibility is that changes in the three-dimensional structure of the collagen fibers make it harder for collagenases, which are upregulated during corneal melting, to dock and exert their action."

Dr. Hafezi notes that the use of CXL to address resistant corneal ulcers is not yet widespread. "This is still in the pilot phase," he says. "I would compare it to the use of CXL to address keratoconus back in 2002. Proof of concept had been given, but it had not caught on yet."

Dr. Hafezi says it's not yet clear what conditions might contraindicate this use of CXL, or whether there is a downside to the treatment. "We observed a slight increase in the size of a hypopyon in one patient," he says. "When thinking about it, this seems logical: We killed a lot of pathogens



ILEVRO™ Suspension

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

ONCE-DAILY POST-OP

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

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

INDICATIONS AND USAGE

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

Dosage and Administration

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

IMPORTANT SAFETY INFORMATION

Contraindications

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

Warnings and Precautions

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

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

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

Adverse Reactions

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

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

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

ILEVRO™ (nepafenac ophthalmic suspension) 0.3%

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 2/13 ILV13030JAD

ILEVRO™

(nepafenac ophthalmic suspension) 0.3%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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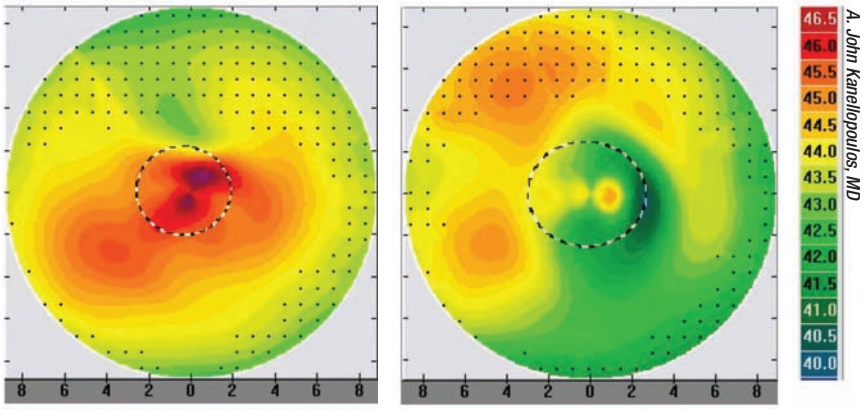
Fort Worth, Texas 76134 USA

simultaneously, so the size of the hypopyon had to increase immediately postoperatively. A similar reaction has been seen in the treatment of tuberculosis, where it's called a Jarish-Herxheimer reaction."

Dr. Hafezi believes this use of CXL may become more important than treating keratoconus. "I believe that PACK-CXL will have a much greater impact on global ophthalmology," he says. "It addresses the third leading cause of global blindness—corneal infections, according to the World Health Organization—rather than a rare disease like keratoconus or postoperative ectasia. However, to reach that point we have to make the treatment faster; we have to move the treatment out of the operating theatre; and we have to make this type of technology inexpensive so that everyone can have equal access to it. My research group is working to address all three of these concerns."



A 2.5 D refractive correction done with cross-linking; no tissue was removed. Left: before treatment; right: six months after. The changes were stable during this time. A. John Kanellopoulos, MD, has performed this procedure on 50 eyes to date, producing predictable, reproducible refractive corrections of small refractive errors (±2 to 3 D), including regular and irregular astigmatism. (Several articles are currently in press.)

Correcting Refractive Error

CXL is also being investigated as a nonsurgical method for correcting refractive error. Avedro, a company based in Waltham, Mass., recently received the CE Mark in Europe for its KXL II system, which can be used to deliver user-specified CXL patterns, including patterns designed to alter the patient's refraction.

William J. Dupps Jr., MD, PhD, who performs cornea and refractive surgery at the Cole Eye Institute in Cleveland and is director of the Ocular Biomechanics and Imaging Lab at the Cleveland Clinic, has been researching CXL for many years. "We published a paper in 2011[2] that tested the concept of doing focal treatments with CXL, to see if we could leverage the shape change more specifically," Dr. Dupps explains. "In computational models, we decentered the treatment toward the steepest part of the cornea and manipulated the treatment parameters to enhance the results. The modified treatments showed double or triple the topographic improvement achieved in the same models with a standard treatment."

Dr. Dupps is now collaborating with John Kanellopoulos, MD, in Athens, Greece, who has been performing customized CXL on patients since it was approved in 2013. Dr. Kanellopoulos's clinical work is bearing out what Dr. Dupps and his team observed in their modeling research. For example, one of his recent keratoconus patients was treated using a focal approach—without debriding the epithelium—and the result was a 5.5-D flattening of the cone, rather than the 1- or 2-D flattening that would be considered a very favorable result with a standard procedure. Other cases have produced similar results.

"Corneal tissue treated with CXL displays a focal flattening effect, not unlike that caused by a corneal scar," Dr. Dupps continues. "By placing that zone of flattening carefully, changing the shape of the zone and adjusting other parameters like the depth of the treatment and the dosing of the light, we can customize the refractive result we achieve. The work done so far—both in the lab and with live patients—has shown that using CXL to correct refractive error is feasible."

Does the effect last? Dr. Kanellopolous has observed that results are consistent over a six-month follow-up. Over the long-term, Dr. Dupps says data from earlier cross-linking trials may provide a tentative answer. "In the first published clinical trial, reported in 2003, patients were followed for as long as four years," he says. "What shocked a lot of people was that instead of seeing loss of effect and progression of the disease after the first several months, the data showed an ongoing flattening effect in 70 percent of patients.[3]

"This wouldn't necessarily be desirable in a refractive correction, of course, but these treatments treated the entire cornea and they treated diseased corneas, so it's not clear that this would occur to the same extent in an otherwise healthy cornea," he says. "One concept that's been discussed as a means to address this is using a stabilizing treatment to lock in the refractive change you create. Such a treatment is under development."

Dr. Dupps says the process of titrating the exact amount of correction created by a treatment requires ongoing study. "A bigger question is, what's the maximum effect we'll be able to achieve?" he notes. "We have a pa-

per in press that describes computer simulations of what happens if we use different patterns and intensities to treat astigmatism, starting with tomographic maps of real patient eyes. A modest amount of corneal stiffening produced astigmatic corrections between 1 and 3 D. Most eyes with astigmatism fall within that range, and it's possible to generate greater levels of corneal stiffening than we simulated."

Dr. Dupps believes that within a few years this approach to refractive correction could give LASIK a run for its money—particularly in some patient groups. "I think many patients with lower refractive error would find it attractive to have an option that doesn't involve removing tissue from the cornea," he says. "And for patients who might be suspects for keratoconus, a treatment that stiffens the cornea while correcting refractive error would make a lot more sense than one that could potentially tip the balance toward ectasia by destabilizing the cornea.

"As a standalone treatment, the range of refractive correction will be more limited than some other procedures," he adds. "But there are a lot of people living with low to moderate refractive error, and refractive CXL offers a completely different treatment paradigm for correction." REVIEW

Dr. Dupps is listed as an inventor on related modeling technology being developed at the Cleveland Clinic. He serves as a consultant for Ziemer and has received research support from Zeiss, Avedro, NIH and The Ohio Third Frontier Commission. Dr. Hafezi has no financial connections to any products mentioned.

1. Iseli HP, Thiel MA, et al. Ultraviolet A/Riboflavin Corneal Cross-linking for Infectious Keratitis Associated With Corneal Melts. Cornea 2008;27:590-94.
2. Roy AS, Dupps WJ Jr. Patient-specific computational modeling of keratoconus progression and differential responses to collagen cross-linking. Invest Ophthalmol Vis Sci 2011;52:12:9174-87.
3. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. Am J Ophthalmol 2003;135:5:620-7.

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New Ways to Skin a Cataract

Walter Bethke, Managing Editor

A look at the latest advances in phaco technology and beyond.

When surveying the cataract surgery landscape, some surgeons have viewed the latest technology on the scene, the femtosecond laser, with a mixture of appreciation and exasperation. "It's great that it can perform incisions and segment the nucleus," they say, "but when will we have a device that does that and removes the cataract? Why are we still using phaco?" The answer is, apparently, that phaco remains the most powerful, versatile, efficient way to remove even very hard cataracts, and looks to remain a staple of the surgeon's armamentarium for years to come.

Here, surgeons discuss new advances in phaco, as well as technologies that, if they can't overthrow the king, can maybe make cataract surgery a little safer in softer nuclei by avoiding the use of ultrasonic energy for every cataract.

Alcon

The Centurion's Active Fluidics system modulates inflow to maintain a constant intraocular pressure in the eye.

Alcon's Centurion System

In the fall of 2013, Alcon introduced a new phaco system designed to give surgeons more control over the phaco environment within the eye and help make the procedure safer and more efficient. Following are the functions built into the new system:

• ***Active Fluidics.*** One of the primary features introduced with the new system is the ability for the surgeon to set a target intraocular pressure for the eye and have the system automatically modulate flow to maintain that IOP throughout the case. "Traditionally, phaco machines have used a bottle height at a level that the surgeon desired to create flow into the eye," says Robert Cionni, MD, of the Cincinnati Eye Institute. "That's a static system and, typically during quadrant removal or removal of cor-

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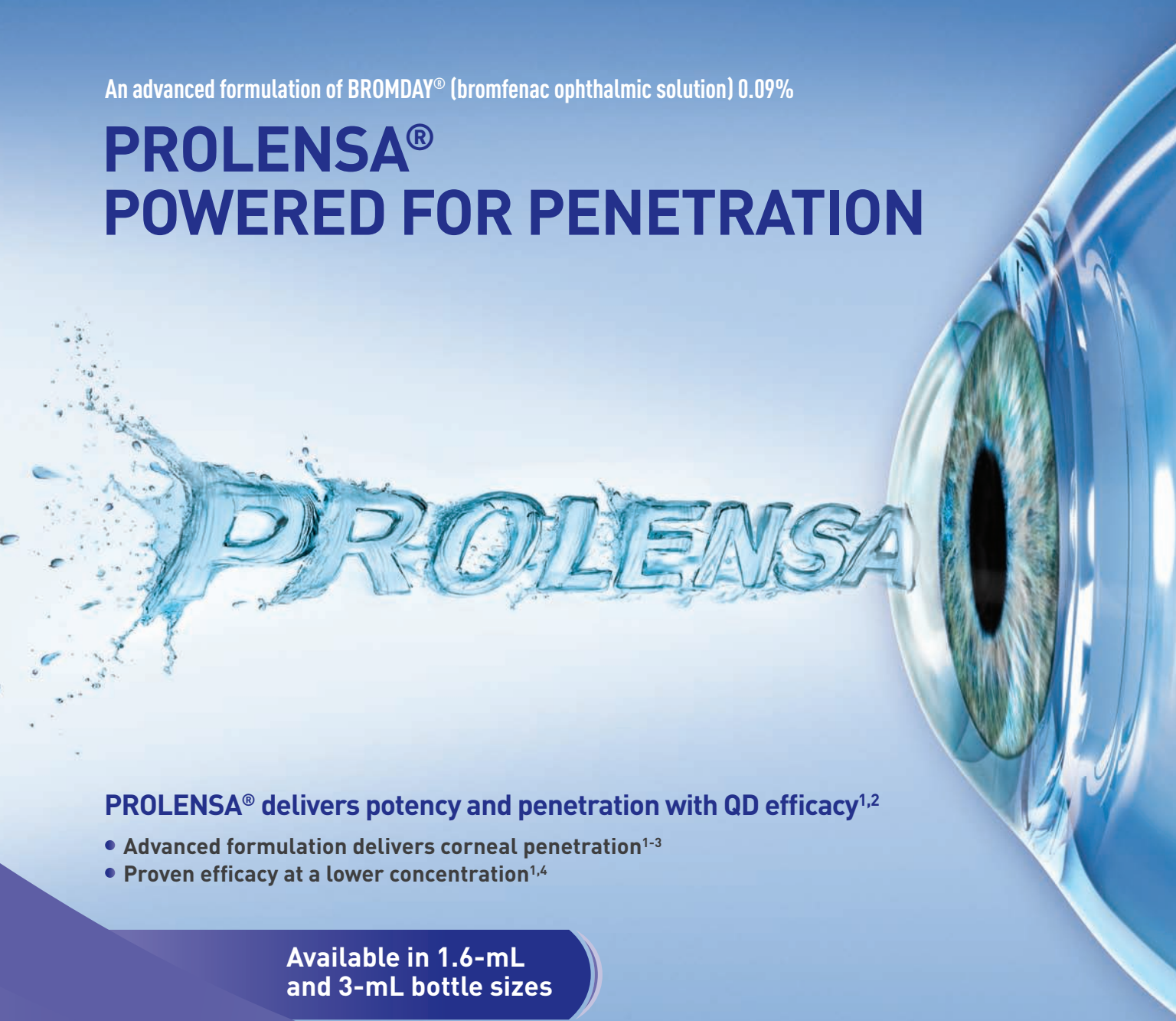

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- Advanced formulation delivers corneal penetration[1-3]
- Proven efficacy at a lower concentration[1,4]

Available in 1.6-mL and 3-mL bottle sizes

IMPORTANT RISK INFORMATION ABOUT PROLENSA®

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

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

Please see brief summary of full Prescribing Information on adjacent page.

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

BAUSCH + LOMB

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

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

PROLENSA®
(bromfenac ophthalmic solution) 0.07%

Brief Summary

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Recommended Dosing

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

Use with Other Topical Ophthalmic Medications

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

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Sulfite Allergic Reactions

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

Slow or Delayed Healing

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

Potential for Cross-Sensitivity

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

Increased Bleeding Time

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

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

Keratitis and Corneal Reactions

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

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

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

Contact Lens Wear

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

ADVERSE REACTIONS

Clinical Trial Experience

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

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

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

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis and Impairment of Fertility

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

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

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

PATIENT COUNSELING INFORMATION

Slowed or Delayed Healing

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

Sterility of Dropper Tip

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

Concomitant Use of Contact Lenses

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

Concomitant Topical Ocular Therapy

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

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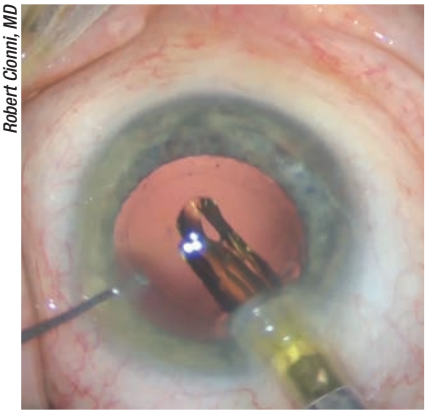
Osaka, Japan 541-0046

 9317600

tex or viscoelastic, surgeons usually ran a bottle height of 100 cc. There wasn't a really good understanding of what that's doing to pressure or flow in the eye, however, and we'd kind of titrate our vacuum to a certain bottle height. That kind of system is good and has worked for years, but it tends not to be very responsive to changes to the pressure in the eye, specifically with regard to occlusion breaks.

"For example, say a nuclear chip is occluding the tip," Dr. Cionni continues. "The vacuum goes up to 350, 400 or whatever the surgeon had the maximum vacuum set at, and when phaco breaks up the chip, the occlusion goes away very quickly and suddenly you have a tremendous influx of fluid into the tip. This influx causes a fluctuation in the chamber, or a chamber collapse, in which the iris and posterior capsule come toward the tip. This sets up a dangerous situation and limits the vacuum level we can use during phaco. The lower the vacuum level, the less efficient phaco is, while the higher the vacuum level, the more efficiently material moves into the tip and the cataract can be removed with less ultrasound time and fluid being used. However, the ultrasound time, the amount of energy delivered to the eye and the amount of fluid that goes into the eye correlate with the amount of edema you see postoperatively.

"The active fluidics system works differently," Dr. Cionni adds. "You don't hang a bottle. Instead, inside the machine there's a collapsible plastic bag of infusion BSS that is compressed by pressure plates. In order to maintain a specific pressure in the eye, the pressure plates can squeeze the bag or relax their pressure on it. For instance, take the case of a myopic patient who has had a vitrectomy. If the pressure goes from zero to whatever the bottle was hung at, then you can have a sudden pressure change in the eye and a severe pupillary block—a very painful situation for the patient. With Centurion, we can tell it to bring the pressure up to 60 mmHg, but to do it over a period of a couple of seconds rather than immediately. This more gradual pressure rise is more manageable by the surgeon and there's less pain. Likewise, when you get an occlusion break, the pressure sensors can squeeze the bag very quickly to give an instant influx of fluid so you have less of a chamber collapse." Several years ago, B + L instituted a similar system in its Stellaris phaco machine to achieve gas-forced infusion to help keep chambers deep during occlusion break situations.



Robert Cionni, MD

In addition to controlling the fluidics, the Alcon Centurion's foot pedal also allows the surgeon to control the IOL inserter.

To give a sense of how this compares during surgery to Alcon's previous system, the Infiniti, Dr. Cionni provides some numbers. "With Infiniti, with a bottle height of 100 cc and an IOP of 84 mmHg, the max vacuum pressure I'd recommend for surgery would be 350 mmHg, controlled linearly," he says. "So, this means that the farther down on the pedal you push, the more vacuum you get. With Centurion, I can go to a vacuum level of 600 mmHg—almost double—to give a more efficient procedure, but set the IOP at 60, which would be equivalent to a bottle height of 84 cc. So, we'd have a lower pressure in the eye, a more stable chamber and more efficient phacoemulsification."

• ***Separate control over flow and vacuum.*** University of Utah surgeon Alan Crandall says the system's functions allow it to somewhat mimic a venturi-based system in different situations. "For your average cases, you probably won't notice a difference with it," he says. "But it's been helpful for unusual cases. For example, let's say the patient is the average pseudoexfoliation patient, meaning the pupil doesn't dilate very well. In this patient, the capsules are a little fragile and the cataract is moderately hard. In this setting, you want to do everything that's zonule-friendly. So, I'd most likely be in a slow-motion, low-flow mode, but I'd like the vacuum to allow me to bring these pieces to the safe center zone without a lot of manipulation so I could then phaco them. So in this instance I'd say I'd probably keep the IOP at 50 mmHg, which would equate to a low bottle height—and so there's your flow. Then I'd increase the vacuum a little bit to let me bring the pieces in and get them to the center, and maybe even change it once I got them to the safe zone; I could increase the target IOP to keep things away from the phaco tip, and then drop it back down immediately. You can fine-tune it on the fly."

Nano Laser Phaco

When faced with the prospect of battling such an efficient, entrenched procedure as phaco, some companies have taken the approach of "if you can't beat them, join them." It's with this thought in mind that Germany's A.R.C. Laser company developed its nano laser phaco system, Cetus.

Rather than existing as a standalone box with all the irrigation/aspiration equipment of a phaco machine, Cetus is designed to be hooked up to a surgeon's existing phaco machine to help emulsify relatively soft nuclei—grade 3 and below—using less energy than regular phacoemulsifica-

A.R.C. Laser

The Cetus nano laser phaco system houses a laser in the tip. The laser strikes a titanium target, and the resulting shockwaves emulsify the nuclear material.

tion and without the use of a sharp phaco tip in the eye. "The philosophy is that we only provide a machine for energy delivery, but instead of using ultrasound energy we use a laser," explains Rudolf Walker, PhD, A.R.C. Laser's head of applications. "The inflow and outflow we take from the surgeon's ultrasound machine. We instead deliver a module. So, to use the nano laser, you take the I/A of your original phaco machine and combine it with our system. We also don't replace manual surgical steps such as the capsulorhexis and the incision." To accomplish these steps, surgeons still need to use a manual technique or a femtosecond laser.

The Cetus operates by using a YAG laser inside its tip to create a shockwave that emulsifies material. "Instead of a large, bulky ultrasound handpiece, we use a small, disposable plastic handpiece," Dr. Walker explains. "The handpiece works by the laser striking a titanium target at the tip—so the laser doesn't interact with any tissue. It's the laser hitting the target that causes the emulsification."

There are several purported benefits of the Cetus laser system. First, Dr. Walker says it uses a half or even a third of the energy that ultrasound does in the eye, which theoretically would decrease rates of complications such as postop macular edema. Second, the tip is round and polished, not sharp like a phaco probe. This rounded edge means that it's safe for ocular structures, and Dr. Walker says a surgeon can even touch the capsular bag safely with it as he might do with an I/A tip. Finally, since the entire Cetus handpiece is disposable, Dr. Walker says that means there is no risk of infection from the handpiece as there is with a reusable phaco handpiece.

One of the limitations of the technology, though, is that it doesn't work for all cataracts, so surgeons' phaco handpieces should be waiting in the wings for patients with greater than 3+ nuclei. "When the nucleus gets very hard, the efficiency with our nano laser isn't as good as our ultrasound system," he says. "We can't replace ultrasound completely. So, with nuclei graded 4 or harder, you're better off using ultrasound. However, Cetus can replace ultrasound for 50 to 70 percent of a surgeons' patients, depending on his patient cohort, of course." Dr. Walker says studies are currently under way to analyze the system's energy usage and its effect on endothelial cell counts.

In terms of approval status, the Cetus is available in Europe, but not in the United States. "The techniques and basic operation of the laser come from the old Dodick laser system that was approved by the Food and Drug Administration in 1999," says Dr. Walker. "We changed the handpiece to a coaxial one from a bimanual, which was big step forward. So, we will see if we can get a quick approval because the Dodick system is already approved."

Catapulse

The Med-Logics Catapulse system is also designed to do away with ultrasound energy, at least for softer cataracts. However, instead of using a laser, the Catapulse uses pulsating vacuum power. The Catapulse is currently in development, and isn't available for sale.

"As IOL technology gets better, cataract surgery is moving toward the refractive end of the spectrum," says Antonio Mendez Noble, MD, a surgeon from Tijuana, Mexico, who has helped study the Catapulse for Med-Logics. "Because of this refractive emphasis, the cataracts we're removing now often aren't very hard; instead they're soft and don't require that much energy. So, we started working with vacuum rather than ultrasound energy, and found that by turning the vacuum on and off very quickly when the nuclear fragment hits the tip an energy is produced that will break up almost anything."

The Catapulse uses its own irrigation/aspiration unit and uses a plastic, 0.9-mm rounded tip. "The tip doesn't have a sharp edge or produce heat," says Dr. Mendez Noble. "For the Catapulse procedure, it's important to pre-fracture the nucleus, because the tip can't burrow into it. Any type of nucleus fracturing technique works. I use the Akahoshi pre-chopper instrument for this, though, of course, the system also works well with the

femtosecond laser for segmenting the nucleus."

To provide irrigation during the surgery, Dr. Mendez Noble says the current Catapulse technique involves a bimanual approach. "Right now, the second instrument I use is an irrigator," he says. "I can add any type of tip or manipulator to the irrigator, as well, but right now I just use irrigation." He says the Catapulse machine currently uses a duty cycle that the surgeon sets in order to control the device's vacuum pulsations, but neither he nor the company have hit on what the ideal pulsation rate is. "We're playing around with that right now," he says.

As to where the Catapulse device may fit into the cataract surgery spectrum, and what it brings to the table, Dr. Mendez Noble says the machine's primary benefit is safety. "There's no assembly, the handpiece comes complete with the tubes and the cassette, and you just hook up the cassette to the machine," he explains. He says this avoids some difficult situations that can occur with conventional phacoemulsification. "In phaco, I've experienced situations where for some reason the tubing isn't seated well on the back of the handpiece and I subsequently get into trouble. Or, the tip of the phacoemulsifier isn't tight enough and you have problems with phacoemulsification. Other times, you may put the sleeve over the tip and find that the sleeve ruptures or has a small hole in it for some reason. All these potential problems are avoided with Catapulse because it's just one piece that you hook up and begin using. Also, again, there's no heat or energy released from the tip. Though there is the possibility of maybe catching the capsule and rupturing it, at the times when we've gotten into iris or capsule, we haven't had any ruptures or iris burns."

However, even though Catapulse may theoretically make the procedure safer for some cataracts, as with Cetus, surgeons can't throw away their ultrasound phaco equipment. "Anything over grade 3, you'll need ultrasonic phaco," says Dr. Mendez Noble, who adds that though he'd like to do away with using ultrasound energy for cataracts, it may always have a place in ophthalmology. "Everything we do now is to try to avoid using ultrasound [in cataract surgery]. We know phaco works and is especially great for hard cataracts, and maybe developing countries will still need phaco for the cataracts there, which tend to be harder. There, it's still the ideal procedure." REVIEW

Managing Surgical Complications

Christopher Kent, Senior Editor

Despite the cutting-edge technology used in cataract surgery, the unexpected can still happen. Here's help.

Cataract surgery is the most frequently performed surgery in the world. Outcomes are overwhelmingly positive, but the sheer number of surgeries increases the odds that every surgeon will encounter an unpleasant surprise from time to time. With that in mind, three experienced surgeons offer their advice on dealing with some of the complications a cataract surgeon may encounter—and when possible, how to prevent them in the first place.

Proactive Preparation

Clearly, the best way to manage intraoperative complications is to do two things: First, take steps ahead of time to minimize the risk of an occurrence; and second, be prepared should a setback occur. Along those lines, Audrey R. Talley Rostov, MD, cornea, cataract and refractive surgeon and partner at Northwest Eye Surgeons in Seattle, offers these suggestions.

• ***As much as possible, anticipate problems.*** "There are several ways to prepare for potential problems beforehand," notes Dr. Rostov. "First, if you know this will be a more complicated case than normal, one that you don't encounter very often, such as a sutured IOL, review the surgery with your staff ahead of time.

"Second, know when to use special equipment to prevent a complication from arising," she continues. "For example, in a very young patient the capsule is much more elastic and the capsulorhexis will be much more difficult. If you have a femtosecond laser available to do the capsulorhexis, that might be a good situation in which to use it.

"Third, have special tools available," she says. "If the patient is in his 90s or is very young, has a rock-hard nucleus or a traumatic cataract, or has a suspected or visible zonular dehiscence or dialysis, you want to have all the tools you might need to deal with those situations prepared ahead of time. For example, if a patient has a very advanced, dense, white or brunescent cataract, then I want to have Malyugin rings, iris hooks, Trypan blue, intraoperative epinephrine and a vitrectomy setup available in the room to help in the event of a complication. Obviously you don't need those for every single case, but if you have the equipment easily available your OR staff doesn't have to go hunting for it.

"Fourth, always have a backup lens available in case there's a problem with the bag or the zonules," she says. "This isn't a common situation, but you need to be prepared for it. Probably the best sulcus lens is the

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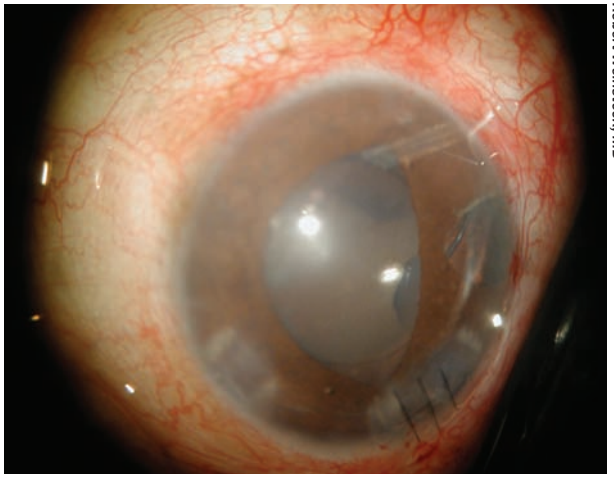
STAAR AQ2010, because the length is 13.5 mm rather than 13 mm. At least have a three-piece IOL available as a backup; you can use those in the sulcus, as long as you're mindful of their limitations. Hopefully by now every surgeon knows never to place a one-piece acrylic IOL in the sulcus."

• ***Use alternate techniques in difficult circumstances.*** "Complications can arise if you stick to standard protocol when the situation is nonstandard," notes Dr. Rostov. "For example, if a nucleus is very dense and adherent to the capsule, using phaco chop can lead to complications. In that situation, I sculpt as much as I can and make an enormous bowl that will then collapse upon itself. I can then use viscoelastic to viscodissect it from the posterior capsule. This significantly reduces the likelihood of a complication."

• ***Avoid having your view obscured.*** "Sometimes when the assistant is squirting BSS on the cornea, it can obscure your view momentarily," notes Dr. Rostov. "During that momentary obscuration of your view, you could end up phacoing the capsule or putting a hole in the posterior capsule or grabbing onto the anterior capsule. The solution is to make sure your assistant just irrigates very briefly, and only when you ask for it. Then, you'll know when to anticipate it and your view won't be obscured when you're not expecting it, such as in the middle of an important maneuver."

• ***Be alert for warning signs.*** "Whenever something occurs that seems out of the ordinary, stop and take a moment," she says. "Look around and be very aware of what's going on. That's especially important in cases that are not routine or have the potential to be more complicated."



Robert Weinstock, MD

Although uncommon, wound burns can still occur, even with today's advanced phaco technology. If you suspect an occlusion has occured during phaco, stop and clear the blockage immediately to prevent a wound burn. If a burn does occur, it will induce signicant astigmatism and the wound will require extra steps to ensure closure, possibly including multiple sutures.

Corneal Complications

With clear corneal incisions now a common choice in modern cataract surgery, several corneal complications can occur.

• ***Corneal abrasions.*** "Corneal abrasions can happen during wound creation or as the result of an instrument slipping across the eye, for example when inserting the speculum," says Robert Weinstock, MD, director of cataract and refractive surgery at the Eye Institute of West Florida in Largo, Fla. "Just about any instrument in cataract surgery is capable of causing an epithelial abrasion, and sometimes an epithelial abrasion can actually obstruct the surgeon's view during the surgery.

"Depending on the size and location of the abrasion, the surgeon has several options for handling this," he continues. "One option is to place a cohesive viscoelastic on the cornea to improve the surgical view and mask the abrasion. Another option is to debride the central epithelium, but this is usually done as a last resort, and only if there is a severely limited view into the eye because of a hazy or damaged epithelium.

"At the end of the case I recommend a soft contact lens be placed on the eye to avoid severe pain and aid in healing," he adds.

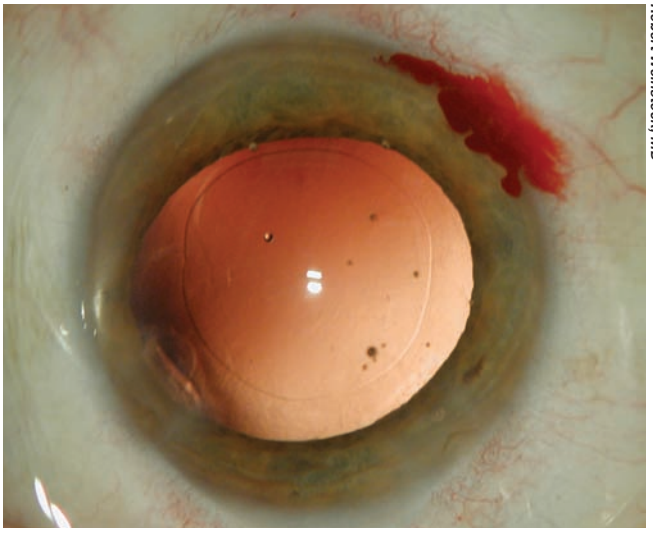
• ***Wound burn.*** "Wound burn is not as common these days with advanced phaco power modulation and laser cataract softening, but it's still possible if you have a very dense nuclear piece that gets stuck in the phaco needle handpiece or tubing and blocks aspiration flow out of the eye," says Dr. Weinstock. "If you're in foot position three and there's no fluid moving out of the eye through the needle, it will heat up enough to cause thermal damage to the cornea. If this happens, it can be pretty devastating.

"In order for this chain of events to take place, something must be clogging the phaco needle, handpiece or tubing," he continues. "Sometimes, a clog is caused by a thick dispersive viscoelastic or a particle of the nucleus. If you step on the phaco pedal when a clog prevents movement of fluid to cool the phaco needle you may end up with a wound burn, even if you're using one of the new phaco machines that has pulse modalities. There are usually some tip-offs that a problem is occurring; for example, you may see plumes of white smoke in the anterior chamber, and nothing seems to be evacuating out of the eye through the phaco needle. You'll probably also note that the cornea starts to get a whitish, coagulated look to it, usually on the anterior lip of the wound. It's usually 'game over' once you see this.

"If you suspect a clog or occlusion you have to stop immediately," he says. "Take the phaco needle out of the eye and flush the tip, handpiece and tubing. Most of time I find the culprit is

a piece of dense nucleus stuck in the tubing."

Dr. Weinstock notes that when corneal tissue burns, it contracts, leaving a gaping fish-mouth wound. "This type of wound is very difficult to seal just using hydration the way we normally would," he says. "It's even very difficult to seal with a standard single interrupted suture. Sometimes you have to put multiple sutures in, or even a running X suture in order to get the wound to seal. This might also be a good indication for a tissue adhesive.



Robert Weinstock, MD

A tear in Descemet's membrane can be caused by manipulating tools through the wound or a sharp piece of dense nucleus. Often the tissue can be repositioned, but if this occurs at the wound, avoid overhydrating to close the wound; a suture may be preferable.

"A wound burn will also induce a tremendous amount of astigmatism," he adds. "What you usually have to do is help the patient tolerate the astigmatism for a few months, because in general the astigmatism will melt away as the cornea heals and remodels itself. Immediately post-surgery, the astigmatism may be 3, 4 or 5 D, but it will usually come down to 1 or 2 D within two or three months—although in some cases it may take as long as six months. Because wound burns take so long to heal, they are one of the biggest headaches a surgeon can encounter."

"The best way to manage a wound burn is to avoid creating one," notes Amar Agarwal, MD, director of Dr. Agarwal's Eye Hospital in Chennai, India, who has pioneered numerous surgical procedures, including bimanual phaco. "One thing that will help prevent this problem is to have your assistant keep applying fluid to the cornea. If your assistant does this while you're operating, you will never get a corneal burn. However, always be alert so that if you do get a wound burn you'll diagnose the problem immediately.

"If a burn occurs, have the assistant keep putting fluid on the eye while you finish the surgery so that further burn does not occur," he adds. "After the surgery, put a suture on that area to prevent the wound from gaping. If necessary, suture the incision, make another incision in another area and complete the surgery there."

• ***Stripping and scrolling of Descemet's membrane.*** "Although rare, this can happen during cataract surgery, depending on the instrumentation you're using and how dense the cataract is," says Dr. Weinstock. "You can usually notice it while you're operating.

"It generally happens in one of two ways," he explains. "The first is a scroll of tissue at the wound, from your incision or as a result of manipulating things through the wound. I see it a little more often in bimanual surgery because the instruments are a little bit rougher on the tissue; there are some sharper edges, especially with the irrigating choppers and the bare phaco needle. If you do see a little bit of a scroll, you can usually address it at the end of the surgery case by going though the secondary wound and gently irrigating the scroll of tissue back into position. It will usually stick there. Alternatively, you can use viscoelastic to manipulate it into position, or even a Kuglen hook.

"Sometimes a little piece of tissue comes off altogether, right underneath the wound," he says. "If that happens, you'll see a scalloped edge where it's missing. In my experience, other cells migrate over to that area within a couple weeks and the cornea goes back to its normal thickness without any long-term complications.

"However, this situation raises issues concerning hydration," he continues. "If you're hydrating the cornea to thicken it and seal the wound, it's already going to be a little swollen in that area because of the loss of endothelium; as a result, it could take longer than normal to dehydrate afterwards. That means you need to be gentle with your hydration if you see a piece of Descemet's missing. In fact, if you see damage to the endothelium under the wound, you might consider placing a suture instead of overhydrating the cornea to get the wound to seal. The good news is that peripheral corneal swelling doesn't usually impact vision at all."

Dr. Weinstock says a second way you can end up with scrolling of endothelium is if a sharp piece of a dense nucleus or an instrument comes into contact with the cornea. "This event can slice the endothelium and cause a Descemet's scroll or a separation of Descemet's tissue, either centrally or peripherally," he explains. "If this happens, fluid can then hydrodissect Descemet's membrane off of the cornea during the surgery.

"If you see that a cut or slice has created a flap of Descemet's and you have more surgery left to do, stop, come out

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DUREZOL® Emulsion has head-to-head data vs prednisolone acetate in patients with endogenous anterior uveitis.[1]

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INDICATIONS AND USAGE: DUREZOL® Emulsion is a topical corticosteroid that is indicated for:

- The treatment of inflammation and pain associated with ocular surgery.
- The treatment of endogenous anterior uveitis.

Dosage and Administration

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

IMPORTANT SAFETY INFORMATION

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

Warnings and Precautions

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

Most Common Adverse Reactions

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

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

DUREZOL®
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The results you want. The relief they need.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

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

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

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

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

Cataracts
Use of corticosteroids may result in posterior subcapsular cataract formation.

Delayed Healing
The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order beyond 28 days should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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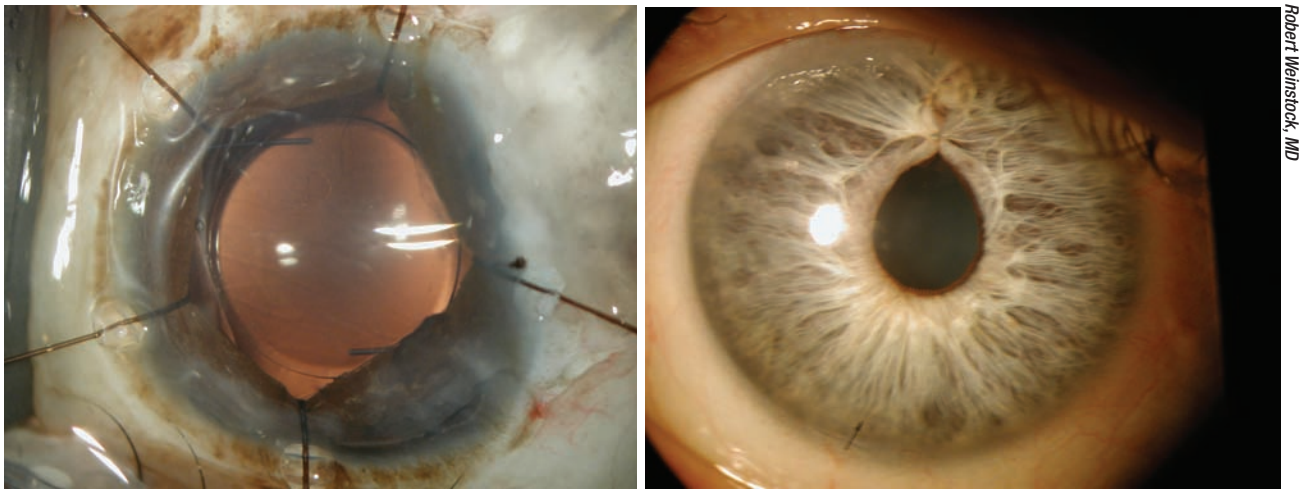


Robert Weinstock, MD

Left: Ballooning of the conjunctiva can occur if the wound is made too far posteriorly, allowing irrigation to flow under the conjunctiva. The surgeon can make an incision to release the fluid or close that wound and make a new incision. Right: An iris repair done after the iris was inadvertently damaged by the phaco needle during surgery.

of the eye and put in a dispersive viscoelastic; use it to push that flapping piece of endothelium and Descemet's back into position. Hopefully it will stay in place for the rest of the case," he says. "Sometimes you have to play around with it a little bit. It's almost like a jigsaw puzzle; you have to manipulate the little flap of tissue so that it fits back into the space that was left when it tore out. You should also leave a thin layer of viscoelastic at the end of surgery so the tissue stays in place.

"Of course, using air to manipulate the torn tissue would not be a good choice during surgery because you wouldn't be able to see well enough to complete the surgery," he adds. "However, if you're at the end of the case and you see some of Descemet's membrane flapping centrally or partially detaching, you can use a large air bubble in the anterior chamber to push the layer of tissue back into its anatomical position, just as you would in a DSAEK case. Then you can have the patient lie in a supine position overnight and check him the next day."

•***Ballooning of the conjunctiva***. "This usually indicates that you made your wound too far posteriorly and irrigation is flowing under the conjunctiva," says Dr. Weinstock. "Wound leakage during irrigation causes the ballooning. If the ballooning gets severe, you can make an incision in the conjunctiva a few millimeters back from the cornea and release the fluid from the sub-conjunctiva and/or sub-Tenon's space. If you think the problem is putting your surgery and visibility at risk, you can close that wound and make a new incision."

Iris Complications

The iris can easily become involved in unfortunate developments during cataract surgery.

• ***Damaging the iris.*** "It's possible to damage the iris with the phaco needle, especially in a small-pupil case," notes Dr. Weinstock. "You can unintentionally grab the iris, leading to hemorrhages, bleeding and damage. Once the phaco needle engages the iris, the damaged tissue becomes even more floppy and can easily prolapse out of the wound, or continue to be sucked into the phaco tip or aspiration tip.

"A dispersive or dual-property viscoelastic like Healon 5 can often help control the bleeding and prolapsing if the surgeon places it on top of the damaged iris, pushing the tissue deep and peripheral," he continues. "A Malyugin ring or iris hooks can also be used to control the situation and protect the iris from further damage. If the bleeding is severe and there's a risk of hyphema, one option is to flush the blood out of the anterior chamber and quickly fill the eye with BSS or viscoelastic, raising the pressure high for a minute or so to slow and hopefully stop the bleeding. Once the bleeding stops, the eye pressure can be slowly lowered by burping the paracentesis and observing to see if the bleeding has stopped. If this does not work, I have also had success with fine needle cautery of the bleeding iris vessels."

• ***Iris prolapse.*** If the wound is too big or the wound architecture is not just right, the iris can prolapse out onto the conjunctiva, causing damage to the iris and challenges for the surgeon.

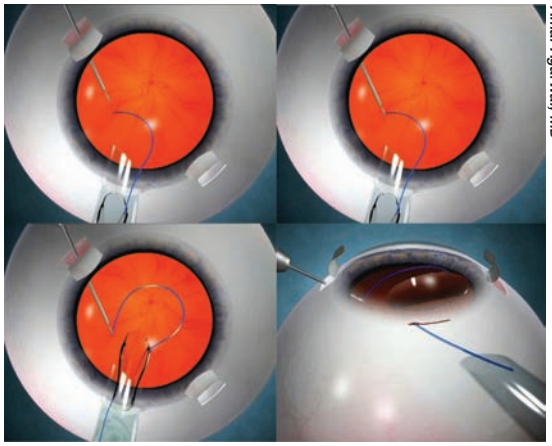
"Floppy iris syndrome is probably the number one risk factor for iris prolapse, especially when coupled with poor wound construction," says Dr. Weinstock. "If the wound is too short or not biplanar or triplanar, the iris can easily pop out. Another risk factor is having the wound size not match up well with the size of your instruments.

If the wound is too big relative to the phaco needle and the sleeve you're putting through it, you'll leave extra room for fluid to squeeze out—and the iris will follow the fluid. That's one reason I use bimanual surgery; the wound size matches the instrument exactly. In addition, the wounds are very small, so there's physically no way for the iris to get out of the eye.

"If the iris does prolapse, act quickly," he continues. "The longer the iris stays out of the eye, the more iris tissue you'll lose and the less chance the iris will look natural afterwards. It will have transillumination defects and the sphincter muscle will be damaged, and the incident could have a very irregular, visually significant cosmetic impact.

"If the iris prolapses, one strategy that can buy you a little time is to put a dispersive viscoelastic such as Healon GV or Viscoat into the eye subincisionally and blow the iris back into the wound posteriorly," he notes. "This can hold it in place temporarily by acting as a blockade. If you feel that there's a risk of destroying the iris, another strategy is to use viscoelastic to push the iris back into the eye, suture the wound and make a fresh wound with better architecture next to it."

Dr. Weinstock points out that one factor that can lead to an iris prolapse is having the pressure inside the eye too high at the end of the case. "Overinflation at the end of surgery—especially if the patient has floppy iris syndrome—can blow the iris anterior and out through the wound, or wounds," he explains. "If you see this happening, before you try to use viscoelastic or BSS to push the iris back in, go to your smaller wound and decompress the eye to soften it. This will relieve the pressure and the iris usually falls back in.



Amar Agarwal, MD

If there's no useable capsule remaining after a rupture, a good alternative is to place a posterior chamber IOL using glued intrascleral haptic fixation. Above: Leading haptic externalization. Top left: The haptic is outside the cartridge; glued-IOL forceps are ready to grasp the haptic tip. Top right: Haptic tip caught with the forceps. Bottom left: Injection of the IOL continues until the optic unfolds inside the anterior chamber. Bottom right: Haptic externalization started. (Facing page: Managing the trailing haptic.) Both figures copyright Elsevier, Inc.; used with permission.

"If I have wound prolapse during a case, I almost always put in a suture at the end of the case," he adds. "That's because if the eye were to collapse postoperatively, that iris is going to come right out. It has already shown a tendency to do that, and it's already weakened."

• ***The syringe tip comes off.*** "This is most likely to occur if you use a non-Luer-locked syringe, or fail to check that the connection is secure before surgery," notes Dr. Weinstock. "If the syringe tip comes off in the eye it can cause damage and hemorrhaging inside the eye, possibly an iridodialysis where it rips the iris root away, or a cyclodialysis cleft. In theory the needle could even penetrate through the iris and tear the retina. If you ever encounter this during surgery, make sure to do a peripheral retinal evaluation afterwards and check everything inside the eye. Treat the accident as a penetrating trauma.

"Obviously, the best solution here is prevention," he adds. "Use Luer-locked syringes and make sure that the tip is screwed down very tight. Double-check that yourself, every time you go into the eye. The most common time for this to happen is if there is a clog in the cannula tip, so always ensure that the cannula is patent with a quick test squirt before you enter the eye."

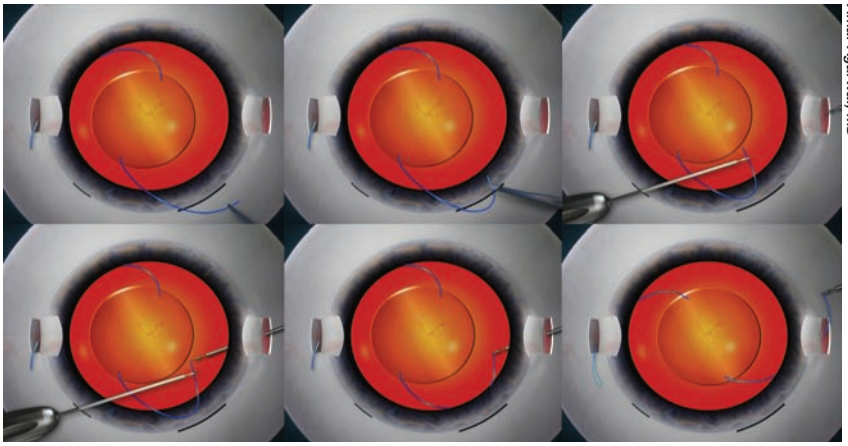
Capsule-Related Concerns

Some of the most potentially devastating complications involve the anterior or posterior capsule or the zonules.

• ***If the capsulorhexis veers outward.*** "If this happens, the way you respond should depend partly on what you think is the cause," says Dr. Rostov. "For example, it could mean that the chamber is shallowing. In that case, adding more viscoelastic can be helpful. It could indicate that something is raising the patient's IOP. Is the patient's blood pressure going up? Is the lid speculum causing undue pressure on the eye? Is the patient holding his breath? Is the patient anxious? If you suspect the latter, a little more IV sedation on board can be helpful.

"If none of these factors is present, and you suddenly find that you can't really tell where your capsulorhexis is going, you can decide to prolapse the nucleus into the anterior chamber and do supercapsular phaco," she continues. "Or, you can add relaxing radial incisions into the capsulorhexis itself to relieve stress on the capsule, and then proceed with your phaco. You can also make relaxing incisions in the capsulorhexis if you decide to prolapse the nucleus out, to make it easier to move the nucleus. Another option is to inject a little Trypan blue, which stiffens the capsule tissue a little."

• ***Zonular issues.*** "In most cases, you'll know ahead of time that the zon-



Amar Agarwal, MD

Trailing haptic externalization. Top left: Trailing haptic caught with the first pair of glued-IOL forceps. Top middle: Haptic flexed into the anterior chamber. Top right: Haptic transferred from first forceps to the second forceps, which are inserted through the side port, using the handshake technique. Bottom left: First forceps is passed through the sclerotomy under the scleral flap. Haptic is transferred from the second forceps back to the first. Bottom middle: Haptic is pulled toward the sclerotomy. Bottom right: Haptic is externalized.

ules are going to be an issue," says Dr. Rostov. "This is more likely in a patient with exfoliation, a smaller pupil, a traumatic cataract or a very dense cataract. If you do run into trouble, be generous with your viscoelastic and use capsular tension rings and/or segments as necessary. Don't try to pull the bag away from the area of weakness; pull toward the area of weakness, so you don't cause a bigger problem."

• ***Managing a posterior capsule rupture.*** "If you notice a sudden deepening of the anterior chamber, that may indicate a posterior capsular tear or rupture," Dr. Rostov points out. "If that occurs, be sure you don't remove the irrigating handpiece from the eye. You want to keep the pressure up inside the eye; you don't want to withdraw it and suddenly change the pressure gradient."

Dr. Agarwal notes that if he's doing phaco and the posterior capsule ruptures with the nucleus still inside the bag, he has several options. "One option is to extend the incision and remove the nucleus," he says. "A second option is to extend the incision, apply a Sheets glide under the nucleus and then remove the nucleus pieces. Either way, once the incision is extended, after removing the nucleus I have to suture the wound, then do cortical removal and then open up the eye again for IOL implantation.

"In this situation, we've started using a technique we call IOL scaffold," he says. "First, we bring the nucleus up above the iris. Then, we inject a three-piece foldable IOL in such a way that the IOL lies between the nucleus and the iris. The IOL prevents the nucleus from going down onto the vitreous. Now, with the phaco probe, I can emulsify the nucleus while the IOL acts like a scaffold, a temporary platform. Once the nucleus and cortex are removed, I can move the lens into the sulcus. (This technique was recently described in the journal *Ophthalmology*.)[1]

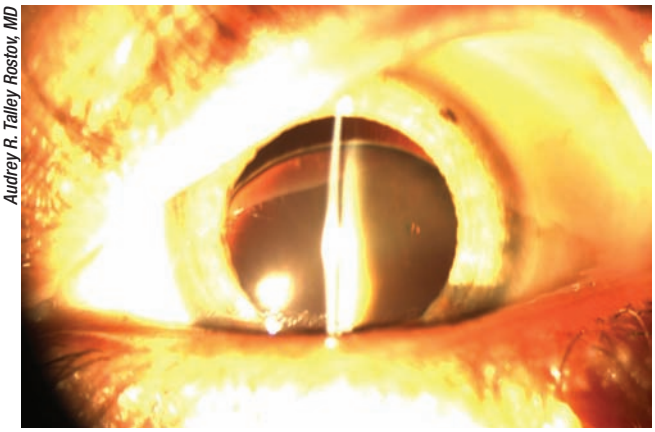
"It's also important to know how to glue an IOL in place, in case you have no useable capsule after a rupture," he continues. "In this situation, a surgeon might consider several other options, such as leaving the patient aphakic, implanting an anterior chamber IOL or suturing an IOL to the iris. However, our preferred alternative is glued intrascleral haptic fixation of a posterior chamber IOL.

"In our technique we implant the lens, externalize the haptics, create a Scharioth intrascleral pocket, tuck the haptics in and then apply Tisseel fibrin sealant glue, which is made from human plasma," he explains. *[See example, left and facing page.]* "Once this is done, the eye is sealed and the case is completed. The advantage of a glued IOL is that it's fixed firmly in position. There's no movement of the IOL at all—no pseudophacodonesis."

Dr. Agarwal notes that the best way to deal with a posterior capsule rupture is to prevent it in the first place. "One of the best ways to prevent this type of complication is by using pressurized infusion," he says. "In standard phaco surgery the fluid going into the eye is moved by gravity. Back in 1999 we developed a system that pumps air into the bottle, so that the amount of fluid that comes out is much greater—with the result that you never get any surge or have a chamber collapse that leads to posterior capsule rupture. This is called pressurized infusion, or gas-forced infusion. Today, the Bausch + Lomb Stellaris has it built in, and a modification of this system is built into the Alcon Centurion phaco machine as well.

"If you use this approach, the chamber becomes deep," he explains. "If your rhexis is lost, you can bring the nucleus out of the bag. Because the chamber is deep, the phaco probe is away from the posterior capsule and away from the cornea; you can emulsify the nucleus immediately. I find this to be the best approach when performing phaco, and I use it in all of my patients."

Dr. Agarwal notes that if you don't have a Stellaris or Centurion machine, you can pressurize the infusion flow for almost no cost by purchasing an aquarium pump at a pet store, normally used to pump air into the water in a fish tank to ensure that the fish can breathe. "Take an IV tube and connect it from the aquarium pump to the IV bottle. It's a very simple and inexpen-



Audrey R. Talley Rostov, MD

This partially subluxated lens was addressed with a capsular tension ring and capsular hooks to help stabilize the capsule during the capsulorhexis. The surgeon was also prepared for the possibility of a vitrectomy, but none was needed.

sive way to achieve this result."

• ***Dropped nucleus.*** On rare occasions, despite the surgeon's best efforts, the nucleus may drop to the back of the eye. "In that situation, finish up the case, unless you have a retina person onsite who can retrieve the nucleus or you yourself feel comfortable retrieving it," says Dr. Rostov. "Do your limited anterior or pars plana vitrectomy and insert an IOL of your choice, probably a sulcus IOL in this situation. Then close up, suture the wound and call your retina person and arrange for the patient to be seen by him or her the next day. The retina person can decide when to retrieve the nucleus."

Stay Calm and Carry On

Maybe the most important advice when something does go wrong is to monitor your own reaction. "When a complication occurs, especially a serious one, stop and take your own pulse," suggests Dr. Rostov. "Remember that you're still in charge. Take a deep breath and then proceed with the case. It's important to keep any anxiety you have under control; otherwise your hand or foot can shake, and you might not be able to think clearly. Also, seeing that you're calm will help your OR team remain calm." REVIEW

Drs. Rostov, Agarwal and Weinstock have no financial interest in any product mentioned.

1. Narang P, Agarwal A, Kumar DA, Jacob S, Agarwal A, Agarwal A. Clinical outcomes of intraocular lens scaffold surgery: A one-year study. Ophthalmology 2013;120:12:2442-8.

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Femtosecond Cuts into Cataract Practices

Walter Bethke, Managing Editor

The cutting-edge technology has gained in popularity in our annual survey.

The femtosecond laser continues to make inroads in cataract surgery. Despite controversy over its expense and logistics, the percentage of surgeons on our annual e-survey on cataract surgery who say they use the femtosecond laser jumped from 8 percent last year to 23 percent on the current survey. Though there are many vocal dissenters, some of the reasons given for its appeal are the quality of its cuts and its contribution to decreasing the amount of phaco energy used during cases. On the other hand, the survey surgeons seem less keen on high-tech intraoperative aberrometry, with only 9 percent using it. In addition to these technological points of interest, surgeons responding to this year's survey also weighed in on other techniques and methods they like most.

The e-mail survey on cataract surgery was opened by 1,583 of 10,000 subscribers to *Review*'s electronic mail service (16 percent open rate) and, of those, 142 filled in their answers.

High-tech Techniques

The 23 percent of respondents who are using the femtosecond say they're experiencing various benefits from it.

"It's good for Fuch's, zonular instability, mature cataracts and the treatment of low amounts of astigmatism," says Chambersburg, Pa., surgeon David Ludwick. "It results in a much higher percentage of patients with 20/20 or 20/25 postop uncorrected visual acuity." Another surgeon, who wished to remain anonymous, says it creates a better central continuous curvilinear capsulorhexis and "its nuclear fragmentation reduces phaco energy." One surgeon says he's very likely to begin using the femtosecond in the coming year. "I want to offer it as a learning option for our residents," he says. "I look forward to its use in limbal relaxing incisions." John Sheppard, MD, of Norfolk, Va., uses the femtosecond laser for everything from the entry wound and capsulorhexis to nucleus fragmentation. "It gives precise wound management," he says. "It's high-tech, a practice builder and fun." But he adds that it also has drawbacks. "Its expensive, and it slows surgery," he says. "Also, cortex extraction is difficult."

However, 73 percent of the respondents who don't currently perform femtosecond-assisted cataract surgery say they're unlikely to begin performing it in the next 12 months, and many have very strong opinions about why. "I don't see a true benefit to patients yet," says Kentucky ophthalmologist Brad Ballard. "It's not much safer, the

outcomes are no better, and it costs them more money. Right now, it appears to be a marketing benefit for ophthalmologists." A surgeon from New Jersey feels similarly, saying, "It's too expensive and doesn't increase the safety of the procedure. It's also not covered by Medicare and I find it unethical to promote it for correction of astigmatism when, in fact, in many cases little or no astigmatism exists." Cost is also an issue for another cataract surgeon. "It's an unreimbursed cost in my patient population, which cannot even afford their Medicare copay," he says.

Scott Corin, MD, of Dartmouth, Mass., is also looking for results before changing his way of operating. "A $500,000 machine to do what two $15 blades and a $300 forceps can do just as well?" he opines. "It is all marketing and zero science." A surgeon from Nebraska hopes that there's more than marketing to the technology. "There's been no proven benefit in peer-reviewed studies," he says. "I have major concerns about our profession being driven by industry and greed as opposed to demonstrated patient care and improved outcomes. Femto is a very 'cool' technique, but it requires increased OR time, increases healthcare expense and until good data exists to demonstrate patient benefit, should not be promoted as providing it. It will undoubtedly improve over time and may very well become standard of care if demonstrated benefits for patients are shown in the future."

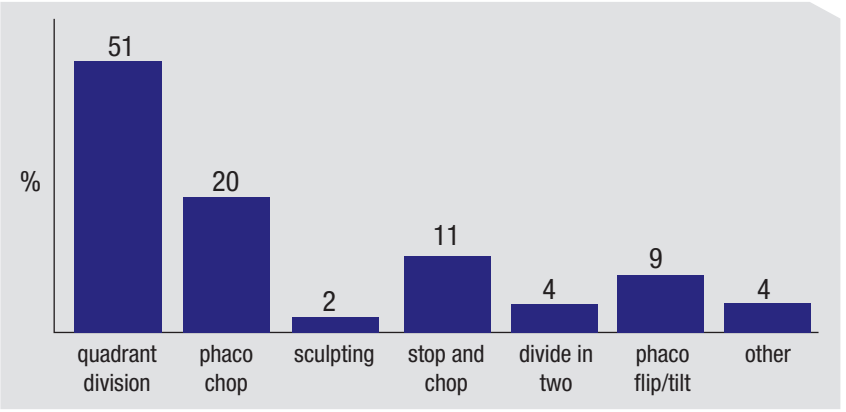
Turning toward other cataract surgery technology, surgeons also weighed in on intraoperative wavefront aberrometry. Only 9 percent say they currently use it, and 75 percent of the non-users say they're unlikely to begin using it in the coming year. Most of the reasons given for not adopting it relate to either cost/benefit ratio or a surgeon's facility just not springing for it.

"The startup cost [is one reason]," says a surgeon from Arkansas. "And it gives a 2 to 3 percent increase in postop refractive prediction outcome when my outcomes are at 96 percent already. Patients are happy, and I've got excellent outcomes in a wide range of patients." Juan Nieto, MD, of Dubuque, Iowa, is in the same boat, saying, "I'm not convinced that it will improve on my outcomes." A surgeon from Arizona also feels it might be overkill. "I can't remember the last time I had a refractive surprise using conventional measurements preop," he says. One surgeon from Alabama speaks for a group of surgeons who might like to use it but their facilities won't invest in it. "My hospital won't buy it," he says. One surgeon from New York thinks the method by which the device gets its data might give him problems. "It's a waste of time," he says. "The results are not good if the cornea is starting to swell." Finally, a surgeon from Baltimore succinctly sums up many of his colleagues' doubts by saying, "I don't feel the juice is worth the squeeze."

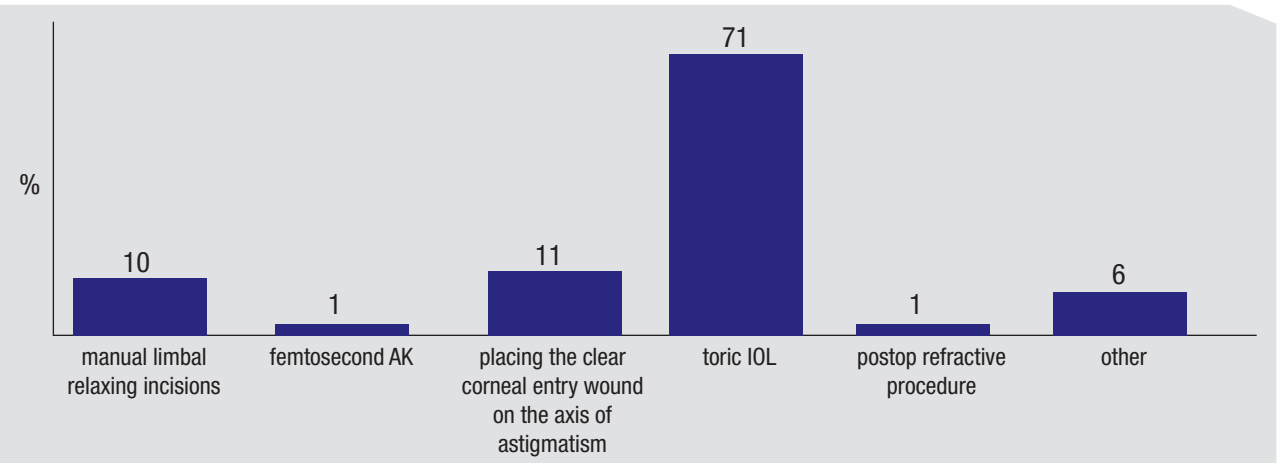
For the surgeons who use intraoperative aberrometry, or who are raring to try it, they say they see a benefit in the technology. "I think it's finally getting improved enough to help our outcomes," says Luther Fry, MD, of Garden City, Kan. "We are debating as to whether to wait until the Clarity HOLOS [intraoperative aberrometer] is available." A surgeon from Wisconsin also looks forward to using it. "It would improve our accuracy for post-refractive surgery eyes and for toric IOL implantations," he says. A surgeon from New York already uses it, and likes his results. "I feel that it's a big plus for advanced-technology IOLs," he says. "And, it's a necessity for post-refractive surgery cataract patients." Terry Croyle, MD, a surgeon from Moultrie, Ga., who is likely to add it to his practice, says it complements other high-tech additions. "I've added a femtosecond cataract package," he says. "This seems to be a logical extension of a premium or refractive cataract procedure." Steven Stiles, MD, of Tarzana, Calif., uses it and likes it, but warns to be on-guard for occasional hiccups. "It works very well most times," he says. "However, it's certainly not infallible. I just had a case where the ORA corroborated my office power but I wound up with -2 D when I was looking for plano!"

Finally, Robert Lehmann, MD, of Nacogdoches, Texas, says it feels as if history is repeating itself as new technology comes on-line. "For those who think the femtosecond laser and intraocular aberrometry aren't valuable," he says, "remember LASIK before femto and planned ECCE before phaco!"

Preferred Phacoemulsification Technique



Preferred Way to Manage Pre-existing Astigmatism in a Cataract Patient



Astigmatism Management

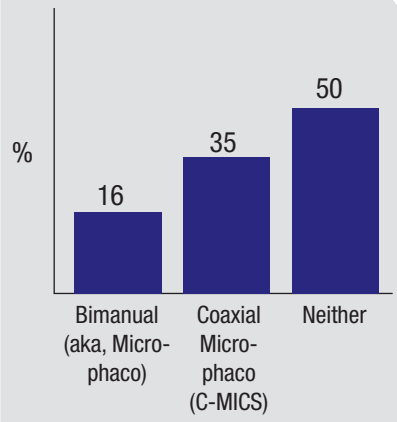
Toric IOLs continue to hold sway in terms of treating a patient's astigmatism, with 71 percent of the respondents saying toric lenses are their preferred method. Ten percent prefer manual limbal relaxing incisions, 11 percent like to place the clear corneal entry wound on the astigmatic axis, 1 percent use a postop refractive procedure and another 1 percent use femtosecond astigmatic keratotomy. Six percent say they choose some other method.

"Toric IOLs give excellent results and add little complexity to the procedure," says a surgeon from New Jersey. "Arcuate incisions are less consistent and can exacerbate dry eye." A surgeon from New York thinks lenses yield the best results, saying, "They're an accurate method to fix most levels of astigmatism."

For the surgeons who prefer manual LRIs, though, they think they're the right tool for the job. "Using manual LRIs, I can control the astigmatism quite well," says Christopher Papp, MD, of South Lyon, Mich. "And, it's cheaper for the patient and the medical system in general." A surgeon from Oregon also appreciates the cost-effectiveness of incisions. "They work," he says. "And they're not dependent on expensive equipment."

Some surgeons, though, will segment their astigmats based on the level of their astigmatism, and choose a procedure based on that. "Toric IOLs are effective for larger amounts of astigmatism," says a surgeon from Maryland. "I also uses manual LRIs, femto AKs, incisions on the steep axis and occasionally an in-office LRI." Russell Wolfe, MD, of Hollywood, Fla., says he starts with spectacles and works up from there. "I most commonly treat astigmatism with glasses," Dr. Wolfe says. "For small amounts I recommend arcuate femtosecond keratotomy, and for larger amounts, the toric IOL." Ivan Mac, MD, of Charlotte, N.C., says the amount of astigmatism makes the difference for him. "For patients with up to 1.5 D, femtosecond AK is very accurate," he says. "Over this level, I prefer toric lenses."

Bimanual and C-MICS Use



Cracking the Nucleus

For attacking the cataract, 51 percent of surgeons prefer quadrant division, a fifth like phaco chop, 11 percent use mainly use stop-and-chop and 9 percent like phaco flip/tilt. For the rest, 4 percent divide the nucleus into halves, 2 percent perform sculpting and 4 percent choose some other method.

"I'm ambidextrous," says a surgeon from Texas who prefers quadrant division. "So, I can sculpt, rotate, sculpt, phaco the quadrant, rotate, chop and then chop/phaco the remaining pieces. My hands are at 3 and 9 o'clock." A surgeon from Florida thinks quadrants work best in terms of safety. "The quadrant size is more manageable for phaco within the bag," he says, "thus keeping the ultrasound power farther away from the endothelium." A surgeon from Connecticut says quadrant division is "quick, safe and simple." Dr. Lehmann explains why quadrant division is so popular. "It's efficient," he says. "I groove, split in half, then crack

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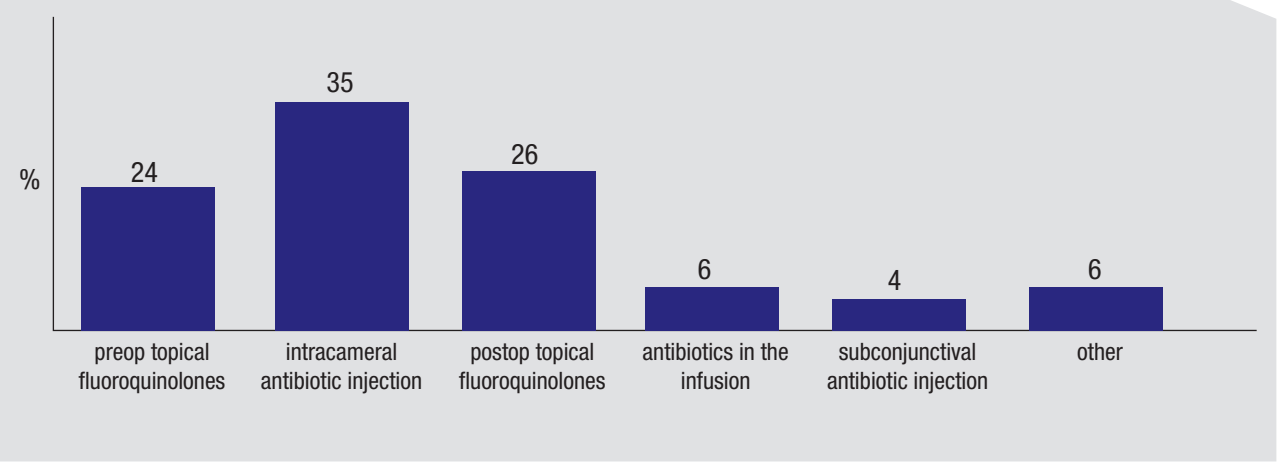

the first half into quarters. Then, the second half is removed without further cracking."

The surgeons who like phaco chop think it has strong points, as well. "It's efficient, versatile, minimizes phaco time and the risk of capsular issues, and is friendly to the endothelium," says a surgeon from Georgia. Florida's Dr. Wolfe says, "I find that phaco chop is efficient, allowing the removal of various densities of cataracts with relatively low phaco times." Another surgeon from Georgia likes phaco chop's versatility. "I can use horizontal chop for any cataract hardness," he says. "The second instrument tip is blunt for capsular protection, and I use less phaco power than with divide and conquer."

The surgeons who like a stop-and-chop technique highlight its safety. "I use stop-and-chop, and then Jim Davison's 'inside-out phaco' technique, doing most of the firm nucleus emulsification posterior to the iris," says Dr. Fry. "I think my corneas look better with this technique, even though it takes a little longer."

Preventing Infection

In recent years, data on antibiotics in the infusion has led to debates about the best way to prevent infection with cataract surgery (aside from the use of povidone iodine). Thirty-five percent of the surgeons on our survey say that they think intracameral antibiotic injection is best, followed by 26 percent who prefer postop topical fluoroquinolones, 24 percent who like preop topical fluoroquinolones, 6 percent who put antibiotics in the infusion line and 4 percent who prefer subconjunctival antibiotic injections. Another 6 percent say they prefer to use some other method of infection prevention.

"I also irrigate the fornices with copious amounts of BSS after draping and before starting surgery," says a surgeon from Illinois. "I suspect decreasing the bacterial concentration in the conjunctival fornices is helpful in lowering the risk of infection."

Surgical Pearls

In addition to commenting on specific aspects of cataract surgery, surgeons also provided their top surgical pearls for getting the best, safest results.

"I use conjunctival pledgets in the superior and inferior fornices soaked in lidocaine and marcaine for five minutes prior to surgery," says Carol Johnston, MD, of Jacksonville, N.C. "I rarely need any intraocular lidocaine unless using a Malyugin ring or a very deep chamber in a post-vitrectomy eye. Next, I use traction sutures at the site of my pledgets, which gives me great exposure and avoids dealing with eye movement and Bell's phenomenon in patients."

Since intraocular floppy iris syndrome is such a problematic complication, Dr. Fry takes steps to prevent it. "Use intracameral Shugarcaine in all Flomaxers and in all small pupils," he says. "You never know who has been exposed to alpha-1a blockers." Robert Bahr, MD, of Providence, R.I., says a possible change in technique might prove to be safer. "One-handed phaco avoids leakage from the sideport incision," he says. "And, it provides a far more stable anterior chamber as well as contact with nuclear material." A surgeon from Iowa says managing astigmatism is one of the keys. "Always do what you can to keep the postop astigmatism under 0.5 D," he says. "Also, do a Mackool incision with premium lenses that might need a follow-up LASIK for residual astigmatism."

Finally, if the stresses of a complicated cataract surgery case begin to get to you, Kentucky's Dr. Ballard says it helps to take a philosophical approach to things. "Relax," Dr. Ballard says. "You could have been an OB-GYN." REVIEW

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

Important Risk Information about LOTEMAX® GEL

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

Please see brief summary of full prescribing information on adjacent page.

References: 1. LOTEMAX GEL Prescribing Information, September 2012. **2.** Fong R, Leitritz M, Siou-Mermet R, Erb T. Loteprednol etabonate gel 0.5% for postoperative pain and inflammation after cataract surgery: results of a multicenter trial. *Clin Ophthalmol.* 2012;6:1113-1124. **3.** Shaikh R, Singh TRR, Garland MJ, Woolfson AD, Donnelly RF. Mucoadhesive drug delivery systems. *J Pharm Bioallied Sci.* 2011;3(1):89-100. **4.** Data on file, Bausch & Lomb Incorporated. **5.** Coffey MJ, Davio SR. Viscoelastic and sedimentation characterization of loteprednol etabonate ophthalmic gel, 0.5%. Poster presented at: Association for Research in Vision and Ophthalmology (ARVO); May 6-10, 2012; Fort Lauderdale, FL. Poster #6283/D1143. **6.** Lotemax Prescribing Information, April 2006. **7.** Rajpal RK, Roel I, Siou-Mermet R, Erb T. Efficacy and safety of loteprednol etabonate 0.5% gel in the treatment of ocular inflammation and pain after cataract surgery. *J Cataract Refract Surg.* 2013;39:158-167.

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INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Intraocular Pressure (IOP) Increase

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

Cataracts

Use of corticosteroids may result in posterior subcapsular cataract formation.

Delayed Healing

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

Bacterial Infections

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

Viral Infections

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

Fungal Infections

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

Contact Lens Wear

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

ADVERSE REACTIONS

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C.

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

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

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

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment Of Fertility

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

PATIENT COUNSELING INFORMATION

Administration

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

Risk of Contamination

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

Contact Lens Wear

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

Risk of Secondary Infection

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

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Compounded Drugs: Understand the Risks

Michelle Stephenson, Contributing Editor

Ask questions—a lot of questions—before you rely on a compounding pharmacy to supply drugs.

During the past few years, compounding pharmacies have received a lot of press. In 2012, a story involving a compounding pharmacy received national attention when as many as 14,000 people received contaminated injections of a steroid medication. A total of 751 patients contracted meningitis or other infections from the injections, and 64 people in 20 states died.[1]

A year before this nationwide outbreak, ophthalmologists at Bascom Palmer Eye Institute in Miami were treating patients who had received intraocular injections of tainted Avastin. As early as November 2011, Roger A. Goldberg, MD, MBA, reported a series of 12 patients who developed *Streptococcus* endophthalmitis after injection with intravitreal bevacizumab.[2,3] These 12 patients presented to Bascom Palmer with severe intraocular infections one to six days after receiving an intravitreal injection of bevacizumab. The injections occurred at four different clinics in south Florida, but all doses of bevacizumab were prepared by the same compounding pharmacy in Broward County.

None of the patients received injections at Bascom Palmer, but nine patients presented to its tertiary-care ophthalmic emergency room for treatment, and three others were seen in consultation. Initially, all patients were treated with vitreous tap and injections, and eight patients later received a vitrectomy. Microbiology cultures for 10 patients were positive for *Streptococcus mitis/oralis*. Seven unused syringes of bevacizumab prepared by the compounding pharmacy at the same time as those prepared for the affected patients were also positive for *S. mitis/oralis*. After four months of follow-up, all but one patient had count fingers or worse visual acuity, and seven ultimately required evisceration or enucleation.

Dr. Goldberg, who is now in practice at Tufts New England Eye Center and Ophthalmic Consultants of Boston, explains that many of the patients in the Miami outbreak of endophthalmitis were part of the same health insurance group.

"They mandated the use of a specific compounding pharmacy for their patients, and this placed the contracted retinologists in a difficult situation," says Dr. Goldberg. "They were told that they had to get their Avastin from a particular pharmacy for this subset of their patients. The syringes were labeled for each patient and were shipped to

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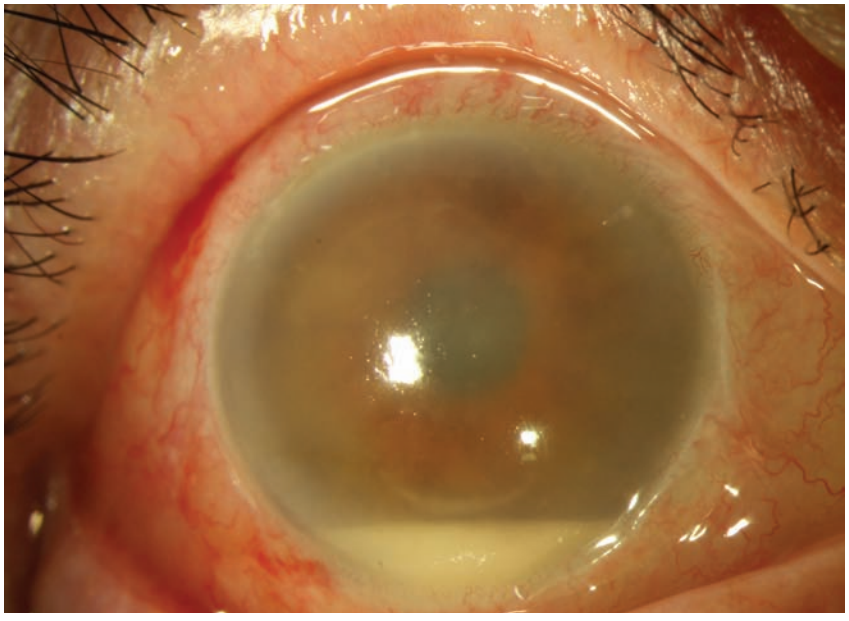

A patient who presented at Bascom Palmer Eye Institute with endophthalmitis caused by an intraocular injection of tainted Avastin.

the doctor's office in advance of the patient visit. One patient expected to only need an injection in one eye, so a syringe was sent for that patient. On exam, the patient had a new submacular hemorrhage in the other eye and required treatment in the fellow eye as well. The fellow eye received Avastin from another source, and this eye did not develop endophthalmitis, despite being treated on the same day. So, we know it wasn't the doctor's injection technique that caused the infection."

In another practice, four patients from this medical group were no-shows for their appointment, and Dr. Goldberg and his colleagues were able to track down the four unused syringes, and they were culture-positive with the same bacteria. "We know that the bacteria came in the syringes. It was not introduced by the physicians," he adds.

Reports in the media have increased awareness about compounding pharmacies and how they operate. "To be honest, I didn't know much about the compounding process and the regulations and guidelines associated with it until this happened," Dr. Goldberg says. "In ophthalmology, since the 12-case outbreak of endophthalmitis, we have seen several more small outbreaks associated not just with Avastin, but with triamcinolone and brilliant blue dye. Awareness of the issue has grown over the past few years, and more than a dozen compounding pharmacies have recalled Avastin syringes and other drugs due to sterility concerns."

Compounding pharmacies are not all the same in terms of their size, their breadth and how many states they operate in. "The south Florida endophthalmitis outbreak originated from a relatively small pharmacy; the nationwide meningitis outbreak was a much larger pharmacy," Dr. Goldberg says. "Both had problems with how they were handling drugs, inspecting equipment, maintaining sterility and ensuring sufficient documentation. One of the issues that the investigators in south Florida had was tracking down all of the syringes that were made at the time that these contaminated syringes were made. Because the documentation wasn't in order, it made the Department of Health inspector's job more difficult."

He notes that Bascom Palmer has prepared nearly 100,000 Avastin syringes without any incidence of contamination, so they can be prepared safely. "The CATT trial compared the effectiveness of Avastin with Lucentis, and there were no more episodes of endophthalmitis with Avastin than there were with Lucentis," he says. "Avastin would be more expensive if it was prepared in the way that the CATT trial prepared it, but still a lot less than $2,000, which is what Lucentis costs."

Legislation

On November 27, 2013, President Obama signed the Drug Quality and Security Act. The legislation was aimed at regulating compounding pharmacies and establishing a track-and-trace pedigree system for drugs.

Under the DQSA, a compounder can become an "outsourcing facility," though this is not required. Outsourcing facilities must comply with current good manufacturing practices requirements; will be inspected by the Food and Drug Administration according to a risk-based schedule; and must meet certain other conditions, such as reporting adverse events and providing the FDA with certain information about the products they compound.

If compounders register with the FDA as outsourcing facilities, patients could be assured that drugs from those facilities were subject to CGMP requirements and federal oversight.

The FDA anticipates that state boards of pharmacy will continue their oversight and regulation of the practice of pharmacy, including traditional pharmacy compounding.

"It is too soon to tell what impact

the law will have on patient safety," says David G. Miller, RPh, executive vice president and CEO of the International Academy of Compounding Pharmacists. "There are components in the law that should help. First and foremost, the new outsourcing facility registrations are designed to give the FDA clear authority and knowledge about companies that are producing sterile medications/compounds and placing them into the marketplace throughout the country. From a regulatory oversight standpoint, that is one definite step in the direction to improve patient safety. There are new sections of the law that will require the FDA to create lists of medicines that should not be compounded because either they represent a safety issue to patients or because making the medications is so difficult that it presents a potential risk. These are clear steps forward in terms of protecting patient safety."

The act also implements track and trace, which will be phased in. "This is the process by which we protect the entire drug supply system by having a formal reporting from the supplier of the raw ingredient to a manufacturer and from the drug manufacturer to a wholesaler and from the wholesaler to the pharmacy or the physician so that we can prevent the introduction of contaminated or counterfeit drugs into our drug supply system, so that's a huge step forward for us as a country. The law is not just about compounds, it's about all prescription drugs," Dr. Miller adds.

Charles Leiter, PharmD, president of Leiter's Compounding Pharmacy in San Jose, Calif., cites quality control as the most important issue in a compounding pharmacy. "Signing up for the FDA program is voluntary, and states have their own rules, so the 50 separate states will be doing 50 different things," he says. "I don't think this new legislation has a whole lot of teeth. It just adds another level of complexity. There is always going to be someone out there trying to sell more drug and make more money and cut more corners. We have actually increased our prices to cover our increasing testing of drugs and processes. The FDA really needs to crack down and make sure pharmacies are providing the best possible product that they can. It's pretty obvious that there were people out there who didn't know what they were doing."

Dr. Goldberg agrees. "Different states have different degrees with which they mandate certain things from their compounding pharmacies, including the use of personal protective equipment and the frequency with which equipment has to be inspected, and there are striking differences. Perhaps this is a type of situation where there needs to be more consistency across state lines," he adds.

He also notes that there is uncertainty regarding whether an individual patient-specific prescription will be required for each Avastin syringe. "Many states have put this requirement in place to keep compounding pharmacies from acting like manufacturers," he says. "Each syringe produced has to be earmarked for a particular patient. The American Society of Retina Specialists has expressed concern that this will limit patient access to Avastin."

In chronic disease conditions like macular degeneration, where patients sometimes need to be seen and receive injections every month, Dr. Goldberg says it's not realistic to have them come in every month and then have them come back a week later for their injection. "It's just too great of a burden on the patient and on the practice," he says. "Complicating this issue is that several insurance companies in various states are saying that they will only reimburse the branded drugs if Avastin has been tried and doesn't work. The [ASRS] is also fighting those policies. We want to have Avastin that is safe and readily available, but we don't want to be mandated to use it. Ultimately, it is in the best interest of our patients if we are able to customize care for each patient."

Do Your Homework

Even with the new act in place, it is up to physicians to determine which compounding pharmacies to use. "When evaluating a potential compounding pharmacy, use a checklist," says IACP's Dr. Miller. "For example, before you select a pharmacy, ask if the pharmacy is appropriately licensed. Is it accredited? Have there been any disciplinary actions? Make sure when you are entering into a relationship with a compounding pharmacy that you are focusing on who and what and how and not on where patients can get a drug at the lowest cost. You want physicians to have the same comfort level with their compounding pharmacy that they have with other physicians to whom they are referring patients. The decision should be based on knowledge, understanding, reputation and relationships, not based on price."

In 2011, the IACP developed a new assessment questionnaire to assist hospitals and physicians in identifying and evaluating compounding pharmacies. This comprehensive checklist is based on *United States Pharmacopeia* standards and can be accessed online and printed out.[4]

Dr. Miller notes that everyone should be doing their homework whenever decisions are being made about a patient's health care. "There are two ways to find out

(continued on page 83)


Glaucoma in the Clinic: What Not to Miss

With more patients and less time, clinicians need a high-priority checklist to make sure nothing important is overlooked.

Jeffrey M. Liebmann, MD, New York City

Since early glaucoma is typically asymptomatic, detection of the disease depends almost entirely on the clinical examination. In contrast, a patient suffering from macular degeneration will probably know that something is amiss; with glaucoma it may only be late in the disease that the patient has a complaint. Furthermore, even after a patient has been diagnosed, progression can be subtle.

Strategies that would help diagnose other diseases may be less helpful when the problem is glaucoma. For example, most physicians are trained to take a careful history as an aid to making a correct diagnosis. Occasionally, a patient at risk for glaucoma may be able to contribute some useful information, such as a strong family history that suggests increased risk. This is a rarity; even the most knowledgeable patients may be unaware that other family members are affected. Although some systemic conditions such as migraine, Raynaud's phenomenon or low systemic blood pressure, African or Latino ancestry, older age or myopia might suggest a higher risk for glaucoma, the history is generally not as helpful as we might wish.

In most cases, detecting glaucoma requires an eye examination. Early in the course of the disease, this means looking at the optic nerve for signs of glaucomatous disease, such as damage to the disc rim or disc hemorrhages. (Fifty percent of the progression found in the Ocular Hypertension Treatment Study was discovered during the optic nerve exam.) Of course, even that isn't foolproof; sometimes it's not possible to be certain that the nerve is suffering early damage.

Given these realities, the best way to ensure that glaucoma and progression don't go undetected is for the clinician to have a list of things at the top of his mind when faced with a patient. Here, I'd like to offer such a list, divided into six clinical pearls of "what not to miss:" 1) Try to make the best diagnosis. 2) Assess for major glaucoma risk factors. 3) Use all the tools at your disposal to detect progression. 4) Don't underestimate a patient's life expectancy. 5) Don't assume that glaucomatous damage will only be peripheral. 6) Don't miss a good screening opportunity.

Make the Right Diagnosis

A simple screening, such as taking the patient's intraocular pressure, may uncover some patients with early primary open-angle glaucoma. But without a more complete exam, other forms of the disease will go undetected:

- ***Normal-tension glaucoma.*** Fifty percent of patients who have glaucoma may present with a normal pressure at the time of diagnosis. Many physicians apply the term "low-tension glaucoma" to these patients. Because of these normal pressures, screening by pressure alone would miss half of the cases of glaucoma coming into your office. The only way to catch those patients is by examining the optic nerve. That makes it an essential part of the exam.
- ***Angle-closure glaucoma.*** Missing angle-closure glaucoma can have serious consequences, in part because you may end up treating the patient as if he has open-angle glaucoma. The vast majority of narrow-angle patients can be cured by laser iridotomy, but if you misdiagnose and give the patient medications instead, you may fail to

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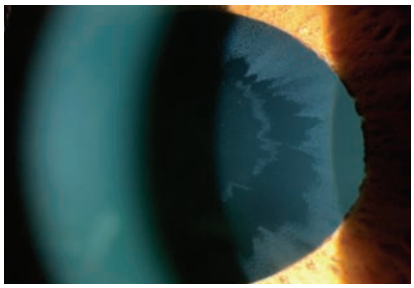


Exfoliation material on the anterior lens capsule. Patients with exfoliation progress more rapidly, have higher pressures and have a high risk of complications during cataract surgery.

prevent progression and make the disease more difficult to manage.

Unfortunately, early in the course of angle closure the IOP may be normal, with an area of iris-trabecular contact that's easy to miss. The way to ensure that angle closure doesn't escape your notice is to always do careful gonioscopy. Gonioscopy using an indentation gonioprism with an artificial tear interface is very easy to do and takes less than 15 seconds once you're in the habit of doing it. (Dynamic gonioscopy, in which you indent the cornea, allows the clinician to differentiate synechial angle closure and appositional angle closure).

Virtually every patient should have gonioscopy at least once in a lifetime, preferably the first time you meet the patient. Even if the patient doesn't have angle-closure glaucoma at the time of the exam, gonioscopy will tell you whether he has an anatomically narrow angle, putting him at greater risk. (Part of our job, after all, is to risk-stratify patients and determine how quickly they should return for the next exam.) If you discover that a patient has an anatomically narrow angle, you may want that person to come back in a year, so you can make sure the angle hasn't narrowed further and turned into angle closure. On the other hand, if the patient has a wide-open angle, she may not need gonioscopy again for five or more years. In either case, gonioscopy should be done again at some point because the angle can change over time.

One alternative to gonioscopy is using an imaging technology such as optical coherence tomography to visualize the angle. However, OCT has limitations in this context. You can't use indentation to see its effect on the angle; it takes more time than gonioscopy; and it's a very expensive piece of equipment. I find gonioscopy to be quick, easy and effective.

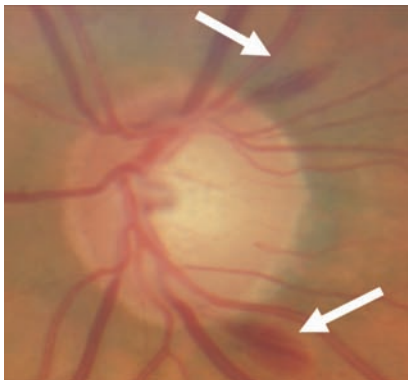
• ***Exfoliation glaucoma.*** Another sign you don't want to miss is exfoliation. Most of these patients will have normal pressure when you first meet them, but they are at high risk for the disease; patients with exfoliation progress more rapidly, have higher pressures and also have the greatest risk of complications during cataract surgery. It's a critically important glaucoma diagnosis.

There are several steps you can take to ensure that you don't miss exfoliation. Before the dilation, carefully examine the pupillary border for exfoliation material; once the eye is dilated, carefully examine the anterior lens capsule to make sure there's no exfoliation material present. (Because of the association with problems during cataract surgery, this protocol is important for cataract surgeons as well.) Pay attention to how well the eye dilates. If the pupil doesn't enlarge as much as you expect, check for exfoliation; patients with exfoliation usually don't dilate as well. Also, look for splotchy trabecular pigmentation when doing gonioscopy—another signal that exfoliation may be present.

If you find that exfoliation is present, the patient should be examined every year for glaucoma, as the risk is high.

Watch for Risk Factors

Signs of elevated risk can be divided into two categories: those requiring continuous surveillance and those



Disc hemorrhages are a strong risk factor for progression.

only needing a one-time assessment. Pachymetry—measuring corneal thickness—is a once-in-a-lifetime measurement. (Not every patient requires pachymetry, but every glaucoma patient and suspect does.) Of course, the thinner the cornea, the greater the risk. You should also check at least once for beta-zone peripapillary atrophy. Although this can change over time, usually you either have it or you don't. If you have it, you're at greater risk of glaucoma progression.

Other conditions require continuous surveillance. Disc hemorrhages are an ongoing concern; they are a very strong risk factor for progression. You need to look for them at regular intervals because they come and go; they may last anywhere from two weeks to four months. So, if the patient is an established glaucoma patient or suspect, you want to look at the disc at every visit. Dilation isn't necessary; you can look at the disc using a 78- or 90-D lens to check for hemorrhages. It's very quick, taking only about 10 seconds. Of course, if you find a hemorrhage you may want to follow the patient more carefully and/or advance treatment.

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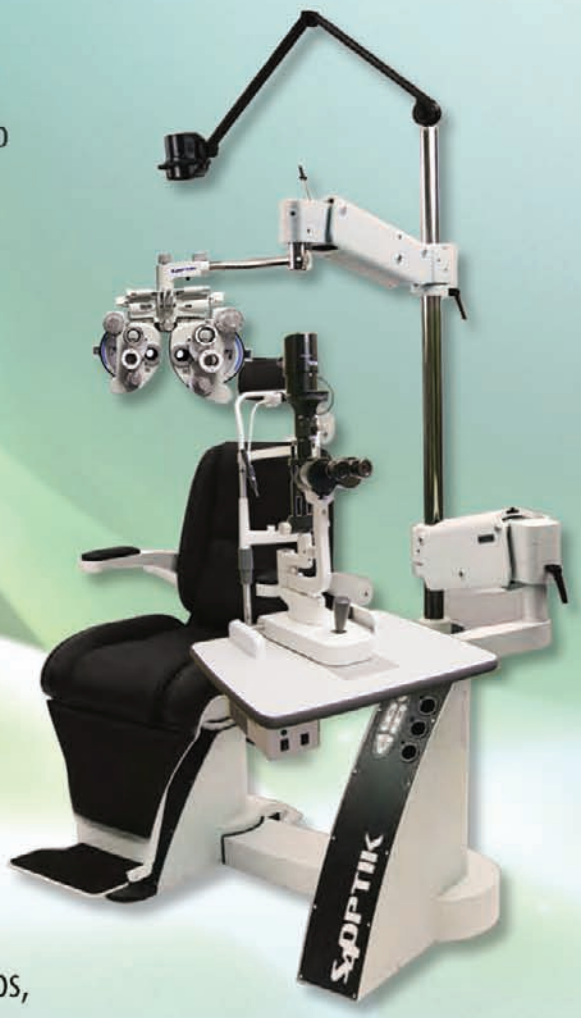

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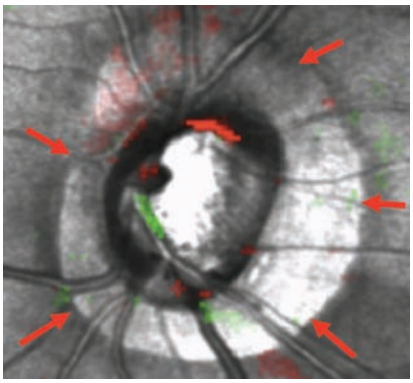
The Life Expectancy Factor

When managing a disease like glaucoma that takes a long time to unfold, the amount of time left in a patient's life is an important consideration. A slow rate of progression isn't likely to lead to blindness in a patient who is 80 years old, but a patient progressing slowly at age 40 has a serious problem; he may live another 50 years. Dealing with this is a challenging aspect of glaucoma management that every clinician struggles with. How do you make a decision for a 40-year-old that might impact him 50 years later?

One mistake to avoid is underestimating life expectancy. That's easy to do because clinicians don't always realize that life expectancy shifts the longer a person lives. At birth the average life expectancy for a man in the United States is about 75 years. But if you make it to 40, a lot of people have died along the way, so your life expectancy at that point is longer. A person who is 80 years old in the United States today has a median life expectancy of six years, which means half of the people that age will live longer than that; some of them may live 20 more years. In short, at every age group the median expectancy is probably longer than you think. (At the same time, our best risk calculator only covers a five-year period.)

Obviously, we can't predict how long any given patient is going to live, so we have to assume the patient may live longer than the average. This is also a consideration when deciding whether to pursue glaucoma surgery; you have to think about the ramifications down the road.



HRT reflectance image showing the extent of beta zone parapapillary atrophy. This atrophy indicates an increased risk of glaucoma progression.

Check for Central Damage

A fifth factor that can cause us to miss a diagnosis—or progression—is that we tend to think of glaucoma as a peripheral disease. Actually, glaucoma causes diffuse ganglion cell loss across the entire retina, and many patients have noticeable central loss; a patient with glaucoma can develop scotomas and other problems in the paracentral region. Loss of macular ganglion cells can lead to diminished contrast or reading ability. These problems will have visual impacts that are meaningful to the patient; in fact, they're the kind of problems that are associated with falls and fractures.

If a glaucoma patient does have a visual complaint, it's usually the result of central damage; peripheral loss doesn't usually draw a patient's attention unless it is bilateral and severe. Patients don't come in and say, "I have a nasal step." They come in saying "I'm having trouble reading the newspaper." If you hear a complaint like that, you should assume central function is becoming impaired.

Currently, clinicians managing glaucoma seldom check the central region. Our group has been studying glaucoma's effect on this region for the past 10 years, and we advocate testing every patient with a 10-degree visual field at some point, whether or not it looks like the patient has loss on the 24-2 test. We also recommend getting a baseline 10-degree visual field. If it's abnormal, you're aware of it. If it's not, then at least you have a baseline for future comparison. Five years down the road you might want to repeat it to see if the disease is progressing centrally rather than peripherally.

Of course, you don't have to do every test on the first day you encounter a patient; you may be seeing that patient for 30 years, so it's perfectly reasonable to do some of the baseline tests over a period of one or two years. (Furthermore, if you attempt to run every possible test in one visit, the patient will likely wind up frustrated and unhappy.)

For example, suppose you have a new patient who is a glaucoma suspect. You get two visual fields, one at the first encounter and one after six or nine months. If the second field shows no change, you could get a 10-degree visual field the next time the patient comes in. The visit after that, you can go back to the 24-2. You haven't lost anything by switching to the 10-degree test, and you haven't made the patient come back for an extra visit. But you've gotten a baseline of the central field that might be important in the future.

A key part of monitoring what's happening in the patient's central vision is to simply listen to the patient. As noted above, when damage does extend to the central field it begins to affect vision in ways that patients notice. A patient may complain of difficulty reading or say that things look washed out. An astute patient may specify that his contrast

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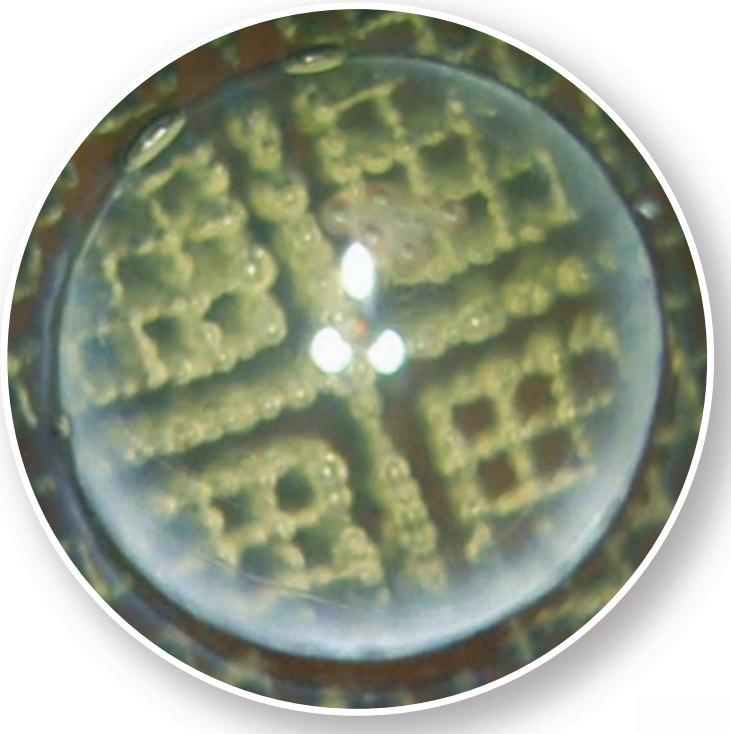

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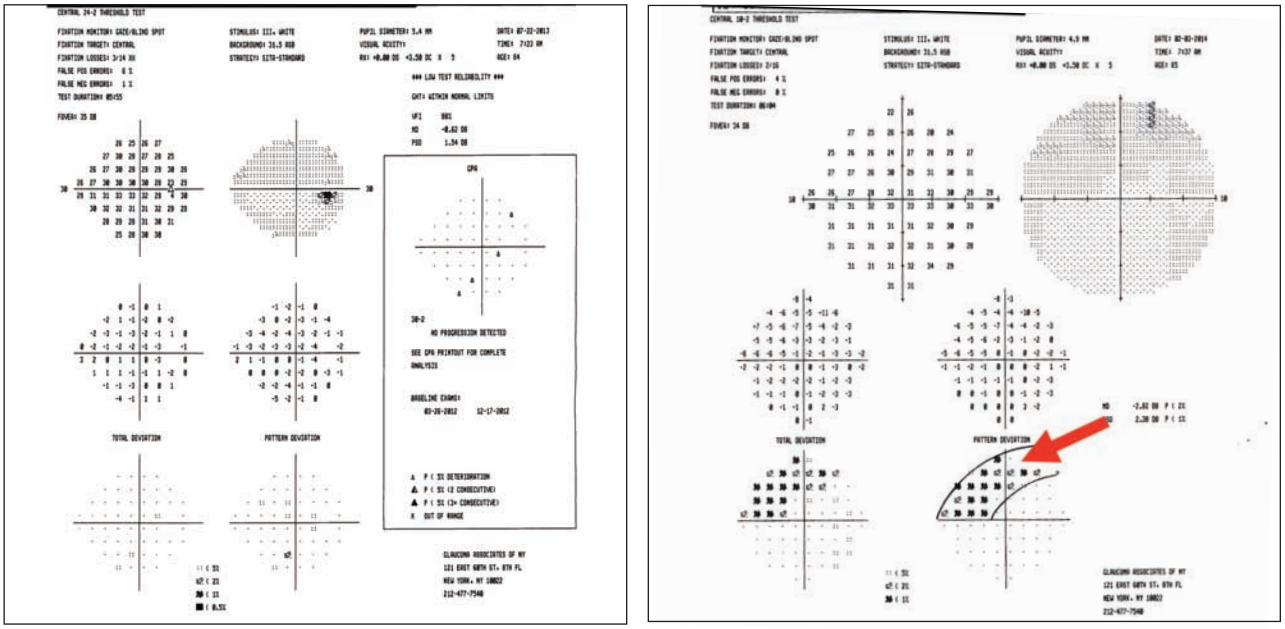

Glaucomatous damage is not always peripheral. For that reason, it's worth checking the central visual field using the 10-2 test early on and periodically over time. The patient above had a normal 24-2 test (left) but an abnormal 10-2 test (right), indicating central damage.

sensitivity has decreased. Most ophthalmologists would assume this indicates the beginning of a cataract, but it could also indicate macular disease—or glaucoma. If a patient with known glaucoma tells you he's having increased difficulty reading, but everything else looks the same, that's probably a sign of progression even if the visual field hasn't changed. In that situation you should definitely get a 10-degree visual field.

Screen Individuals at Risk

The last item on my list is to make sure you don't miss a good screening opportunity. Whenever you know that someone may have an elevated risk of glaucoma, it's worth doing whatever you can to see that that person is examined.

For example, we know that siblings of a POAG patient are at fairly high risk of having the disease—even higher than a child of the patient.[1] Likewise, African Americans are more likely to be affected than Caucasians. So, it's worth encouraging your glaucoma patients to have their siblings come in for an exam. If you examine five siblings of a glaucoma patient, odds are very good that you'll find at least one individual with glaucoma. (That's compared to 1 or 2 percent of the general population.) It is perhaps most important that African-American patients have their family members examined.

We could identify a lot of undetected and undiagnosed glaucoma just by doing this, and that could go a long way toward reducing unnecessary vision loss.

Being on the Lookout

Today, all of us are seeing more patients and we're more pressed for time. Unfortunately, that just increases the odds that we'll miss something potentially important. Almost every ophthalmologist dilates his patients at the first visit and periodically after that, and looking at the optic nerve is a part of a regular eye exam. But if the clinician is just thinking about taking a cataract out, he may very well miss signs of glaucoma. Likewise, if you're focused on a patient's complaint, you might not think to check for signs of glaucomatous damage. But every exam is an opportunity to catch the warning signs that glaucoma is present and the patient is at risk.

To make sure we don't miss those signs, we need to be focused and use optimum detection and management strategies. Keeping the six points mentioned here in mind when examining a patient can help avoid a misdiagnosis and make it easier to do an accurate risk assessment, stratifying patients as to who needs to come back soon and who needs more extensive testing. And that will mean less unnecessary vision loss. REVIEW

Dr. Liebmann is a clinical professor of ophthalmology at New York University School of Medicine, an adjunct professor of clinical ophthalmology at New York Medical College in Valhalla, N.Y., and director of glaucoma services at Manhattan Eye, Ear, and Throat Hospital and New York University Medical Center.

1. Tielsch JM, Katz J, Sommer A, Quigley HA, Javitt JC. Family history and risk of primary open angle glaucoma. The Baltimore Eye Survey. Arch Ophthalmol 1994;112:1:69-73.

Innovative Ways to Quell the Cells

Expert tips on how to avoid getting epithelial ingrowth after LASIK, and how to respond if ingrowth occurs.

Walter Bethke, Managing Editor

Though the risk is low, there's a chance that a LASIK patient, especially one undergoing an enhancement, will experience the growth of epithelial cells in the LASIK interface. Refractive surgeons say, however, that though you can't eliminate the risk, you can take steps to prevent epithelial ingrowth, as well as perform some effective maneuvers to remove the cells if they start to grow. Here are their top techniques.

Prevention and Risk Factors

Surgeons say some things seem to predispose patients toward ingrowth, and knowing about them ahead of time can avoid problems.

"I'd say the incidence is from 1 to 3 percent following LASIK, and most of the time it occurs with enhancements," says Michael Taravella, MD, professor of ophthalmology at the University of Colorado School of Medicine. "The other risk factor, especially with enhancements, is if you're performing a hyperopic correction. With these, because the ablation is outside the original stromal bed, I think that can stimulate the epithelium around the edge, making the patient prone to ingrowth."

Beverly Hills, Calif., surgeon Andrew Caster did a study of ingrowth, and found that when a surgeon did a flap lift enhancement within the first three years, the rate of clinically significant ingrowth was 1 percent.[1] "After three years, though, it jumped to about 7 percent," Dr. Caster says. "And that risk remained stable over time."

Surgeons note there are steps you can take during surgery to decrease the risk of ingrowth.

"When some surgeons lift the flap for an enhancement, they will use an instrument such as a Sinskey hook to find the edge of the flap and then put a spatula in the LASIK interface and run it over the whole circumference of the flap to open it up," says Steven Wilson, MD, of the Cleveland Clinic. "They then lift the flap and do the enhancement. But when you do that, the spatula is dragging microscopic debris from where you're opening the edge of the flap into the interface, throughout the whole circumference of the flap. That's why, in a method I published called flaporhexis, we just open a one clock hour area of the edge of the flap, insert a forceps, then peel the flap back. That's the only area where we've potentially introduced anything into the interface. You don't have any hanging bits of epithelium that you've torn irregularly by running an instrument back and forth in the interface. I still meticulously clean the interface before putting it back down, but I'm much less likely to catch any tongues of epithelium or epithelial debris."

Michael Taravella, MD

Surgeons will usually intervene when cells encroach farther into the visual axis.

Scott MacRae, MD, a professor at the University of Rochester Medical Center, says flap alignment helps, too. "I like to make sure that the flap is well-aligned postop," he says. "Think of it as trying to reunite the cells you bisected. You don't want asymmetry where the flap has shifted to one side, because

that opens up the edge of the flap for invasion by the epithelium."

Dr. MacRae also tries to help the flap's natural sealing process by using a small fan. "Once the epithelial barrier and endothelial pump kick in, and you dry the cornea a little, it osmotically seals," he says. "So, the more you can gently dry it, it probably seals the flap better and makes it less likely to have small tunnels through which the epithelium can migrate. However, if you dry it too much you'll see the flap retract. So, I'll use the small, handheld, batter-powered fan to do some blowing on the cornea from six to eight inches. For primary LASIK, I'll use the fan for 10 to 15 seconds, and for retreatments I'll use it for a minute."

For hyperopic ablations during retreatments for overcorrected primary myopic LASIK, Dr. Taravella uses a tip a colleague mentioned: Protect the epithelium with Goniosol. "I'll take a TB syringe and put a little Goniosol in it, and put a 19-ga. cannula on it. I'll then apply it to the periphery of the cornea, taking care not to let it leak into the stromal bed and interfere with the ablation. Since the hyperopic ablation is sometimes bigger than the myopic ablation's bed, sometimes you'll notice laser spots going outside of the original bed. However, if you shield the epithelium from them, I think you're less likely to stimulate ingrowth."

Managing Ingrowth

For the unfortunate times when ingrowth occurs, surgeons have various approaches that they say help remove the cells and prevent them from recurring.

There is some ingrowth that won't progress and can just be observed, surgeons say. "It's common to see a little bit [of ingrowth] after enhancements," says Dr. Taravella. "However, if it is within 1 mm of the flap edge and isn't causing any flap adherence problems, is stable and not growing, I'll usually just watch the patient carefully, especially in the first week or two after an enhancement to make sure they're not showing any signs of it growing or affecting the refraction. But if it's 2 to 3 mm in, you'll probably have to treat it. The ones you have to be concerned about are those that are progressing, or when you see flap melt occurring." Dr. Taravella also says that early topography can help, since if the area around the ingrowth is elevated and is causing some irregular astigmatism, that's an indication that you need to treat it.

Jules Stein Eye Institute surgeon Kevin Miller says proliferation on all sides usually isn't a good sign. "If it grows from both sides—you get a wraparound—and the edge of the flap is kind of loose, those cases don't tend to do well," he says.

To treat cells, some surgeons like lifting the entire flap, while others just like to expose the area of ingrowth. Dr. Taravella, who flips the whole flap, first marks the cornea. "At the slit lamp, with a marking pen I'll mark the extent of the ingrowth both circumferentially around the edge of the bed and also centrally," he says. "I'll also mark the flap so I know where it is on the flap edge. Then, I'll lift the flap. The ingrowth is usually easy to see and very loose. For the most part, you can remove it with a Weck-Cel sponge and maybe light scraping with a blade, though I think it's important to remove it from both the bed and underside of the flap. I'll then inspect the area on low and high magnification, and under the Visx laser's ring light, which I think highlights epithelial changes better than the oblique light. I'll try to clean it as meticulously as I can."

Dr. MacRae also marks the cornea, but prefers just removing the cells from a local area, rather than lifting the entire flap. "If it's a small area of ingrowth, I may wash it out with an irrigation cannula at the slit lamp and then dry it with the fan," Dr. MacRae says. "If it's more extensive, or if it comes back, I will lift the flap only in the region where I want to remove the ingrowth—there's no sense stirring up the epithelium someplace else. I'll use a spatula to retract the flap and clean out the cells by gently scraping both the flap side and the stromal bed with a 64 blade. For a lot of these patients, I'll place a bandage contact lens, which makes recovery easier."

For a recurrence, Dr. Taravella has had success with a technique described by Minneapolis surgeon David Hardten. "You lift it, meticulously clean the area, re-seat the flap and then apply Tisseel fibrin glue on the entire flap edge," he explains. "You then put on a contact lens."

In tough recurrences, suturing is also an option, though it can induce astigmatism that may not completely resolve. To help deal with this, Dr. MacRae uses a technique he heard about from Overland Park, Kan., surgeon Dan Durrie. "I'll lift the area, clean it out, then suture down the flap," he explains. "Sometimes I'll do a horizontal mattress suture. The key is not to bury the knots, but instead keep the knots in the peripheral untouched cornea and put a bandage contact lens on. When you bury them, it causes a lot of corneal distortion; you have to pull the knots aggressively to tighten them. I've found that, by not lifting the entire flap when you clean it and then putting sutures in and covering it with a contact lens, the cornea will go back to its original flap position."

Surgeons say epithelial ingrowth is a problem that, though infrequent, they're always thinking about and trying to outmaneuver. "Other than ablations that don't fully correct the refractive error," says Dr. Miller, "ingrowth is probably the biggest current problem in LASIK. Though it occurs less frequently than before, this particular problem hasn't gone away yet." REVIEW

1. Caster AI, Friess DW, Schwendeman FJ. Incidence of epithelial ingrowth in primary and retreatment laser in situ keratomileusis. J Cataract Refract Surg 2010;36:1:97-101.

Fight Fire With Fire With Immunotherapy

Continued exposure to an antigen may overcome an allergy, but there are still hurdles to clear before this approach is common.

Mark B. Abelson, MD, CM, FRCSC, FARVO, Paul Gomes, and James McLaughlin, PhD, Andover, Mass.

Similia similibus curentur, the law of similars, puts forth a simple proposition: The best cure for a disease can be found in that which caused it. In other words, like cures like. The concept is the basis for the rather dubious medical philosophy of homeopathy, but it also finds a place in some mainstream medical thinking. One such approach, allergen immunotherapy, is a treatment designed to reduce or eliminate atopic diseases such as rhinitis, allergic conjunctivitis or even allergic asthma by retraining the body's response to common allergens such as grass or ragweed pollens. This "hair of the dog" strategy is much more common outside the United States. Here, its use is primarily limited to those with the most severe allergic symptomology.

This month we'll take a closer look at AIT, examine prospects for an immunization approach to treatments for ocular allergy and discuss how current and future clinical trials might be optimized for AC indications.

Turning Off the Allergic Switch

Use of plant or pollen extracts to reduce signs and symptoms of "hay fever" dates back to the early 20th century.[1] It's interesting that despite this long history of AIT for rhinitis, the use of such treatments specifically for AC is much less common. This trend appears to be shifting, with the recent publication of Phase III studies of tablet formulations for AIT therapy of either grass- or ragweed-evoked allergy. In both cases the indications for each treatment are the same: "rhinitis with or without AC."[2,3]

Allergic conjunctivitis is one of several related disorders that involve development of a Th2 T-cell response to common environmental allergens, leading to activation of antigen-specific IgE production and immunological sensitization.[4,5] When these sensitized individuals are subsequently exposed to the allergenic culprit, antibodies can initiate mast cell degranulation and the subsequent sequelae of an allergic response *(See Figure 1)*. The Th2 T-cell pathway also initiates a proliferation of mast cells and basophils, charging the immune system in preparation for the next allergic response.

Now, if dendritic cells or other antigen-presenting cells are repeatedly exposed to the same antigen (particularly at low concentrations), it's possible to initiate a shift in the regulatory balance between the Th2 pathway and the non-allergenic Th1/T0-based signaling paradigm.[4,5] Although this desensitization process is not completely understood, increases in IL-10, TGF-β and INF-γ promote a conversion from IgE to IgG antibody production, a suppression of inflammatory leukocytes and an attenuation of subsequent responses to allergen exposure.

This all sounds so good, one might wonder why immunotherapy isn't a mainstay of allergy therapy. It seems there are limitations to the utility of this treatment, and these, along with the availability of simpler remedies, have slowed the rush towards AIT.

Holding Back on AIT

The current therapeutic approach to ocular allergic disease is dominated by topical and systemic antihistamines, agents that have evolved to once-daily treatments that provide effective symptomatic relief to a large proportion of those with AC. Unfortunately, for 25 to 35 percent of the 40 million

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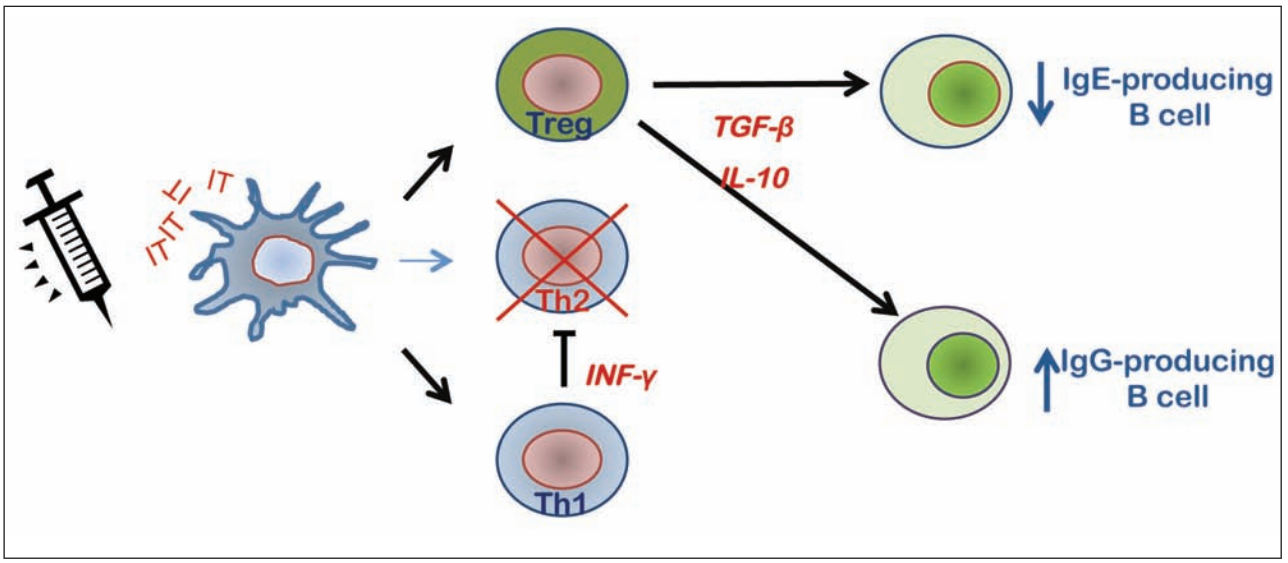

Figure 1: The process of desensitization. In sensitization, in some individuals exposure to allergens initiates a Th2 response, generating IgE antibodies and future sensitization to allergen exposure. This involves maturation of β-cells by IL-4 and IL-13 and presentation of IgE by mast cell surface receptors. In desensitization, continued exposure to antigen (IT in the diagram) can lead to a switching from Th2 responses so that Th1 cells suppress the Th2 pathway while regulatory T cells (Treg) stimulate switching from IgE to IgG or IgA antibodies. This action limits mast cell activation and suppresses allergic responses.

people in the United States with seasonal or perennial allergy, these traditional treatments provide little or no relief.[6] For these patients, AIT is a natural option that has the potential to provide a safe, long-lasting mitigation of allergic symptomatology. Despite this, its use has been constrained by a number of factors.

Most AIT protocols employ a single antigen, even though patients are often allergic to multiple antigens such as pollens of grass, ragweed or birch. This means patients must go through multiple treatments for each allergen, or undergo treatment with allergen mixtures prepared on-site or by compounding pharmacies. Standards adopted by *U.S. Pharmacopeia* and professional associations such as the American Academy of Allergy, Asthma & Immunology include the option of subcutaneous injection of allergen mixtures, but these present a new set of roadblocks.[7] Often allergens have inherent proteolytic activity that can lead to reduction or elimination of antigenicity, especially in mixtures. In addition, despite the establishment of these standards, there are few controlled studies confirming the efficacy of mixed-allergen immunotherapy. Published clinical trial data are mostly based upon studies from Europe, where there is a greater emphasis on monotherapy using European Medicines Agency approved formulations.[7,8]

Another issue that has hindered development of AIT is safety concerns regarding risk of anaphylaxis. This is probably the most important reason that sublingual formulations, either liquid or tablet, are not approved for use in the United States.[9] As the number of studies has grown, however, it appears that such concerns may have been overstated; the incidence of anaphylactic reactions in clinical trials is extremely low.[10] In addition, a review of 11 case reports of anaphylaxis associated with AIT found that each corresponded to non-standard practice or protocol deviation, and none of these reported cases involved a fatality.[11] When properly used, it appears that AIT has an excellent margin of safety.

Other issues may also play a part in the limited inroads of AIT in treatment of ocular allergy. There is a belief that AIT requires a long duration of therapy before significant relief can develop, even though most studies have shown a reduction in allergic symptomology within weeks of therapy initiation.[12] One factor that still appears unresolved is how different dosing regimens should be developed and validated. Perhaps most important is that despite the high numbers of recent trials using grass, ragweed and dust mite AIT, very few of these studies explicitly addressed ocular signs and symptoms. Without such objective metrics it's hard to judge whether a given treatment specifically addresses the needs of patients with AC.

Sublingual Immunotherapy

We mentioned earlier that, in the United States, virtually all immunotherapy employs subcutaneous injection as the route of administration, making the need for repeated office visits a major impediment to growth of this therapy. It's fair to say that the reason AIT is so much more common

in the EU compared to the United States is the availability of oral and topical delivery formulations of antigen.[9] Both of these treatment modalities have shown similar efficacy and safety profiles when compared to subcutaneous antigen delivery. Recent large-scale trials in the United States have focused on sublingual immunotherapy, or SLIT, a modality that has the potential to expand the use of AIT to a much greater patient population.[2,3] Despite this advance, most of these trials haven't addressed the efficacy of SLIT in relief of ocular allergy.

Patients with allergies commonly experience a spectrum of symptoms that includes ocular itching, hyperemia and chemosis. More than 80 percent of allergy sufferers report experiencing some ocular symptomology,[13] yet the latest trials in the United States have been environmental exposure-based studies that provided only limited measures of ocular symptoms as part of a six-part composite score. This daily symptom score included values for "gritty/itchy/red eyes" or "teary/watery eyes."[2,3] Such categories don't reflect an accurate measure for AC, and can be impacted by conditions other than allergy. In these and other recent trials, no scores providing a direct measure of ocular itching are collected.

Most trials also lack a positive comparator group such as antihistamine or steroid therapy (though such controls would present problems to blinding). The second scoring metric in these studies is a daily medication score (including eye drops) that affords some evidence of ocular efficacy, but doesn't provide a comparison between AIT and established allergy treatments. Overall, flaws in study design may be a reflection of the low statistical power inherent in all environmental trials.[14]

Environmental trials depend upon naturally occurring levels of antigen, and thus may tend to underreport the effectiveness of a given test treatment. We've shown the unique value of allergen-challenge based trials for development of therapeutics for ocular allergy over more than 30 years of studies. An approach similar to the conjunctival allergen challenge methodology is likely to provide a rapid, accurate assessment of AIT efficacy in treatment of both ocular and nasal symptoms.

As a strategy to validate AIT, provocation tests have already been shown to provide a reliable metric of therapeutic efficacy. In an early trial of birch pollen AIT, subjects received a 28-day course of allergen followed by a three-month maintenance treatment.[15] Evaluation before and after treatment (four months after the last maintenance dose) was by skin-prick and conjunctival provocation test in a dilution series to determine the threshold of allergic sensitivity. Patients also underwent a two-hour exposure to birch pollen in a chamber. Following AIT treatment, the amount of allergen required to elicit symptoms in the conjunctival provocation that were comparable to the pre-AIT response was significantly increased. The skin test and nasal assessments also showed statistically significant improvements from AIT compared to placebo. While the number of such studies is low, they all demonstrate the utility of a provocation test alternative to environmental exposure-based trials for assessment of AIT.

The few studies that include conjunctival challenge data suggest that ocular itching may be a more sensitive measure of efficacy than environmental symptom scores alone. In a recent report, ocular itching was reduced 30 to 48 percent from placebo, while the threshold for conjunctival response to allergen provocation was significantly increased.[16] When compared to the best reported nasal or ocular symptom score improvements of 24 to 28 percent, it seems that some of these early studies may have omitted a valuable endpoint from their trials.

Allergen challenge has been used to measure efficacy of allergen desensitization, and can provide an objective measure of the treatment effects on either nasal or ocular symptoms. In addition, conjunctival allergen challenge protocols such as the CAC are validated metrics that provide established endpoints for Food and Drug Administration assessment of AC therapies. Metrics like the CAC have not been employed to develop new AIT-based therapies to date, but we think they should be. If we are to fight fire with fire, it's especially critical to employ the best possible tools to gauge our progress, because we'll never know the battle is won unless we keep our eyes open. REVIEW

Dr. Abelson is a clinical professor of ophthalmology at Harvard Medical School. Mr. Gomes is vice president of allergy at Ora; Dr. McLaughlin is a medical writer at Ora Inc.

1. Noon L. Prophylactic inoculation against hay fever. Lancet 1911;1:1572–3.
2. Maloney J, Bernstein DI, Nelson H, et al. Efficacy and safety of grass sublingual immunotherapy tablet, MK-7243: A large randomized controlled trial. Ann Allergy Asthma Immunol 2014;112:146-153.
3. Creticos PS, Maloney J, Bernstein DI, et al. Randomized controlled trial of a ragweed allergy immunotherapy tablet in North American and European adults. J Allergy Clin Immunol 2013;131:1342–1349.
4. Fujita H, Soyka MB, Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy. Clin Transl Allergy 2012;2:2.
5. Nelson HS. Subcutaneous Injection Immunotherapy for Optimal Effectiveness. Immunol Allergy Clin N Am 2011;31:211-226.
6. Blaiss MS. Allergic rhinoconjunctivitis: Burden of disease. Allergy Asthma Proc 2007;28:393–397.
7. Cox L, Esch RE, Corbett M, et al. Allergen Immunotherapy Practice in the United States: guidelines, measures, outcomes. Ann Allergy Asthma Immunol 2011;107:289-301.
8. Cox L, Jacobsen L. Comparison of allergen immunotherapy practice patterns in the United States and Europe. Ann Allergy Asthma Immunol 2009;103:451-460.
9. Nelson HS. Is sublingual immunotherapy ready for use in the United States? JAMA 2013:309;1297-98.
10. Lin SY, Erekosima N, Kim JM, et al. Sublingual Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and Asthma. A Systematic Review JAMA 2013;309:1278-1288.
11. Calderon MA, Simons FE, Malling HJ, Lockey RF, Moingeon P, Demoly P. Sublingual allergen immunotherapy: Mode of action and its relationship with the safety profile. Allergy 2012;67:302.
12. Calderón MA, Frankland AW, Demoly P. Allergen immunotherapy and allergic rhinitis: False beliefs. BMC Med 2013;11:255.
13. Tan BK, Chandra RK, Pollak J. Incidence and associated premorbid diagnoses of patients with chronic rhinosinusitis. J Allergy Clin Immunol 2013;131:1350-1360.
14. Abelson MB. Comparison of the conjunctival allergen challenge model with the environmental model of allergic conjunctivitis. Acta Ophthalmol Scand Suppl 1999;228:38-42.
15. Horak F, Stübner P, Berger UE, Marks B, Toth J, Jäger S. Immunotherapy with sublingual birch pollen extract. J Invest Allergol Clin Immunol 1998;8:3:165-71.
16. Calderon MA, Penagos M, Sheikh A, Canonica GW, Durham SR. Sublingual immunotherapy for allergic conjunctivitis: Cochrane systematic review and meta-analysis. Clin Exp Allergy 2011;41:1263-72.

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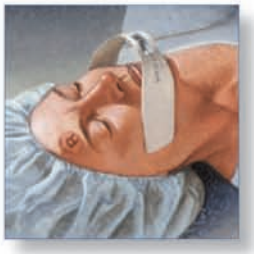

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Association of Statin Use With Cataracts

Contrary to the prior hypothesis that statin antioxidant effects may slow the natural aging process of the lens, researchers utilizing a military health-care system database for a cohort analysis have concluded that the risk of cataract is increased among statin users compared to non-statin users. The risk-benefit ratio of statin use, specifically for primary prevention, should be carefully weighed with this knowledge.

In order to compare the risks of development of cataracts between statin users and nonusers, researchers created a propensity score-matched cohort using 46,249 patients, 44 variables and retrospective data from October 1, 2003 to March 1, 2010. Primary analysis examined the risk of cataract in the cohort. Secondary analysis examined the risk of cataract in patients with no comorbidities according to the Charlson Comorbidity Index. A sensitivity analysis was conducted to repeat the secondary analysis in patients taking statins for two, four and six years.

Based on medication fills during fiscal year 2005, patients were divided into two groups: Group 1 (n=13,626), statin users who received at least a 90-day supply of statins; and Group 2 (n=32,623), nonusers who never received a statin throughout the study. For the primary analysis, 6,972 pairs of statin users and nonusers were matched. The risk of cataract was higher among statin users in comparison with nonusers in the matched cohort (odds ratio: 1.09; 95 percent CI, 1.02-1.17). In secondary analysis, after adjusting for identified confounders, the incidence of cataract was higher in statin users than nonusers (odds ratio: 1.27; 95 percent CI, 1.15-1.40). Sensitivity analysis confirmed this relationship.

JAMA Ophthalmol 2013;131:1427-1434.
Leuschen J, Mortensen E, Frei C, Mansi E, et al.

CXL for Progressive Keratoconus: Two-year Outcomes

A progressive case series of 42 eyes from 32 patients with progressive keratoconus treated with corneal cross-linking shows that CXL is effective in improving uncorrected distance visual acuity, corrected distance visual acuity, topographic measures and most corneal higher-order aberrations. A significant reduction was observed in apical keratometry; this reduction directly correlated with an improvement in visual acuity.

Main outcomes (UDVA; CDVA; refractive changes; topographic data; corneal aberrations) were measured at baseline, six, 12 and 24 months after treatment. Two years after CXL treatment, the UDVA ($p<0.001$), CDVA ($p<0.001$) and spherical equivalent ($p=0.048$) improved significantly. The corneal topographic data revealed significant decreases in apical keratometry ($p<0.001$), differential keratometry ($p=0.031$) and central keratometry ($p=0.003$) compared with baseline measurements. Aberration analyses revealed a significant reduction in coma ($p=0.016$), trefoil ($p=0.018$), secondary astigmatism ($p<0.001$), quatrefoil ($p=0.031$), secondary coma ($p<0.001$) and secondary trefoil ($p=0.001$). Corneal HOA (except quatrefoil) demonstrated a significant correlation with postoperative CDVA; the highest correlations were for coma (rho=0.701, $p<0.001$), secondary astigmatism (rho=0.519, $p=0.001$) and total HOA (rho=0.487, $p=0.001$). However, the corneal HOA changes were not statistically associated with improved visual acuity. After treatment, the reduction in apical keratometry was the only variable that correlated with the improvement in CDVA (rho=0.319, $p=0.042$).

Cornea 2014;33:43-48.
Ghanem R, Santhiago M, Berti T, Netto M, et al.

IOP After Phaco in Medically Controlled OAG Patients

University of Washington researchers found a small average decrease in IOP in patients with open-angle glaucoma after phacoemulsification; however, a sizeable proportion of medically controlled glaucoma patients experienced an increase in IOP or required more aggressive treatment to control IOP postoperatively.

In this retrospective case series, a total of 157 eyes of 157 open-angle glaucoma patients without prior incisional glaucoma surgery undergoing phacoemulsification by a single surgeon between January 1997 and October 2011 were evaluated. Patient charts were reviewed to obtain demographic information; preoperative glaucoma medications; severity and treatments measures; and preoperative and postoperative IOP.

The average preoperative IOP of 16.3 ±3.6 mmHg decreased to 14.5 ±3.3 mmHg at one year ($p<0.001$). Sixty eyes (38 percent) required additional medications or laser for IOP control within the first year postoperatively, or had a higher IOP at postoperative year one without medication change. Among eyes without postoperative medication changes (n=102), higher preoperative IOP ($p<0.001$), older age ($p=0.006$) and deeper anterior chamber depth ($p=0.015$) were associated with lower postoperative IOP.

Am J Ophthalmol 2014;157:26-31.
Slabaugh M, Bojikian K, Moore D, Chen P.

Risk Calculation Variability in Ocular Hypertensive Subjects

Researchers investigating the longitudinal variability of glaucoma risk calculation in ocular hypertensive subjects have shown that the estimated five-year risk of conversion to primary open-angle glaucoma among untreated OHT patients varies significantly, with a trend towards increasing over time. Within the same individual, the estimated risk can vary almost tenfold based on the variability of IOP, central corneal thickness, vertical cup-to-disc ratio (VCDR) and visual field pattern standard deviation (VFPSD). Therefore, a single risk calculation measurement may not be sufficient for accurate risk assessment, informed decision-making by patients and physician treatment recommendations.

Clinical variables collected at baseline and during follow-up include age, CCT, IOP, VCDR and VFPSD. These variables were used to calculate the five-year risk of conversion to POAG at each follow-up visit using the Ocular Hypertension Treatment Study and European Glaucoma Prevention Study calculator (found at ohts.wustl.edu/risk/calculator.html). The researchers also calculated the risk of POAG conversion based on the fluctuation of measured variables over time, assuming the worst-case scenarios (final age; highest pattern standard deviation; lowest CCT; highest IOP; highest VCDR) for each patient. Risk probabilities were plotted against follow-up time to generate slopes of risk change over time.

The charts of 27 untreated OHT patients (54 eyes) followed for a mean of 98.3 ±18.5 months were reviewed. Seven individuals (25.9 percent) converted to POAG during follow-up. The mean five-year risk of conversion for all patients in the study group ranged from 2.9 percent to 52.3 percent during follow-up. The mean slope of risk change over time was 0.37 ±0.81 percent increase per year. The mean slope for patients who reached a POAG endpoint was significantly greater than for those who did not (1.3 ±0.79 vs. 0.042 ±0.52 percent per year, $p<0.01$). In each patient, the mean risk of POAG conversion increased almost tenfold when comparing the best-case scenario with the worst-case scenario (5 percent vs. 45.7 percent, $p<0.01$).

J Glaucoma 2014;23:1-4.
Song C, de Moraes C, Forchheimer I, Prata T, et al.

Continuous Monitoring of IOP Using a Contact Lens Sensor

French researchers evaluating a new contact lens sensor (CLS) proposed to continuously monitor intraocular pressure over 24 hours found that while the CLS is an accurate and reproducible method to characterize nyctohemeral IOP rhythm in healthy participants, it does not allow for estimating IOP value in millimeters of mercury corresponding to the relative variation of the electrical signal measured.

Twelve healthy young volunteers were housed in a sleep laboratory and underwent four 24-hour sessions of IOP measurements over six months. After initial randomized attribution, the IOP of the first eye was continuously monitored using a CLS and the IOP of the fellow eye was measured hourly using noncontact tonometry. Two sessions with NCT measurements in one eye and CLS measurements in the fellow eye, one session with CLS measurements in only one eye and one session with NCT measurements in both eyes were performed.

A nonlinear least squares, dual-harmonic regression analysis was used to model the 24-hour IOP rhythm. Comparison of acrophase, bathyphase, amplitude, midline estimating statistic of rhythm, IOP values, IOP changes and agreement were evaluated in the three tonometry methods. A significant nyctohemeral IOP rhythm was found in 31 of 36 sessions (86 percent) using NCT and in all sessions using CLS. Hourly awakening during NCT measurements did not significantly change the mean phases of the 24-hour IOP pattern evaluated using CLS in the contralateral eye. Throughout the sessions, intraclass correlation of coefficients of the CLS acrophase (0.6, $p=0.01$; 95 percent CI, 0.1-0.9); CLS bathyphase (0.7, $p=0.01$; 95 percent CI; 0.1-0.9); NCT amplitude (0.7, $p=0.01$; 95 percent CI, 0.1-0.9); and NCT midline estimating statistic of rhythm (0.9, $p<0.01$; 95 percent CI, 0.9-1) were significant. When performing NCT measurements in one eye and CLS measurements in the contralateral eye, the IOP change at each point, normalized from the first measurement (9 a.m.), was not symmetric individually or within the population.

JAMA Ophthalmol 2013;131:1507-1216.
Mottet B, Aptel F, Romanet JP, Hubanova R, et al.

The Genetic Basis of Oculoplastic Disorders

Orbital and adnexal disorders often have a genetic basis. Here is a review of the most common disorders.

Anuradha Ganesh, MD, Abdullah Al-Mujaini, FRCSC, Muscat, Oman, Alex V. Levin, MD, MHSc FRCSC, Philadelphia

Many orbital and adnexal disorders are known to have a genetic basis, the recognition of which is crucial, as it makes possible comprehensive care encompassing diagnosis, therapy, rehabilitation and counseling of affected patients and their families.

Development

Ocular development begins with the formation of the optic vesicle from the neuroectoderm largely under the influence of the Sonic hedgehog (*SSH*), *PAX2* and *PAX6* genes. The optic vesicle and subsequent growth of the eye influences the formation of the surrounding orbital soft tissue contents and the bony orbital walls.

Various developmental genes regulate tissue interactions during embryogenesis, including fibroblast growth factor receptors (*FGFR*) *1, 2* and *3*, and Twist homologue 1 (*TWIST1*), and the transforming growth factor, beta receptor 1 (*TGFBR1*). Awareness of orbital, ocular and adnexal development and the migratory pattern of neural crest cells is useful for understanding the etiology of congenital orbital, eyelid and lacrimal anomalies. The typical location of dermoid cysts at the frontozygomatic and frontoethmoidal suture lines is the result of a sequestration of surface ectoderm in areas of neural crest cell fusion. The superficial spread and deep invasion of basal cell carcinoma on the midface has been attributed to the location of the embryonic fusion planes.

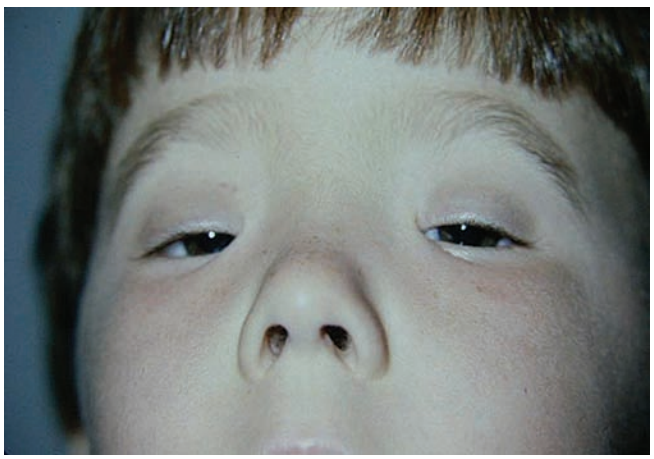

Figure 1. A child with the blepharophimosis-ptosis-epicanthus inversus syndrome (BPES). He demonstrates the classic findings of blepharophimosis, telecanthus, bilateral symmetric ptosis and epicanthus inversus. Note the upward tilt of the head adopted to compensate for the severe ptosis.

Genetic Anomalies of the Eyelids

The genetic forms of ptosis are summarized in Table 1.

• ***Congenital ptosis.*** Congenital ptosis resulting from a localized dysgenesis of the levator muscle can occur in isolation or in combination with other malformations. Isolated congenital ptosis is usually not heritable. A few reports indicate the possibility of dominant inheritance and linkage to 1p34.1-p32, or Xq24-q27.1.[1,2] The *ZFH4* gene (8q21.1) may be a candidate gene.[3] Syndromic ptosis may be associated with trisomy 13, Turner syndrome, Cornelia de Lange syndrome, Noonan syndrome and

Baraitser-Winter syndrome, among others.[4,5]

Autosomal-dominant blepharophimosis-ptosis-epicanthus inversus syndrome (BPES) results from mutation or deletion of the *FOXL2* gene (3q22.3; *See Figure 1*). BPES1 is associated with premature ovarian failure and infertility in girls. BPES2 is not associated with ovarian failure, and can be transmitted by both males and females. Intellectual disability in patients with BPES may be due to larger deletions involving 3q22.3, or part of the blepharophimosis-ptosis-intellectual disability syndrome (BPIDS) caused by heterozygous mutations in the *UBE3B* gene (12q23).[6]

Congenital fibrosis of the extraocular muscles (CFEOM) types 1, 2 and 3 are characterized by ptosis and complete ophthalmoplegia or other restricted eye movements. CFEOM is considered a congenital cranial dysinnervation disorder (CCDD) and is believed to result from aberrant innervation of the extraocular muscles. In CFEOM1, the primary position of both eyes is below the horizontal midline with severe restriction of elevation of either eye above the midline. Horizontal movements of the eyes range from normal to severely restricted. Marcus Gunn jaw wink may be present. The condition is autosomal dominant and results from heterozygous mutations in *KIF21A* (12q12). CFEOM2 is an autosomal recessive disorder characterized by congenital bilateral exotropic ophthalmoplegia and ptosis, with pupillary abnormalities, in particular miosis. It is due to mutations in *PHOX2A* (11q13). CFEOM3 patients manifest with ptosis and ophthalmoplegia, and typically demonstrate a broader variation in phenotype than CFEOM1 and CFEOM2 patients. The CFEOM3 phenotype is genetically heterogeneous and may be caused by mutations in the *TUBB3* (16q24.3) or *KIF21A* genes. Patients with CFEOM3 may also have facial dysmorphism, cognitive impairment, thin corpus callosum or digital anomalies.

Table 1. Genetic Forms of Ptosis

Ocular Phenotype	Chromosomal location	Gene	Inheritance
Eyelids			
Congenital Ptosis			
Isolated congenital ptosis	1p34.1-p32 Xq24-q27.1 8q21.1	nc nc ZFH4	AD AD AD
Blepharophimosis blepharophimosis-ptosis-epicanthus inversus syndrome (BPES) blepharophimosis-ptosis-intellectual disability syndrome (BPIDS)	3q22.3 12q23	FOXL2 UBE3B	AD AD
Congenital fibrosis of extraocular muscles (CFEOM) Type 1 Type 2 Type 3	 12q12 11q13 16q24.3/12q12	 KIF21A PHOX2A TUBB3/KIF21A	 AD AR AD
Congenital myasthenic syndromes*	11p11.2-p11.1 9q31.3-q32	RAPSN MUSK	AR AR
Acquired Ptosis			
Mitochondrial myopathies** Chronic progressive external ophthalmoplegia (CPEO) Kearns-Sayre syndrome (KSS)	 15q25 4q34 10q24	 POLG ANT1 C10orf2	 AR AR AR
Oculo-pharyngeal muscular dystrophy	14q11.2	PABPN1	AD
Neurofibromatosis (NF1)	17q11.2	NF1	AD

* Genetically heterogeneous. Prominent genes and chromosomal locations are listed.

** Mitochondrial myopathies may be caused by mtDNA deletions or mutations in nuclear DNA. Nuclear DNA involvement is listed.

nc = gene not cloned, AD = autosomal dominant, AR = autosomal recessive

Congenital myasthenic syndromes are genetic disorders of the neuromuscular junction. Patients manifest with ptosis and ophthalmoplegia, easy fatiguability, and facial, bulbar, neck and limb weakness, or respiratory insufficiency. They are associated with mutations in different genes encoding proteins involved in presynaptic, synaptic or postsynaptic neuromuscular transmission, including the *RAPSN* gene (11p11.2-p11.1), which plays an essential role in the clustering of acetylcholine receptors at the endplate, and the muscle-specific protein kinase (*MUSK*, 9q31.3-q32) gene, critical for synaptic differentiation.

• ***Acquired ptosis.*** Ptosis with reduced levator function and/or ophthalmoplegia often points to a myogenic cause. The differential diagnosis includes mitochondrial myopathies, oculopharyngeal muscular dystrophy (OPMD), oculopharyngodistal myopathy (ODM) and myotonic dystrophy.

Chronic progressive external ophthalmoplegia (CPEO) and Kearns-Sayre syndrome (KSS) are common mitochondrial syndromes that present with chronic, progressive, bilateral and mostly symmetric ophthalmoplegia and ptosis, with or without optic atrophy, and pigmentary reti-

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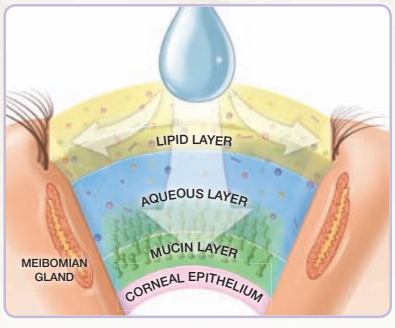

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References: 1. Akpek EK, Smith RA. Overview of age-related ocular conditions. *Am J Manag Care.* 2013;19 (5 suppl):S67-S75. **2.** Korb DR, Blackie CA, Meadows DL, Christensen M, Tudor M. Evaluation of extended tear stability by two emulsion based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

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nopathy. Patients may also manifest with a variety of systemic manifestations, including facial and limb myopathy, deafness and cardiac conduction defects. Mitochondrial dysfunction may be caused by mutations or deletions or insertions in mitochondrial or nuclear DNA. CPEO and KSS are usually sporadic diseases. Autosomal recessive or dominant CPEO may be caused by nuclear DNA mutations in the *POLG* gene (15q25) or *ANT1* (4q34) and *C10orf2* (10q24) genes respectively.

OPMD is characterized by progressive ptosis, external ophthalmoplegia, dysphagia and proximal limb weakness with onset usually in the sixth decade, and is caused by heterozygous mutations in *PABPN1* (14q11.2). ODM is characterized by ptosis, masseter, facial, bulbar muscle and distal limb weakness beginning usually in the patient's 40s. The genetic defect causing ODM has not been elucidated. Myotonic dystrophy is the most common adult-onset muscular dystrophy. Ocular findings include ptosis, ophthalmoplegia, hypotony and polychromatic cataracts. Patients may have frontal alopecia, cardiomyopathy and testicular atrophy. It is caused by expansion of a heterozygous trinucleotide repeat (CTG)n in the *DMPK* gene (19q13).

Ptosis may also be due to eyelid involvement by nodular or plexiform neurofibromas in neurofibromatosis, an autosomal dominant condition characterized by extreme variability of expression both within and among families. The neurofibromin protein, encoded by the *NF1* gene (17q11.2) is a tumor suppressor gene. Plexiform neurofibroma characteristically produces an S-shaped contour to the eyelid which when palpated may feel like "a bag of worms." Orbital involvement in type 1 neurofibromatosis includes optic nerve glioma, other orbital tumors such as neurilemmoma and meningioma, or a defect in the greater wing of the sphenoid bone which can result in pulsating proptosis as the intracranial contents make contact with orbital tissues.

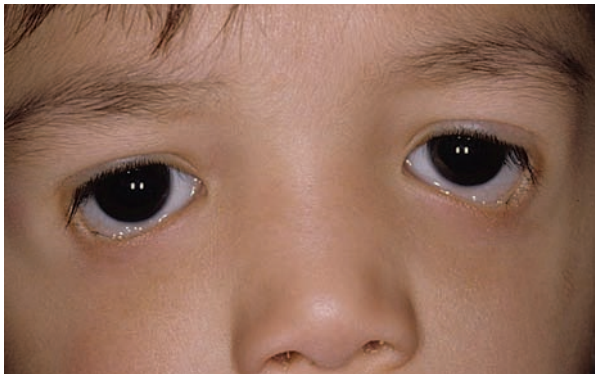

Figure 2. Bilateral lower lid colobomas in a child with Treacher-Collins-Franceshetti syndrome. Note the sharp demarcation of the defect nasally with an upsweep to a normal margin. Eyelashes are absent in the defect.

• ***Eyelid coloboma.*** Eyelid coloboma may be isolated or associated with facial abnormalities.[7] Upper-lid coloboma may be seen in the oculoauriculovertebral spectrum (OAVS), including the subtype known as Goldenhar syndrome. OAVS, due to abnormal development of the first and second branchial arch, is associated with multiple loci and one known gene, *SALL1* (16q12.1) and may be inherited in an autosomal dominant manner.[8]

Lower lid coloboma may be seen in association with Treacher-Collins-Franceshetti syndrome (mandibulofacial dysotosis). The coloboma typically involves the medial two-thirds of the lower eyelid with a sharp demarcation of the defect nasally where there is an upsweep to a normal margin *(See Figure 2)*. Eyelashes are usually absent in the defect, with absent proximal nasolacrimal drainage system. Patients have a marked downslanting of the eyes. The condition is autosomal dominant and associated with mutations in the *TCOF1* (5q32), *POLR1D* (13q12.2) or *POLR1C* genes (6p21.1).

• ***Other eyelid anomalies.*** Lymphedema-distichiasis is an autosomal dominant disorder caused by mutations in the *FOXC2* gene (16q24.1), and presents as distichiasis of upper and lower eyelids and ptosis, with lymphedema of the limbs.

Euryblepharon, characterized by horizontal enlargement of the palpebral fissure with associated lateral canthal malposition and lateral ectropion, may be seen in association with genetic syndromes such as the Niikawa-Kuroki (formerly Kabuki Makeup) syndrome and blepharo-cheilo-dontic syndrome (BCDS). Niikawa-Kuroki syndrome is a congenital mental retardation syndrome with postnatal short stature, facial dysmorphism, a cleft or high-arched palate and skeletal abnormalities of the vertebrae, hands and hip joints. It is caused by heterozygous mutations in the *MLL2* gene (12q12-q14).[9] BCDS is also a rare autosomal-dominant disorder characterized by upper eyelid distichiasis, euryblepharon, bilateral cleft lip and palate and conical teeth. No specific gene or locus has been identified.

Congenital ectropion is rare and often caused by a vertical deficiency of the anterior lamella of the eyelids. It may be associated with genetic disorders such as blepharophimosis syndrome, Down syndrome or ichthyosis (collodion baby). Congenital ichthyosis is a heterogeneous group of disorders of keratinization characterized primarily by abnormal skin scaling over the whole body. Collodion babies have a taut, shiny, translucent or opaque membrane that encases the entire body and lasts for days to weeks. Congenital ichthyosis is autosomal recessive and genetically heterogeneous. Mutations in the *TGM1*(14q12) gene account for majority of cases.

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known as Gorlin-Goltz syndrome or nevoid basal cell carcinoma (BCC) syndrome, is caused by mutations in the *PTCH1* (9q22), *PTCH2* (1p32) or *SUFU* genes (10q24-q25). It is an autosomal-dominant cancer predisposition syndrome resulting in multiple BCCs. Developmental malformations, hamartomas and dysplastic lesions are consistent and striking components of the nevoid BCC syndrome. Clinically, diagnosis of nevoid BCC syndrome is made in the presence of two major or one major and two minor criteria *(See Table 2)*.[10]

Genetic Anomalies: Orbit & Globe

• ***Craniosynostosis.*** The craniosynostoses are a group of disorders characterized by premature fusion of one or more of the cranial sutures resulting in restriction of growth in a direction parallel to the orientation of the fused suture. The bony orbit is often shallow with recession of the orbital rims resulting in exorbitism. Syndromic craniosynostosis (20 percent) such as Crouzon, Apert, Pfeiffer, Muenke and Saethre-Chotzen syndrome occur due to mutations in the *FGFR2*, *FGFR2*, *FGFR1 FGFR3*, and *TWIST1* genes respectively, and are characterized by autosomal dominant inheritance. Common ophthalmic complications include corneal exposure and strabismus associated with a variety of extraocular muscle malformations including absent, malformed, or malpositioned muscles. Ptosis may be seen in the Saethre-Chotzen syndrome. Patients may suffer from a narrow oropharynx requiring tracheostomy, increased intracranial pressure, hearing loss, cleft palate and malformations of the distal extremities.

• ***Facial clefts.*** Facial clefts are congenital anomalies that occur due to failure of fusion of normal embryonic clefts or facial processes. Clefts are defined according to the system of Tessier based on their position, and are grouped into midline, paramedian, orbital, or lateral clefts. They may be associated with cranial anomalies, mostly encephalocele. Frontonasal dysplasia (FND) due to median facial clefting is characterized by ocular hypertelorism, a broad nasal root, unilateral or bilateral clefting of the alae nasi, anterior cranium bifidum occultum, and a V-shaped or widow's peak frontal hairline *(See Figure 3)*. FND is genetically heterogeneous and may be caused by homozygous mutations in the *ALX3* gene (1p13.3), *ALX4* gene (11p11.2) or *ALX1* gene (12q21.3-q22). A type of FND, frontorhiny, is characterized by distinctive features of FND with upper eyelid ptosis and midline dermoid cysts of craniofacial structures.[11]

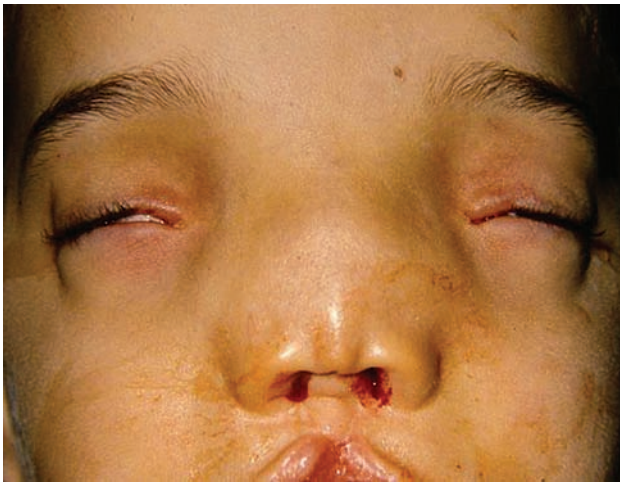

Figure 3. A patient with hypertelorism, broad nasal root and bilateral clefting of the alae nasi due to frontonasal dysplasia (FND). He was found to have an anterior encephalocele through the floor of the anterior cranial fossa, bilateral optic nerve hypoplasia and bilateral fundus coloboma.

• ***Anophthalmia/Microphthalmia.*** True anophthalmia refers to complete absence of the globe. It occurs when the neuroectoderm of the primary optic vesicle fails to develop properly from the anterior neural tube. Microphthalmia is defined as a globe with a total axial length that is at least two standard deviations below the mean for age. Both occur secondary to developmental arrest at various stages of growth of the optic vesicle. Severe microphthalmia may present as clinical anophthalmia with globe remnants only visible by ultrasound or by histology. As the development of the orbital region, as well as the lids and the fornices, is dependent on the presence of a normal-sized eye *in utero*, anophthalmia and microphthalmia result in secondary underdevelopment of the orbit, lids, and socket. Anophthalmia and microphthalmia may occur unilaterally or bilaterally, in isolation or in association with systemic disease. Genetic causes include chromosomal aberrations (e.g. trisomy 13 and 18), mutations or deletions involving the *SOX2*, *SIX6*, *STRA6*, *HESX1*, *BCOR*, *SHH*, *PAX6* and *RAX* genes, and syndromes such as Goltz, Meckel-Gruber, Seckel, cerebro-oculo-nasal, branchio-oculo-facial, Walker-Warburg, and CHARGE syndromes, among others.[12]

• ***Cryptophthalmos.*** Complete cryptophthalmos is characterized by absence of the eyelids, which are replaced by skin extending in continuity with the cheek over the orbit. A new grading of upper eyelid colobomas and cryptophthalmos suggests that the two entities may represent opposite ends of the same eyelid malformation spectrum.[7] Cryptophthalmos may be isolated or syndromic. Fraser syndrome is an autosomal recessive disorder characterized by cryptophthalmos, cutaneous syndactyly, malformations of the larynx and genitourinary tract, craniofacial

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Table 2. Clinical Criteria for Diagnosis of Gorlin-Goltz Syndrome*

Major Criteria:
Multiple (>2) basal cell carcinomas at any age or one basal cell carcinoma at less than 30 years of age
Histologically proven odontogenic keratocyst or a polyostotic bone cyst
Palmar or plantar pits (3 or more)
Ectopic calcification: lamellar or early (<20 years) calcification of falx cerebri
First-degree relative with Gorlin-Goltz syndrome

Minor Criteria:
Congenital skeletal anomaly: bifid, fused, splayed or missing rib, or bifid, wedged or fused vertebra
Occipitofrontal circumference >97th percentile, with frontal bossing
Cardiac or ovarian fibroma
Medulloblastoma
Lymphomesenteric cysts
Congenital malformation: cleft lip and/or palate, polydactyly, congenital ocular anomaly (cataract, microphthalmos, coloboma)

*Diagnosis requires two major / one major and two minor criteria.

dysmorphism, orofacial clefting and mental retardation. It can be caused by homozygous or compound heterozygous mutations in the *FRAS1* (4q21), *FREM2* (13q13), or *GRIP1* genes (12q14).[13] The Manitoba oculotrichoanal syndrome (MOTA) is also caused by mutations in *FRAS1*.

Lacrimal Gland, Drainage System

• ***Congenital alacrimia.*** Autosomal dominant aplasia of the lacrimal glands with or without aplasia of the salivary glands is a rare condition characterized by dry eye and, in the latter case, xerostomia. It is caused by mutations in the gene encoding *FGF10* (5p12) although two other loci are known.[14] Lacrimoauriculodentodigital syndrome (LADD), also known as Levy-Hollister syndrome, is an allelic disorder with a more severe phenotype.[15] Besides alacrimia and xerostomia, it is characterized by malformation of the external ears, teeth (unerupted and dysplastic teeth), kidneys (renal agenesis, nephrosclerosis) and ditory system (malformation of the auricles (auricular dysplasia, congenital hearing loss). Allgrove syndrome, also known as Triple-A syndrome or Achalasia-Addisonianism-Alacrimia syndrome, is a rare, autosomal recessive disorder. It is caused by mutations in the *AAAS* gene (12q13.13). Patients with this condition may also have autonomic dysfunction such as pupillary abnormalities, abnormal reaction to intradermal histamine, abnormal sweating and orthostatic hypotension. Another condition associated with defective lacrimation and autonomic dysfunction is familial dysautonomia (Riley-Day syndrome), an autosomal recessive disorder caused by mutations in the *IKBKAP* gene (9q31).

• ***Nasolacrimal drainage system anomalies.*** Congenital nasolacrimal duct obstruction is a common disorder that may be associated with many genetic disorders, such as branchiooculofacial syndrome (*TFAP2A* gene mutations, 6p24.3), trisomy 21 (Down syndrome), Johanson-Blizzard syndrome (*UBR1* gene mutations, 15q13-21.1), dyskeratosis congenita (*DKC1* gene mutations, Xq28) and the Treacher-Collins-Franceschetti syndrome. Lacrimal sac fistula is seen in Down syndrome. Patients with Down syndrome may also experience epiphora due to floppy lid syndrome, congenital ectropion or hypotonia of the pump mechanism. REVIEW

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1. Engle EC, Castro AE, Macy ME, et al. A gene for isolated congenital ptosis maps to a 3 cM region within 1p32-p34.1. Am J Hum Genet 1997;60:1150-7.
2. McMullanTFW, Collins AR, Tyers AG, et al. A novel X-linked dominant condition: X-linked congenital, isolated ptosis. Am J Hum Genet 2000;66:1455-60.
3. McMullan TFW, Crolla JA, Gregory SG, et al. A candidate gene for congenital bilateral isolated ptosis identified by molecular analysis of a de novo balanced translocation. Hum Genet 2002;110:244-50.
4. Ganesh A, Al-Kindi A, Jain R, Raeburn S. The phenotypic spectrum of Baraitser - Winter Syndrome: A new case and review of literature. JAAPOS 2005;9:604-6.
5. Pao KY, Levin AV. Genetics in Oculoplastics. In: Black EH, Nesi FA, Gladstone GJ, Levine MR, eds. Smith and Nesi's Ophthalmic Plastic and Reconstructive Surgery. 3rd ed. New York: Springer; 2012:1249-64.
6. Basel-Vanagaite L, Dallapiccola B, Ramirez-Solis R, et al. Deficiency for the ubiquitin ligase UBE3B in a blepharophimosis-ptosis-intellectual-disability syndrome. Am J Hum Genet 2012;91:998-1010.
7. Nouby G. Congenital upper eyelid coloboma and cryptophthalmos. Ophthal Plast Reconstr Surg 2002;18:373-7.
8. Vendramini-Pittoli S, Kokitsu-Nakata NM. Oculoauriculovertebral spectrum: Report of nine familial cases with evidence of autosomal dominant inheritance and review of the literature. Clinical Dysmorphology 2009;18:67-77.
9. Li Y, Bogershausen N, Alanay Y, et al. A mutation screen in patients with Kabuki syndrome. Hum Genet 2011;130:715-24.
10. Honavar SG, Shields JA, Shields CL, Eagle RC Jr, Demirci H, Mahmood EZ. Basal cell carcinoma of the eyelid associated with Gorlin-Goltz syndrome. Ophthalmology 2001;108:1115-23.
11. Twigg SRF, Versnel SL, Nurnberg G, et al. Frontorhiny, a distinctive presentation of frontonasal dysplasia caused by recessive mutations in the ALX3 homeobox gene. Am J Hum Genet 2009;84:698-705.
12. Bardakjian T, Weiss A, Schneider AS, editors. Anophthalmia/Microphthalmia Overview. [monograph on the internet] Gene Reviews; 2006 [cited 2013 Aug 16]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1378/
13. Vogel MJ, van Zon P, Brueton L, et al. Mutations in GRIP1 cause Fraser syndrome. J Med Genet 2012;49:303-6.
14. Entesarian M, Matsson H, Klar J, et al. Mutations in the gene encoding fibroblast growth factor 10 are associated with aplasia of lacrimal and salivary glands. Nature Genet 2005;37:125-8.
15. Milunsky JM, Zhao G, Maher TA, Colby R, Everman DB. LADD syndrome is caused by FGF10 mutations. Clin Genet 2006;69:349-54.


Pseudophakic Cystoid Macular Edema

Pseudophakic CME remains a common cause of reduced vision after cataract surgery. A look at its causes and treatment.

By David R. Lally, MD, and Chirag P. Shah, MD, MPH, Boston

Pseudophakic cystoid macular edema, also known as Irvine-Gass syndrome, was first reported by A. Ray Irvine Jr., MD in 1953 and later elucidated with fluorescein angiography by J. Donald M. Gass, MD, in 1969.[1,2] Despite advances in phacoemulsification for cataract extraction, pseudophakic CME remains a common cause of reduced vision following uncomplicated and complicated cataract surgery.[3]

The detection of CME can be either through clinical examination, angiographic examination or optical coherence tomography examination. Of the three techniques, optical coherence tomography has the highest sensitivity, followed by angiography and then clinical examination. Therefore, the incidence of pseudophakic CME varies depending on which technique is employed. The incidence of CME measured by OCT and fluorescein angiogram after uneventful cataract surgery is up to 41 percent and 30 percent, respectively.[4,5] The detection of CME with these sensitive instruments does not always correlate to visual acuity. In the past, clinical pseudophakic CME was defined as reduced visual acuity in the presence of angiographic petaloid CME following cataract extraction, and the reported incidence was 1 percent to 2 percent.[6] More recently, OCT has emerged as a less invasive, more sensitive tool for detection. The incidence of pseudophakic CME with reduced vision measured by OCT is up to 14 percent.[7]

Histopathology

Histopathological specimens of CME following cataract surgery exhibit retinal capillary dilation, serous fluid in the outer plexiform and outer nuclear layers, and inflammatory cells in the iris, ciliary body and around blood vessels.[8] Intracytoplasmic edema of Müller cells and displacement of photoreceptor nuclei and receptor axons can result in perifoveal cysts or lamellar holes in severe cases. Subretinal fluid can also be seen. Other findings include swollen mitochondria in prelaminar ganglion cell axons, astrocyte degeneration and occlusion of laminar blood vessels.[9] Figure 1 exemplifies the histopathology of a fovea with pseudophakic cystoid macular edema.

Pathophysiology

The pathogenesis of pseudophakic CME appears multifactorial based on experimental studies and clinical observations.[5,10] Proposed etiologic factors include inflammation, vitreous traction and hypotony.[11,12] Of these, the core mechanism is likely surgically induced anterior segment inflammation that results in the release of endogenous inflammatory mediators. Prostaglandins, cytokines and other vasopermeability factors disrupt the perifoveal retinal capillaries, resulting in fluid accumulation.

Prostaglandins are products of the arachidonic acid cascade and have been studied widely as contributors to edema in systemic tissues including the eye.[13] Surgically induced trauma to the iris, ciliary body and lens epithelium disrupts the blood-aqueous barrier resulting in release of prostaglandins, vascular endothelial growth factor, insulin-like growth factor-1 and other inflammatory mediators.[14] These chemical transmitters diffuse through the vitreous to the retina where they disrupt

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the blood-retinal barrier. A critical threshold of inflammatory mediators in the aqueous is likely required for detectable edema.

Risk Factors

The development of pseudophakic CME is influenced by pre-existing systemic and ocular conditions, as well as complications during surgery. It is important to identify risk factors for prophylaxis and treatment.

Diabetes mellitus, even in the absence of diabetic retinopathy, has been shown to almost double pseudophakic CME incidence rates.[15] The incidence of CME post-cataract surgery has also been reported higher in eyes with diabetic retinopathy.[16] Another analysis, however, suggests insufficient evidence for phacoemulsification surgery causing progression of macular edema.[17] Optimally treating diabetic retinopathy and macular edema is advised prior to proceeding with cataract surgery.

Uveitic eyes have a higher incidence of pseudophakic CME detected by OCT than non-uveitic eyes.[18] Strict control of ocular inflammation for at least three months is recommended prior to cataract surgery. Other ocular conditions associated with a higher incidence of pseudophakic CME include epiretinal membrane, vitreomacular traction, retinal vein occlusion and topical prostaglandin use.[19,20]

Before extracapsular cataract extraction technique, the rates of CME were higher with intracapsular cataract extraction. Despite advancements in phacoemulsification technique, surgical complications can still occur and increase the risk of CME. Retained lens fragments have a reported CME incidence up to 46 percent.[21]

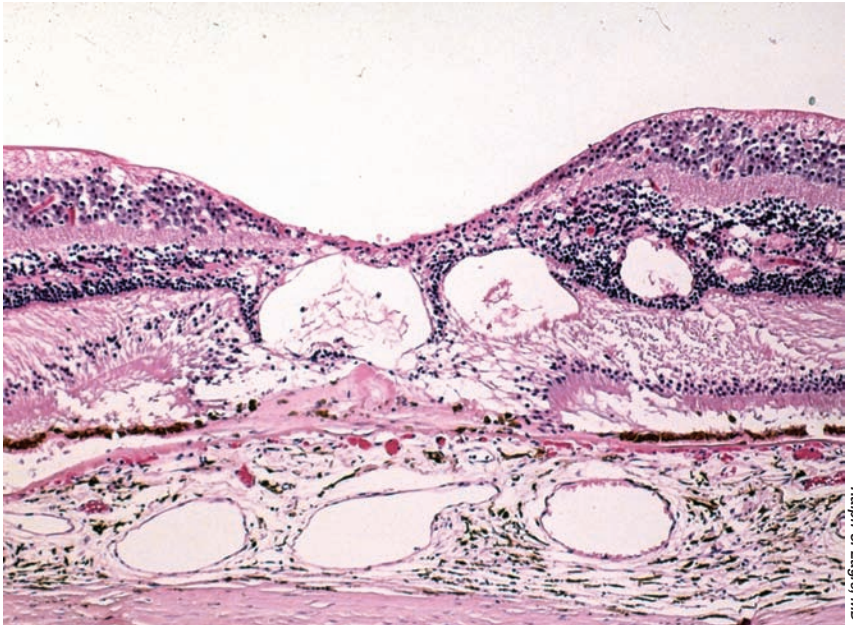
Vitreous loss, vitreous to the wound, iris incarceration in the wound, posterior capsule rupture and YAG capsulotomy have all been reported to predispose to CME.[5] Selection of the intraocular lens also plays a role in CME development. Iris-fixated IOLs have the highest reported rate of CME, and anterior chamber intraocular lenses have a higher rate than posterior chamber intraocular lenses.[5]

Diagnosis

Reduced visual acuity following cataract surgery is the most common clinical finding in pseudophakic CME. The onset is typically four to 12 weeks after surgery, reaching a peak incidence four to six weeks postoperatively. Patients may complain of metamorphopsia, central scotoma and reduced contrast sensitivity. Refraction may show a hyperopic shift. Clinical examination shows loss of the foveal depression and retinal thickening. Intraretinal parafoveal cysts may be observed, occasionally with splinter retinal hemorrhages. The use of a contact lens or narrow-slit beam with slit-lamp biomicroscopy may be helpful in identifying intraretinal cystic changes.

Fluorescein angiography findings include perifoveal capillary leakage beginning in the early to mid-frames that increase in size and intensity to a "petaloid" appearance in later frames *(See Figure 2)*. Late staining of the optic disc is a common finding and helpful in differentiating CME caused by cataract surgery from other causes. Other angiographic findings include capillary dilatation and retinal telangiectasis. On average, around 20 percent of patients undergoing uncomplicated phacoemulsification will develop angiographic CME.[22]

Spectral-domain OCT has emerged as a sensitive tool for detecting and monitoring pseudophakic CME. OCT is an objective, noninvasive and reproducible instrument showing cystic spaces in the outer nuclear and outer plexiform layers *(See Figure 2)*. Occasionally,



Ralph C. Eagle, MD

Figure 1. Histopathology of fovea, hematoxylin and eosin, x10. Large cystoid cavities with transudate are noted within the outer plexiform and outer nuclear layers. The subfoveal photoreceptor layer appears disorganized with disruption of the retinal pigment epithelium.

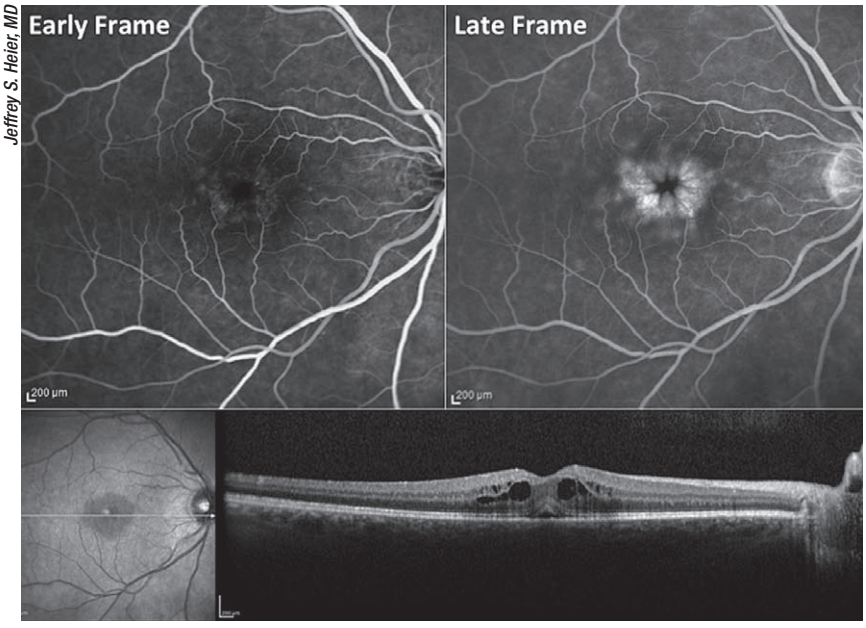


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Figure 2. Fluorescein angiogram of a right eye with pseudophakic cystoid macular edema. Early frame discloses leakage of the perifoveal capillaries (upper left) that increases in size and intensity to a "petaloid" appearance in the later frame (upper right). Spectral-domain optical coherence tomography of the eye is shown in the fluorescein angiogram (bottom). Cystoid spaces are observed in the outer retina with a small amount of foveal subretinal fluid.

intraretinal thickening is present on OCT that lacks the distinct intraretinal cystic pattern. Detachment of the neurosensory retina with subretinal fluid may also be seen.

The natural history of pseudophakic CME is spontaneous resolution of edema with visual improvement in three to 12 months in 80 percent of patients *(See Figure 3)*.[23] Only a small proportion of patients will suffer chronic visual morbidity.

Prophylaxis and Treatment

Currently no standardized protocol exists for the prophylaxis and management of pseudophakic CME because of a lack of prospective randomized clinical trials. Therapeutic interventions are based on the proposed pathogenesis of edema, mainly inflammation and vitreous traction.

In an attempt to reduce the risk of postoperative CME, all pre-existing ocular conditions should be controlled prior to cataract surgery. Eyes with diabetic retinopathy should have appropriate evaluation and management. Uveitic eyes should have adequate inflammation control for at least three months prior to proceeding with cataract surgery.

Topical non-steroidal anti-inflammatory drugs are frequently used off-label in the prophylaxis and treatment of pseudophakic CME. Currently NSAIDs are approved by the Food and Drug Administration for postoperative inflammation only. NSAIDs are potent inhibitors of prostaglandins, a vital mediator in CME development. NSAIDs competitively inhibit cyclooxygenase isoforms COX-1 and COX-2. Of the two isoforms, COX-2 is the predominant isoform in the retinal pigment epithelium.[24] Cyclooxygenase catalyzes arachidonic acid from cell membrane phospholipids to prostaglandins. Numerous studies have reported NSAIDs' efficacy in the prophylaxis of pseudophakic CME. A meta-analysis by Luca Rosetti, MD, and colleagues in 1998 concluded topical NSAID administration was beneficial in lowering the incidence of angiographically and clinically diagnosed pseudophakic CME.[25] A recent randomized, controlled trial examined topical indomethacin for pseudophakic CME prophylaxis and treatment.[26] The study of 189 eyes reported a pseudophakic CME incidence of 0 percent for eyes receiving preoperative and postoperative indomethacin, 15 percent for eyes receiving postoperative indomethacin only, and 33 percent for controls. Another large multicenter RCT reported improvement in visual acuity in the treatment of chronic aphakic and pseudophakic CME using 0.5% ketorolac (Acular, Allergan).[27] Limited data is known about the long-term effects (>one year) of NSAIDs on pseudophakic CME.

The newer NSAIDs on the market include nepafenac and bromfenac, which claim enhanced penetration into the posterior segment based on animal studies.[28,29] Whether similar penetration and improved therapeutic effect is found in human eyes remains unknown. A retrospective review of 450 eyes reported no clinical pseudophakic CME following uneventful phacoemulsification surgery in eyes receiving prophylactic nepafenac compared to five eyes in the control group.[30] This result was statistically significant.

Topical NSAIDs do have side effects that warrant consideration, especially when using NSAIDs for a non-FDA-approved indication like pseudophakic CME. Common side effects include stinging, burning, conjunctival hyperemia and allergy. NSAIDs can be toxic to the cornea, ranging from punctate epithelial erosions to corneal infiltrates or even melt. Delayed corneal epithelial healing has also been reported.

In addition to NSAIDs, topical

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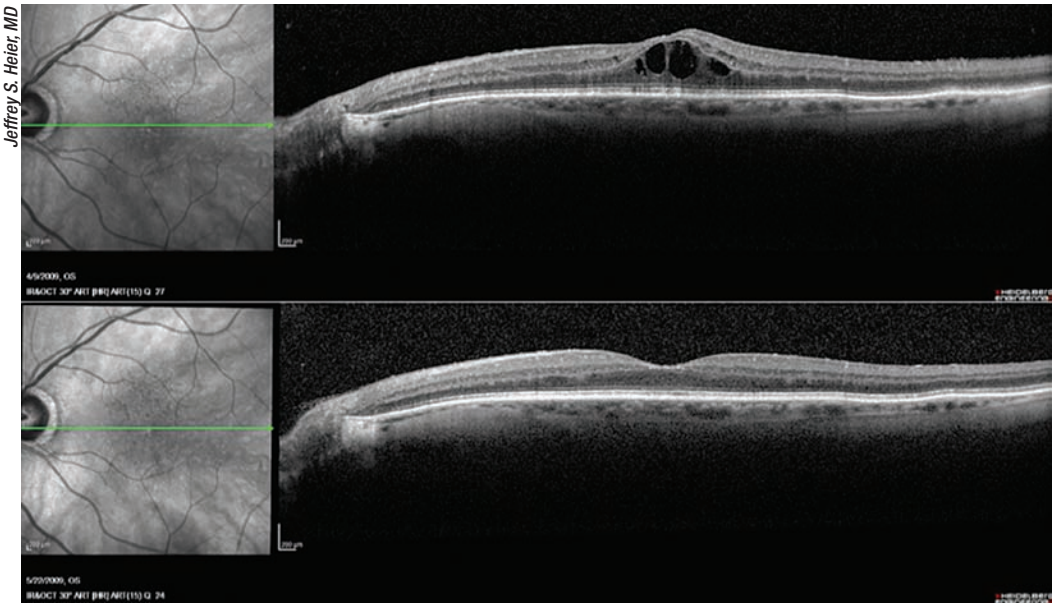

Figure 3. SD-OCT of the left eye reveals CME six weeks following cataract extraction (top) that resolved without therapeutic intervention six weeks later (bottom).

corticosteroids are commonly used in prophylaxis and treatment. Studies reporting the efficacy of corticosteroids in pseudophakic CME are often confounded by concomitant topical NSAID administration. It does appear that combination therapy with topical NSAID and corticosteroid may be superior to either individual therapy. A small, randomized control trial in 2000 compared topical ketorolac to topical prednisolone to combination therapy for the treatment of pseudophakic CME.[31] Average improvement in Snellen visual acuity over three months was 1.6 lines in the ketorolac group, 1.1 lines in the prednisolone group and 3.8 lines in the combination group. Perhaps a synergistic effect is observed with combination therapy, although more studies are needed.

For pseudophakic CME refractory to topical therapy, periocular corticosteroids given sub-Tenon's or subconjunctivally provide more sustained drug release. Intravitreal triamcinolone acetonide, dexamethasone implant (Ozurdex, Allergan) and fluocinolone acetonide implant (Retisert, Bausch + Lomb) have also been used in refractory cases. The literature reporting their efficacy in macular edema is mainly in diabetic or retinal vein occlusion eyes. Their efficacy in pseudophakic CME is unknown. Side effects of periocular and intravitreal corticosteroids include endophthalmitis and elevated intraocular pressure.

Vascular endothelial growth factor causes breakdown of the blood-retinal barrier and increased vascular permeability, contributing to the development of macular edema. Anti-VEGF with intravitreal bevacizumab (Avastin, Genetech) has been shown effective in refractory pseudophakic CME. A multicentered, retrospective study reported that 72 percent of eyes with refractory pseudophakic CME treated with at least one intravitreal bevacizumab injection had improvement in visual acuity with a reduction in mean central macular thickness at 12 months.[32] Forty-three percent of the eyes required more than one injection for best visual acuity.

Carbonic anhydrase inhibitors like oral acetazolamide affect fluid pumping across the subretinal space by retinal pigment epithelial cells. They have been reported effective in treating macular edema due to retinitis pigmentosa and aphakia, but their efficacy in pseudophakic CME is unknown.

When medical therapy is ineffective in resolving pseudophakic CME, surgical intervention is often the next step. Removal of a malpositioned intraocular lens may be effective in certain refractory cases.[33] Nd:YAG laser and pars plana vitrectomy can be used to lyse abnormal vitreous adhesions to the intraocular lens, corneal wound or iris. Release of vitreomacular traction is believed to allow resolution of macular edema. A multicenter, randomized control trial in 1985 examined eyes with chronic aphakic CME attributed to vitreous adherence to the wound.[34] Eyes that underwent pars plana vitrectomy had improved visual acuity compared to controls.

Other therapies reported in small pilot series as effective for refractory pseudophakic CME include intravitreal infliximab (Remicade, Centocor Ortho Biotech),[35] intravitreal diclofenac 500 µm/0.1 ml,[36] and subcutaneous interferon alpha (Imgenex).[37]

Over the past decade, the detection and monitoring of pseudophakic CME has improved with the development of high-resolution, spectral domain OCT. However, the prevention and management of the disease has remained relatively unchanged.

Topical NSAIDs and corticosteroids remain mainstay therapy. Evidence for NSAID use is stronger than for corticosteroid use, and combination therapy may be superior to single therapy although further studies are needed. REVIEW

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1. Irvine SR. A newly defined vitreous syndrome following cataract surgery. Am J Ophthalmol 1953;36:599-619.
2. Gass JD, Norton EW. Follow-up study of cystoid macular edema following cataract extraction. Trans Am Acad Ophthalmol Otolaryngol 1969;73:665-682.
3. Loewenstein A, Zur D. Postsurgical cystoid macular edema. Dev Ophthalmol 2010;47:148-159.
4. Lobo CL, Faria PM, Soares MA, Bernardes RC, Cunha-Vaz JG. Macular alterations after small-incision cataract surgery. J Cataract Refract Surg 2004;30:752-760.
5. Flach AJ. The incidence, pathogensis and treatment of cystoid macular edema following cataract surgery. Trans Am Ophthalmol Soc 1998;96:557-634.
6. Wright PL, Wilkinson CP, Balyeat HD, et al. Angiographic cystoid macular edema after posterior chamber lens implantation. Arch Ophthalmol 1988;106:740-744.
7. Kim SJ, Belair ML, Bressler NM, et al. A method of reporting macular edema after cataract surgery using optical coherence tomography. Retina 2008;28:870-876.
8. Michels RG, Green WR, Maumenee AE. Cystoid macular edema following cataract extraction (The Irvine-Gass Syndrome): A case studied clinically and histopathologically. Ophthalmic Surg 1971;2:217-221.
9. McDonnell PJ, de la Cruz ZC, Green WR. Vitreous incarceration complicating cataract surgery: A light and electron microscopic study. Ophthalmology 1986;93:247-253.
10. Jampol LM. Aphakic cystoid macular edema: A hypothesis. Arch Ophthalmol 1985;103:1134-1135.
11. Reese AB, Jones IS, Cooper WC. Macular changes secondary to vitreous traction. Trans Am Ophthalmol Soc 1966;64:123-134.
12. Wolter JR. The histopathology of cystoid macular edema. Albrecht Von Graefe's Arch Klin Exp Ophthalmol 1981;216:85-101.
13. Miyake K, Ibaraki N. Prostaglandins and cystoid macular edema. Surv Ophthalmol 2002;47:S203-S218.
14. Murata T, Nakagawa K, Khalil A, et al. The relation between expression of vascular endothelial growth factor and breakdown of the blood-retinal barrier in diabetic rat retinas. Lab Invest 1996;74:819-825.
15. Schmier JK, Halpern MT, Covert DW, et al. Evaluation of costs for cystoid macular edema among patients after cataract surgery. Retina 2007;27:621-628.
16. Hayashi K, Igarashi C, Hirata A, Hayashi H. Changes in diabetic macular oedema after phacoemulsification surgery. Eye (Lond) 2009;23:389-396.
17. Shah AS, Chen SH. Cataract surgery and diabetes. Curr Opin Ophthalmol 2010;21:4-9.
18. Belair ML, Kim SJ, Thorne JE, et al. Incidence of cystoid macular edema after cataract surgery in patients with and without uveitis using optical coherence tomography. Am J Ophthalmol 2009;148:128-135.
19. Henderson BA, Kim JY, Ament CS. Clinical pseudphakic cystoid macular edema: Risk factors for development and duration after treatment. J Cataract Refract Surg 2007;33:1550-1558.
20. Warwar RE, Bullock JD, Ballal D. Cystoid macular edema and anterior uveitis associated with latanoprost use: Experience and incidence in a retrospective review of 94 patients. Ophthalmology 1998;105:263-268.
21. Cohen SM, Davis A, Cukrowski C. Cystoid macular edema after pars plana vitrectomy for retained lens fragments. J Cataract Refract Surg 2006;32:1521-1526.
22. Ursell PG, Spalton DJ, Whitcup SM, Nussenblatt RB. Cystoid macular edema after phacoemulsification : Relationship to blood-aqueous barrier damage and visual acuity. J Cataract Refract Surg 1999;25:1492-1497.
23. Bradford JD, Wilkinson CP Bradford RH. Cystoid macular edema following extracapsular cataract extraction and posterior chamber intraocular lens implantation. Retina 1988;8:161-164.
24. Chin MS, Nagineni CN, Hooper LC, Detrick B, Hooks JJ. Cyclooxygenase-2 gene expression and regulation in human retinal pigment epithelial cells. Invest Ophthalmol Vis Sci 2001;42:2338-2346.
25. Rosetti L, Chaudwi H, Dickersin K. Medical prophylaxis and treatment of cystoid macular edema after cataract surgery: The results of a meta-analysis. Ophthalmology 1998;105:397-405.
26. Yavas GF, Ozturk F, Kusbeci T. Preoperative topical indomethacin to prevent pseudophakic cystoid macular edema. J Cataract Refract Surg 2007;33:804-807.
27. Flach AJ, Jampol LM, Weinberg D, et al. Improvement in visual acuity in chronic aphakic and pseudophakic cystoid macular edema after treatment with topical 0.5% ketorolac tromethamine. Am J Ophthalmol 1991;112:514-519.
28. Gamache DA, Graff G, Brady MT, et al. Nepafenac, a unique nonsteroidal prodrug with potential utility in the treatment of trauma-induced ocular inflammation. I: Assessment of anti-inflammatory efficacy. Inflammation 2000;24:357-370.
29. Baklayan GA, Patterson HM, Song CK, et al. 24-h evaluation of the ocular distribution of (14)C-labeled bromfenac following topical instillation into eyes of New Zealand White rabbits. J Ocul Pharmacol Ther 2008;24:392-398.
30. Wolf EJ, Braunstein A, Shih C, Braunstein RE. Incidence of visually significant pseudophakic macular edema after uneventful phacoemulsification in patients treated with nepafenac. J Cataract Refract Surg 2007;33:1546-1549.
31. Heier JS, Topping TM, Baumann W, Dirks MS, Chern S. Ketorolac versus prednisolone versus combination therapy in the treatment of acute pseudophakic cystoid macular edema. Ophthalmology 2000;107:2034-2039.
32. Arevalo JF, Maia M, Garcia-Amaris RA, et al; Pan-American Collaborative Retina Study Group (PACORES). Intravitreal bevacizumab for refractory pseudophakic cystoid macular edema: The Pan-American Collaborative Retina Study Group results. Ophthalmology 2009;116:1481-1487.
33. Shepard DD. The fate of eyes from which intraocular lenses have been removed. Ophthalmic Surg 1979;10:58-60.
34. Fung WE, Vitrectomy-ACME Study Group. Vitrectomy for chronic aphakic cystoid macular edema. Results of a national, collaborative, prospective, randomized investigation. Ophthalmology 1985;92:1102-1111.
35. Wu L, Arevalo JF, Hernandez-Bogantes E, Roca JA. Intravitreal infliximab for refractory pseudophakic cystoid macular edema: Results of the pan-american collaborative retina study group. Int Ophthalmol 2012;32:235-243.
36. Soheilian M, Karimi S, Ramezani A, Peyman GA. Pilot study of intraviteal injection of diclofenac for treatment of macular edema of various etiologies. Retina 2010;30:509-515.
37. Deuter CM, Gelisken F, Stubiger N, et al. Successful treatment of chronic pseudophakic macular edema (Irvine-Gass syndrome) with interferon alpha: A report of three cases. Ocul Immunol Inflamm 2011;19:216-218.

REVIEW Advertising Index

Keeler Debuts New 40H Slit-Lamp

Keeler says its 40H slit-lamp has been designed to deliver Keeler's proven optics and quality construction in an elegant and contemporary design.

The 40H optical system uses Galilean converging binoculars and a rotating five-step drum that offers up to x40 magnification. The tower illumination and slit projection system

has continuously variable slit widths between 0 and 12mm. Blue, red-free and neutral density filters and an integral diffuser provide a good visual of the whole eye at low magnification. To assess for uveitis, a 1-mm square graticule is included within the aperture selections.

The controls are placed for ease of use. An integral yellow barrier filter is conveniently housed in the optics block, which is easily pushed in place when you are looking to detect subtle corneal staining.

The illumination is controlled by a rheostat positioned adjacent to the gliding joystick. The systems come in standard Halogen lamp or LED illumination, which lowers lifetime ownership costs. Keeler also offers a range of optional and diagnostic accessories, including R and T type KAT (Keeler Applanation Tonometer) tonometers, for use with the 40H slit-lamp.

For information, visit Keelerusa.com; email Keeler@Keelerusa.com; call 1 (800) 523-5620; or contact an authorized dealer.

Sequenom Teams with Nicox to Market RetnaGene AMD Test

Nicox S.A. and Sequenom Inc. have entered into an exclusive agreement in the age-related macular degeneration field. As part of this agreement, Nicox has been granted the North American promotional rights to the Sequenom Laboratories RetnaGene AMD laboratory-developed test, for the evaluation of a patient's risk of AMD disease progression within two, five and 10 years. The RetnaGene AMD test will be promoted by the same Nicox U.S. sales force, which recently launched Sjö, an advanced diagnostic panel for the early detection of Sjögren's syndrome. Nicox expects to begin promoting the RetnaGene AMD test in the United States in the first half of 2014.

The manufacturer says the RetnaGene AMD test is an accurate, safe and noninvasive test that uses a DNA sample collected from a cheek swab. The patient's risk of progressing to advanced choroidal neovascular disease is assessed based on four risk factors: genotype, phenotype (severity of the existing symptoms), age and environment (smoking status). Up to 70 percent of disease risk is inherited and predominantly caused by variations in a handful of genes discovered over the last five to 10 years. Most of the affected genes have been identified in regulatory proteins contained within the alternative complement system involved in innate immunity.

The RetnaGene AMD test includes all of the major single nucleotide polymorphisms (SNPs) that have been proven to have the most significant effect on the risk of developing advanced AMD disease. It is the only test with 100 percent of SNPs validated using the Age-Related Eye Disease Study patient samples, one of the largest clinical trials on AMD. The results of the test will provide a clinician with an individual's risk score for progression to

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CNV, in order to optimize patient management with the goal of preserving vision.

Portable Ophthalmic Imaging with Pictor Plus

Volk Optical's Pictor Plus handheld imager delivers convenient portable ophthalmic imaging in any setting. High-resolution images of the retina and anterior segment can now be captured during non-office exams—on non-ambulatory patient visits, at off-site clinics and during field work.

The Pictor Plus weighs in at just 1 pound and fits easily with its accessories into a small briefcase. High-quality jpeg images easily upload via Wi-Fi to computer, are compatible with most major imaging software programs and are adaptable to any patient database system. Patient ID entry assigns unique identifiers to each file, which can be used for patient records or shared for remote diagnosis and consultation.

The Pictor Plus includes two modules for retina and anterior-segment imaging. The retinal module provides a 40-degree field of view of the fundus. Nine fixation points target different regions of the retina. Using a non-mydriatic imaging method, the device can easily image pupils as small as 3 mm. The anterior module images the eye surface and has a series of cobalt blue LEDs for fluorescent imaging.

For information or to arrange a free three-week trial (U.S. only), visit volk.com, call Volk direct at (440) 942-6161, or contact your authorized Volk distributor.

Lacrivera Announces Launch of Dry-Eye Line

Lacrivera has launched a dry-eye line, including the VeraPlug Punctal Occluder. The VeraPlug is a premium product offering excellent retention and patient comfort and will be available in Sterile Pre-loaded and Non-Sterile Bulk packagings. Other products include VeraC7 Collagen, Vera90 Extended Wear Plug, diagnostic tests and additional products that help to treat dry-eye patients. Visit lacrivera.com for more information. REVIEW

(continued from page 51)

about disciplinary actions against pharmacies," he says. "The first way is to ask them directly if there have been any disciplinary actions pertaining to their compounding practice. Additionally, as a consumer, you can access Board of Pharmacy records on disciplinary actions and the status of an individual pharmacist's license by simply going online to the state board of pharmacy's website. You can also check out your local pharmacy on the state board's website. If your state board doesn't have a website, you can call."

Dr. Leiter recommends asking whether the pharmacy has a quality-control department. However, it should be noted that not all testing is the same. "When the pharmacy sends things out for testing," he says, "what is it testing for? What size sampling does it test? For example, if it makes 100 vials, how many does it send out for testing? Testing is just one piece. The person who makes the drug and who does it day in and day out should be evaluated for his or her process and procedures. This needs to be done for every single drug. My pharmacy is basically becoming a manufacturer. I want to be doing this for a long time, and I want to be doing the best job that I can. I now have four people in my quality-control department, and that's all they do. They analyze processes. If there is an error, they analyze that and come back with ideas on why, and they are completely independent from everyone else in the pharmacy. Doctors should call the pharmacy that they are using and quiz them. If they are close by, they should go visit, because if something happens they will get sued. They need to do their due diligence in finding a pharmacy. Many times, the phone calls I get are just about price. I just raised my prices because my cost went way up."

Dr. Goldberg thinks that ophthalmologists across the country are becoming much more conscientious and cognizant of where their Avastin is coming from, and the amount of due diligence that is being done has increased because of these outbreaks and because of this awareness. "Treating physicians should be ensuring that their compounding pharmacy is in compliance with *USP Chapter 797* and is certified by the Pharmacy Compounding Accreditation Board," he says. "When a pharmacy voluntarily submits to this, certified compounding pharmacy inspectors come out and inspect the pharmacy and the processes that are in place to help ensure sterility." REVIEW

1. http://www.bostonglobe.com/metro/2013/12/23/meningitis/E97yWKhnC2LylHRek4KjKJ/story.html
2. Goldberg RA, Flynn HW Jr, Isom RF, Miller D, Gonzalez S. An outbreak of streptococcus endophthalmitis after intravitreal injection of bevacizumab. Am J Ophthalmol 2012;153:204-208.
3. Goldberg RA, Flynn HW Jr, Miller D, Gonzalez S, Isom RF. Streptococcus endophthalmitis outbreak after intravitreal injection of bevacizumab: One-year outcomes and investigative results. Ophthalmology 2013;120:1448-1453.
4. http://www.iacprx.org/associations/13421/files/IACP%20CPAQ%20October%202013.pdf.

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REVIEW® of Ophthalmology

When a patient's decreased visual acuity following cataract surgery persists, she is referred to the Neuro-ophthalmology Service.

Alia K. Durrani, MD

Presentation

A 64-year-old Chinese female presented to the Wills Eye Hospital Neuro-ophthalmology Service for evaluation of decreasing vision after cataract surgery in the left eye. She was originally seen by her primary ophthalmologist outside of Wills eight weeks prior for evaluation of cataracts and was found to have 3+ nuclear sclerosis in both eyes with uncorrected vision of 20/40 and 20/70. She underwent uncomplicated cataract extraction with posterior chamber intraocular lens implantation in the left eye, but the three week postoperative visual acuity was 20/100 with pinhole to 20/70. There was no afferent pupillary defect, extraocular movements were full and intraocular pressure was 15 mmHg in both eyes. Optical coherence tomography of both the macula and optic nerve was normal. She was treated with Pred Forte 1% four times daily, but returned to her ophthalmologist three days later with a vision of count fingers at 3 feet. She was then referred to the Wills Eye Neuro-ophthamology service for evaluation. She denied any numbness, tingling, weakness, headache, jaw claudication, pain on eye movement, myalgias or fevers on presentation.

Medical History

Past medical history was significant for hypertension and cataract in the right eye. She was on unknown anti-hypertensive medications. Family history was non-contributory.

Examination

Ocular examination in the neuro-ophthalmology clinic at Wills revealed visual acuity of 20/25 in the right eye and count fingers at 5 feet in the left eye with a 3+ afferent pupillary defect on the left. Motility was full and IOP was 15 mmHg in the right eye and 12 in the left eye. She correctly identified 11 of 11 color plates in the right eye but only the test plate in the left eye. Slit-lamp examination was notable only for 3+ nuclear sclerosis in the right eye and a PCIOL in the left eye. Dilated fundus examination was unremarkable in the right eye and in the left showed posterior vitreous detachment, attenuated vessels and a pale optic nerve without elevation, edema or hemorrhages.

What is your differential diagnosis? What further workup would you pursue? Please turn to p. 88

Diagnosis, Workup and Treatment

Given the patient's presentation to the neuro-ophthalmology clinic and prior testing, a broad differential diagnosis for optic neuropathy was considered, although giant cell arteritis and NAION were considered to be most likely. Laboratory testing showed a normal erythrocyte sedimentation rate, C-reactive protein and complete blood count. Magnetic resonance imaging with contrast of the brain and orbits revealed a 1.5 x 1.3 cm left ophthalmic segment internal carotid artery (ICA) aneurysm compressing the pre-chiasmatic left optic nerve along with the optic chiasm *(See Figures 1 & 2)*. The patient was sent directly from the imaging center to the Wills Emergency Room, where the exam remain unchanged from her visit to the Neuro-ophthalmology clinic two weeks prior. An emergent neurosurgery consult was placed for evaluation and treatment, and the patient underwent catheter angiography and endovascular embolization.

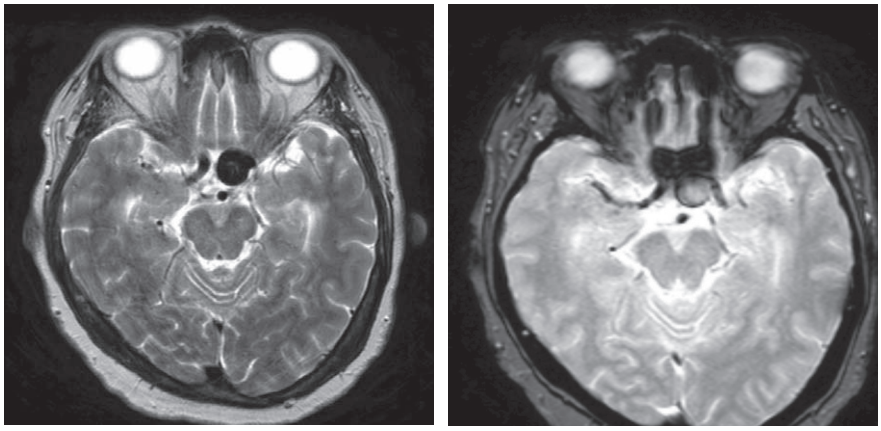

Figure 1. (Left) T2-weighted axial MRI with flow void and (Right) T2-weighted axial MRI post gadolinium contrast administration highlighting a 1.5 x 1.3 cm left ophthalmic segment internal carotid artery aneurysm.

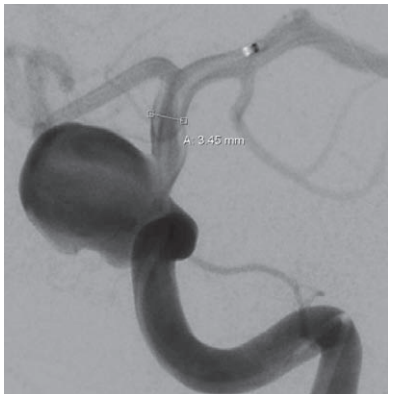

Figure 2. Arterial phase of catheter angiography shows saccular aneurysm arising from the ophthalmic segment of the left internal carotid artery.

Discussion

The differential diagnosis of decreased vision post cataract extraction and PCIOL placement is quite broad. In this particular instance the referring ophthalmologist was concerned for NAION. One early study reported a rate of NAION annually as 10.3 per 100,000.[1] A later published retrospective analysis concluded a post-cataract extraction six-week incidence of 34.6 per 100,000 and six-month incidence of 51.8 per 100,000.[2] Local vasoactive peptide release and IOP fluctuation during and after surgery could result in inadequate blood supply to the posterior ciliary arteries.[3]

Our patient was found to have an aneurysmal dilatation of the ophthalmic segment of the left ICA. Approximately 14 percent of unruptured aneurysms have been reported to present with cranial nerve deficits, subsequently leading to the diagnosis.[4] Of these, the ICA-Posterior Communicating Artery junction aneurysms are the most common, characteristically presenting with a third-nerve palsy.[5] ICA-ophthalmic artery junction aneurysms have been described to cause compression of the optic nerve, chiasm or both. Most commonly, vision loss is slow and progressive, but it may also be painful, mimicking an optic neuritis.[5] Rarely, an aneurysm of the intracavernous ICA may cause vision loss if the dilatation arises from the distal portion of the artery.[5]

The morbidity and mortality of intracerebral aneurysms lie within the risk of rupture and subsequent hemorrhage and vasospasm. There are 30,000 ruptured aneurysms annually in the United States, with a 40- to 50-percent survival rate.[4,6] Of the remaining 50 to 60 percent, approximately 20 percent have no significant neurologic deficits.[4,6]

Ophthalmologic signs and symptoms of aneurysms include mydriasis, cranial nerve palsies, diplopia, decreased vision and pain. The "gold standard" for imaging an aneurysm is catheter angiography. However, computed tomography angiography and magnetic resonance angiography are more commonly performed due to their overall quality without the risks of traditional catheter angiography.

Size and location have been noted to be two major risk factors for aneurysm rupture. The five-year cumulative risk of rupture in our patient is 14.5 percent, whereas in an aneurysm with a diameter of 7 mm or less, the risk is 0 percent.[7] In patients with aneurysms 25 mm or larger, the risk of rupture is

up to 40 percent.[7] Additionally, aneurysmal dilation of the vertibrobasilar or posterior cerebral circulation and the basilar tip confer an increased risk of rupture.[4]

Treatment options for intracerebral aneurysms include observation, open microsurgical clip ligation and endovascular coil embolization.[6] Observation is generally limited to smaller aneurysms with little risk of rupture or aneurysms located in a difficult point to access. Clipping has been best utilized for a wide-necked aneurysm and confers a 1 to 4 percent mortality rate and an additional morbidity rate of 10 to 15 percent cognitive or physical disability.[8] Endovascular coiling, although associated with lower mortality and morbidity rates of 1 to 2 percent and 8 percent, respectively, has resulted in higher recurrence risks.[8] REVIEW

The author would like to thank Mark Moster, MD, of the Wills Eye Hospital Neuro-ophthalmology Service, and Joshua Ehrlich, MD, of the Wills Eye Hospital Residency Program for their time and assistance in preparing this case report.

1. Johnson LN, Arnold A. Incidence of nonarteritic and arteritic ischemic optic neuropathy. Population-based study in the state of Missouri and Los Angeles County, California. J Neuroophthalmol 1994;14(1):38-44.
2. McCulley TJ, Lam BL, Feuer WJ. Incidence of nonarteritic anterior ischemic optic neuropathy associated with cataract extraction. Ophthalmology 2001;108:1275-8.
3. Lee H, Kim CY, Seong GJ, Ma KT. A case of decreased visual field after uneventful cataract surgery: Nonarteritic anterior ischemic optic neuropathy. Korean J Ophthalmol 2010 Feb;24(1):57-61. doi: 10.3341/kjo.2010.24.1.57. Epub 2010 Feb 5.
4. International study of unruptured intracranial aneurysms investigators. Unruptured intracranial aneurysms - risk of rupture and risks of surgical intervention. N England J Med 1998;339:1725-1733.
5. Quiros PA, Hedges TR. Vascular Disorders. In Ophthalmology (3rd Edition). Yanoff M and Duker JS (Eds.). Harcourt, London, 2008.
6. Dhar S, Tremmel M, Mocco J, et al. Morphology parameters for intracranial aneurysm rupture risk assessment. Neurosurg 2008;63:185-197.
7. International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms: Natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet 2003;362(9378):103-10.
8. Johnston C, Higashida RT, Barrow DL, et al. AHA Scientific Statement. Recommendations for the endovascular treatment of intracerebral aneurysms. Stroke 2002;33:2536-2544.

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.

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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%

Allergan at your service