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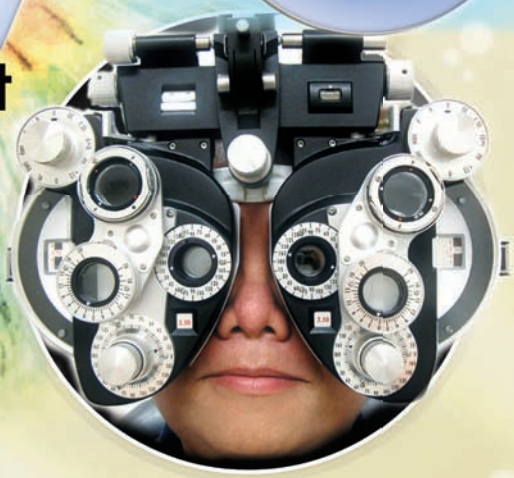
ARVO

Annual Meeting Report



Reports on the latest international research in glaucoma, cataract, refractive surgery, cornea, retina and contact lenses.

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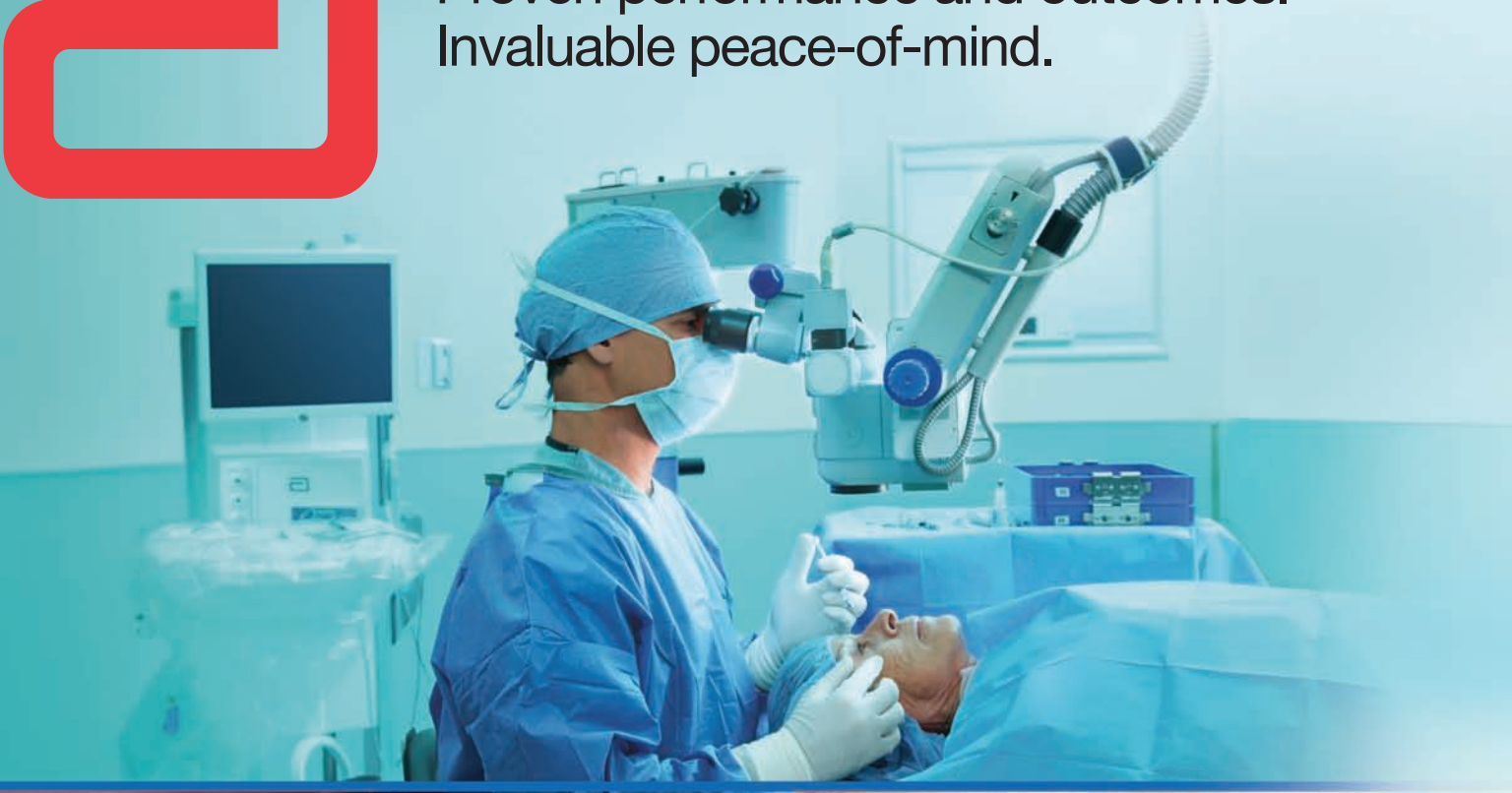

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TECNIS® Multifocal 1-Piece Intraocular Lens (IOL)
Warnings: Physicians considering lens implantation should weight the potential risk/benefit ratio for any conditions described in the TECNIS® Multifocal 1-Piece Intraocular Lens (IOL) Directions for Use that could increase complications or impact patient outcomes. The TECNIS® Multifocal 1-Piece Intraocular lens should not be placed in the ciliary sulcus. Patients should be informed about the possibility that a decrease in contrast sensitivity and an increase in visual disturbances may affect their ability to drive a car under certain environmental conditions, such as driving at night or in poor visibility conditions. **Precautions:** The long term effects of intraocular lens implantation have not been determined. Secondary glaucoma has been reported occasionally in patients with controlled glaucoma who received lens implants. Do not reuse, resterilize or autoclave. **Adverse Events:** The most frequently reported adverse event that occurred during the clinical trial of the TECNIS® Multifocal 1-Piece lens was secondary surgical re-intervention in 3.7% of patients (0.6% lens-related and 3.2% not lens-related). Other reported adverse events were macular edema (2.6%), hypopyon (0.3%) and endophthalmitis (0.3%).

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REVIEW NEWS
Volume XX • No. 5 • May 2013

Ranibizumab May Protect Against Proliferative Retinopathy

A new study by scientists from the Schepens Eye Research Institute/ Massachusetts Eye and Ear and the Department of Ophthalmology, Harvard Medical School, suggests that ranibizumab, an anti-VEGF-A monoclonal antibody fragment, is a potential prophylaxis for proliferative vitreoretinopathy. The study was published on the *American Journal of Pathology* website and scheduled for the May 2013 print edition.

PVR, a serious, sight-threatening complication in people recovering from surgical repair of retinal detachment, is difficult to predict, lacks effective treatment options and substantially reduces an individual's quality of life. Each year 55,000 people are at risk for developing PVR in the United States alone.

"In this manuscript we present basic studies that have clear implications for disease pathogenesis and therapy," said senior author Andrius Kazlauskas, PhD, senior scientist and Sinon Scholar in Retinal Research at Schepens and a professor of ophthalmology at Harvard Medical School.

Researchers found that the putative mediators of PVR pathogenesis are growth factors, which contribute to common diseases such as atherosclerosis and cancer. "Consequently, elucidating functional relationships between growth factors and resolving their contribution to pathogenesis is of wide interest because such information will substantially advance our ability to combat a broad spectrum of diseases," Dr. Kazlauskas said.

While investigating the functional relationships between growth factors known to promote pervasive human diseases, researchers discovered that ranibizumab reduced the bioactivity of vitreous from patients and experimental animals with PVR, and protected rabbits from developing this disease.

These pre-clinical findings suggest that one of the clinically approved approaches to neutralize VEGF-A constitutes a novel prophylactic for an incurable, blinding disease.

"Our discoveries also raise the provocative idea that anti-VEGF-based therapies may be effective for managing more than the angiogenesis—and vascular-permeability-driven pathological conditions," Dr. Kazlauskas says.

Swedish Research Targets CNS for Eye Diseases

Using new technology and new approaches, researchers at Lund University in Sweden hope to be able to explain why people suffer vision loss in eye diseases such as retinal detachment and glaucoma.

Research on diseases of the eye such as retinal detachment and glaucoma has until now focused on the biochemical process that takes place in the eye in connection with the diseases.

Fredrik Ghosh, MD, PhD, and Linnéa Taylor have concentrated instead on attempting to understand what happens on a biomechanical level in the diseases and have produced results that have drawn a lot of interest from experts.

"We have not previously understood the mechanisms behind glaucoma and retinal detachment, but we knew that these diseases had a strong mechanical component. Our findings could form an initial explanation as to why we develop these diseases," said Dr. Ghosh and Ms. Taylor.

Using new technology, the eye researchers at the Department of Clinical Sciences in Lund, in collaboration with researchers at the Department of Biology at Lund University, have developed a method to investigate the importance of the biomechanical environment within the central nervous system.

For their studies, they grow retinal tissue from adult pigs in a stretched state similar to the normal mechanical state present in the living eye. Compared with unstretched tissue, which in cultures dies after a few days when the retina's mechanical balance is disturbed, studies can now be performed for up to 10 days in retina with a well-preserved structure and significantly higher cell survival.

"This gives us new tools to understand in a more concrete manner how biomechanical factors in the central nervous system influence the health of cells when we are healthy and when we suffer from diseases. This will not only have major importance for our understanding of how diseases come about in the central nervous system,

but also for future disease treatment," said the researchers.

The central nervous system, which includes the brain, spinal cord and retinas, is a complicated organ, especially in terms of structure. The entire system is under the mechanical influence of fluid pressure, among other factors. The new data from the group in Lund indicates that when the biomechanical balance is disturbed, as happens in retinal detachment and glaucoma, the normal function of the retina is lost, resulting in serious sight impairment or blindness.

Cholesterol Tied to Macular Disease

A study published on April 2nd in the journal *Cell Metabolism* sheds light on how cholesterol metabolism in white blood cells—called macrophages—contributes to macular degeneration and proposes new drugs, some administered via eye drops, to cure the disease in mice.

"Our increased understanding of cholesterol's role in the growth of ocular blood vessels helped us identify therapeutically modifiable pathways, opening up avenues for new treatments that may help us prevent blindness caused by macular degeneration," says senior study author Rajendra Apte MD, PhD, of Washington University School of Medicine.

Past studies have shown that macrophage cholesterol accumulation is a common feature in AMD. In addition, macrophages promote the abnormal growth of blood vessels in the aged eye, leading to blindness. But until now, the precise mechanisms by which macrophages cause the growth of new blood vessels and potentially blindness, as well as the possible role of cholesterol metabolism in this process, were not known.

In the new study, Dr. Apte and his team found that macrophages taken

from both old mice and human AMD patients had low levels of ABCA1, a cholesterol transporter known to move cholesterol out of the cells. As a result, these old macrophages accumulated high levels of cholesterol and were unable to inhibit the growth of new blood vessels. In order to restore cholesterol transport, the researchers focused on two key cholesterol regulators: Liver X Receptor (LXR), whose activation is known to promote cholesterol efflux, and microRNAs-33, which has been shown to directly decrease ABCA1 expression. Old mice were treated with either an LXR agonist, delivered via eye drops or injection, or a microRNA-33 inhibitor. Both of these drugs increased ABCA1 protein levels and improved cholesterol transport in macrophages, resulting in a reduction in the growth of blood vessels. Because the LXR agonist can be delivered with eye drops, it could potentially cause fewer side effects.

"Abnormal blood vessel growth is a characteristic of not only AMD, but also diverse disease processes outside the eye, including cancers and atherosclerosis, which are both associated with significant morbidity and mortality," Dr. Apte says. "Our findings may have significant relevance in our understanding of the pathobiology of these conditions."

EyeGate: Uveitis Treatment as Good As Eye Drops

EyeGate Pharma announced that the topline results from its Phase III study of EGP-437, a corticosteroid formulation, in anterior uveitis patients demonstrate that two iontophoretic treatments of EGP-437 achieved the same response rate as the positive control, prednisolone acetate 1% ophthalmic suspension administered as multiple daily eye drops, the current standard of care.

In this randomized, double-masked placebo-controlled study conducted at 45 clinical sites in the United States, a total of 193 patients were randomly assigned into one of two treatment arms (iontophoretic treatment on days 0 and 7 or 14 days daily treatment of prednisolone acetate 1% ophthalmic solution, which was followed by two weeks of standard tapering). The primary efficacy endpoint is the proportion of patients with anterior chamber cell count of zero on day 14, which is defined as a complete response.

In all randomized subjects (the intent-to-treat population), only two iontophoretic treatments with EGP-437 (days 0 and 7) resulted in 32 complete responses out of 96 patients on day 14; the standard-of-care uveitis treatment (daily treatment), prednisolone acetate 1% ophthalmic suspension, also yielded 32 complete responses out of 97 patients who received multiple daily self-administered eye drops over the first 14 days (days one to seven: eight drops per day and days eight to 14: six drops per day).

The incidence and severity of treatment-emergent adverse events in both groups were comparable; there were fewer incidences of elevated intraocular pressure in the EGP-437 group.

"Inadequate compliance with aggressive eye drop regimens often leads to treatment failures," said Dr. John Sheppard, the study's principal investigator. "Offering our uveitis patients a safe, effective treatment option that is controlled by the health-care provider rather than the patient represents an important breakthrough, especially when there is a history of poor compliance, difficulty with eye drop self-administration, elevated IOP, glaucoma or preservative toxicity. Iontophoresis technology creates new paradigms for both ocular drug delivery and for uveitis management." REVIEW

B+L's Once-Daily Prolensa Approved for Post-Cataract Care

The Food and Drug Administration has approved Bausch + Lomb's New Drug Application for Prolensa (bromfenac ophthalmic solution) 0.07 % prescription eye drop, a once-daily nonsteroidal anti-inflammatory drug for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery. Prolensa will be available in 1.6 ml and 3 ml bottle sizes.

With the potency of the bromfenac molecule in a formulation designed to facilitate ocular penetration, Prolensa's formulation allows for a lower concentration of bromfenac in a once-daily dosing regimen, B + L says. Prolensa is a solution that does not require shaking to deliver a consistent dose in each drop.

The efficacy of Prolensa was evaluated in two randomized, double-masked, vehicle-controlled studies of patients undergoing cataract surgery. Each patient received Prolensa or vehicle starting with one drop into the surgical eye on the day prior to and the day of surgery, and for 14 days following surgery. The primary efficacy endpoint was complete clearing of ocular inflammation (assessed by the summed ocular inflammation score, SOIS, which includes cells and flare) by day 15. The secondary efficacy endpoint was the number of subjects who were pain-free on day one after surgery.

Results from the pivotal studies demonstrated Prolensa to be superior to vehicle in the treatment of both inflammation and pain following cataract surgery. Twice as many patients as vehicle (46 percent versus 20 percent) demonstrated complete clearance of inflammation (SOIS of 0) at day 15. The difference in the average postoperative inflammation severity between the treatment and vehicle arms was statistically and clinically significant by day eight. Nearly four of five patients treated with Prolensa were pain-free at day one (78.8 percent versus 49.5 percent for vehicle; $p<0.0001$). Patients treated with Prolensa reported a lower incidence of foreign body sensation and photophobia and had less redness than those treated with vehicle. For information, visit bausch.com.

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Ophthalmic Product Development Insights

Matthew Chapin • Ora Inc., Andover, Mass.

The first column in this series discussed the importance of "beginning with the end in mind" and creating the target product profile early in the development process (*See March 2013, p. 6*). This is critical to help define product strategy early and guide preclinical and clinical approaches. This installment will address another key question that early companies or new physician-entrepreneurs commonly ask: "When do I go to meet with FDA?" The regulatory perspective from the Food and Drug Administration is a key input in defining the overall development strategy.

The general guidance is to meet with FDA early, and always transparently. The balance is between going to confirm plans early, or waiting for a later meeting to bring further data in hand. The ophthalmic division at FDA is very open to early discussions in order to help guide the product strategy; it is grounded in clinical science and focused on helping sponsors to be as efficient as possible. The division will raise items that will be very helpful to consider during development. For the clinical study, it is desirable to submit a detailed clinical protocol with full design, inclusion/exclusion criteria, endpoints, visit schedule, details of the clinical scales, and statistical analysis plan for FDA review. This will ensure the most complete feedback from FDA, as opposed to providing them just a brief summary outline.

Here are some brief key considerations to help decide when it may be appropriate for the pre-IND meeting with FDA, which precedes and helps shape the preparation of the IND (Investigational New Drug Application) that must be submitted to FDA prior to initiation of clinical trials. Addressing this question also draws us closer to some key issues encountered during early development, specifically in the areas of toxicology and formulation/CMC (chemistry, manufacturing and controls), and can help avoid costly delays.

Pharmacology

Sometimes a specific pharmacology study is put on the critical path for meeting with FDA. However, in shaping the early discussion with FDA, it is important to balance what might just be interesting to include or test in a preclinical efficacy or pharmacokinetic study, with what will impact decision making. Will this change whether we move ahead, or which lead drug to select to move to IND-enabling studies? Will this study definitively help us to chose a formulation, etc.?

Once preclinical proof of concept is obtained, from the perspective of the timing of a regulatory discussion, the key outcome of these studies—dose selection, route of administration and potential pattern for use—feeds into the pre-IND discussion. Beyond that, the focus and need is safety.

Toxicology

Early interaction in the form of a pre-IND meeting can uncover answers that help the design of the toxicology program. For example, how many species are required? Is the proposed dosing sufficient? And how can the studies be streamlined? While generally two species are required with ocular toxicology for a new IND, if the drug is being repurposed from a non-ocular area in which significant systemic data is already available or human data exists, it may be possible to reduce the program to one species and reduce the systemic assessments. In that case, meeting early can save the company from expending resources that can be used elsewhere. If the compound is a reformulation of an existing ophthalmic product, it's preferable to confirm as early as possible the question of any further GLP ocular toxicology being needed, or whether it is reasonable to reduce the number of animals or treatment arms required. Even a short-term GLP ocular toxicology study of 14 to 28 days in duration of dosing will take several months when considering start-up and reporting by the laboratory. Further, when systemic toxicology is an open question, having at least some information on systemic absorption following ocular dosing will help define the safety margin and ability to use and bridge to existing systemic toxicology, making the discussion with FDA most productive.

It is important for early-stage companies to recognize that you also want to enable the FDA to answer the question as completely as possible. For example, if the intent is to obtain general guidance from FDA on the approach to toxicology, and there are other strategic reasons to go early, one could consider meeting prior to identifying the final clinical formulation or the exact final dose. However, in order to obtain more complete responses from FDA on details of the toxicology requirements, or what aspects can be waived, you should attempt to detail as closely as possible what the final clinical formulation to be used in the initial clinical trial will be, including a list of which excipients (inactive ingredients) the clinical formulation will contain (if not the final formulation), and a target concentration range. An issue arises when the intent is to get FDA to commit to details of a toxicology program too early, before the clinical formulation is defined. For drugs of a novel mechanism, for example, it would be especially prudent to have at least some early toxicology (even non-GLP) studies completed going into the meeting, so that the proper proposal can be included for discussion with FDA.

CMC

One issue that comes up frequently is formulation change, as it impacts the decision making on when to go to FDA. Many times we see formulation changes made after the proof of concept is defined in an appropriate animal model, or after the GLP ocular toxicology is completed with an early formulation, or following the initial human study going into Phase II follow-up studies. While formulation changes may be unavoidable and driven by a need to correct issues seen during stability testing, for example, the impact this may have on pharmacokinetics, comfort, dwell time on the surface of the eye, efficacy and toxicology must all be considered. This highlights the importance of an appropriate, formal, formulation-development process, with some accelerated and room-temperature stability data obtained as soon as possible in the intended container closure system. You need to plan for the FDA meeting when key data will be in hand that will allow proper positioning of the intended formulation and container closure in the pre-IND briefing package.

Many times, minor adjustments are not an issue. However if the new formulation may potentially impact penetration or dwell time significantly, or introduces novel excipients, then a bridging GLP toxicology study may be needed. Sometimes there is a desire driven by need for extended patent coverage to combine a drug with a novel formulation technology as a vehicle to enhance the agent's dwell time or penetration. However, the impact of an enhanced vehicle—for example in the case of dry eye—must be considered in the context of what that will do to the placebo effect and ultimately the ability to show a treatment effect. Further, in that case, inclusion of what is intended to be an excipient, such as a demulcent that is also listed as an active ingredient on the dry-eye monograph (such as HPMC, CMC, glycerin, etc.) will have a regulatory impact and a need to show the contribution of the elements or treatment as a combination product. This is definitely an area that requires a multidisciplinary approach to the decision-making process, and consideration of when the formulation change and future plans should be discussed with FDA to assure there won't be surprises when the IND is filed.

Ultimately, the appropriate timing of the pre-IND meeting comes down to the critical questions the sponsor wants to ask FDA. Even when there may not be significant technical issues, it serves as a key milestone for the board, investors or internal team to vet the program. Other times, prior to embarking on the GLP toxicology studies, the goal may be to confirm the designs and requirements for supporting the IND and initial trial, or to confirm that a formulation change does not require repeating certain toxicology work that was conducted with a prior formulation.

Rushing to request the pre-IND meeting can also be a potential pitfall. It takes a of couple months to get a date with FDA, but this is initiated before a full technical assessment is completed and overlaid with detailed time lines of activities and delivery of key data. Then when the deadline comes for submission of the briefing package (which is one month ahead of the scheduled FDA meeting), the anticipated data may not be available or is not as expected, and plans need to be modified. It comes down to identifying what the critical questions are for the pre-IND meeting and what info you want to submit in the package. Then you backtrack to when any actions need to start in order to have that data.

These are just a few of the elements of the decision process on when to meet with the FDA. It is acceptable to go and have early conceptual discussions, and it is acceptable to go later when all elements are completed and the IND is almost ready to file. It is important to remember that for the questions being asked, the responses from FDA will be directly related to the information provided to them for review. The timing and elements for discussion at the pre-IND meeting with FDA will be guided by these questions about technical, regulatory and business considerations. It is these strategic inputs that will allow determination of when is "not too early, and not too late." REVIEW

Mr. Chapin is vice president, corporate development at Ora Inc. Ora provides a comprehensive range of product development services in ophthalmology.

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Indication

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

Important Safety Information

Warnings and Precautions

- A decrease of ≥ 3 lines of best-corrected visual acuity (BCVA) was experienced by 5.6% of patients treated with JETREA and 3.2% of patients treated with vehicle in the controlled trials. The majority of these decreases in vision were due to progression of the condition with traction and many required surgical intervention. Patients should be monitored appropriately.
- Intravitreal injections are associated with intraocular inflammation/infection, intraocular hemorrhage and increased intraocular pressure (IOP). Patients should be monitored and instructed to report any symptoms without delay. In the controlled trials, intraocular inflammation occurred in 7.1% of patients injected with JETREA vs 3.7% of patients injected with vehicle. Most of the post-injection intraocular inflammation events were mild and transient. If the contralateral eye requires treatment with JETREA, it is not recommended within 7 days of the initial injection in order to monitor the post-injection course in the injected eye.

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

Reference: 1. JETREA [package insert]. Iselin, NJ: ThromboGenics, Inc.; 2012.

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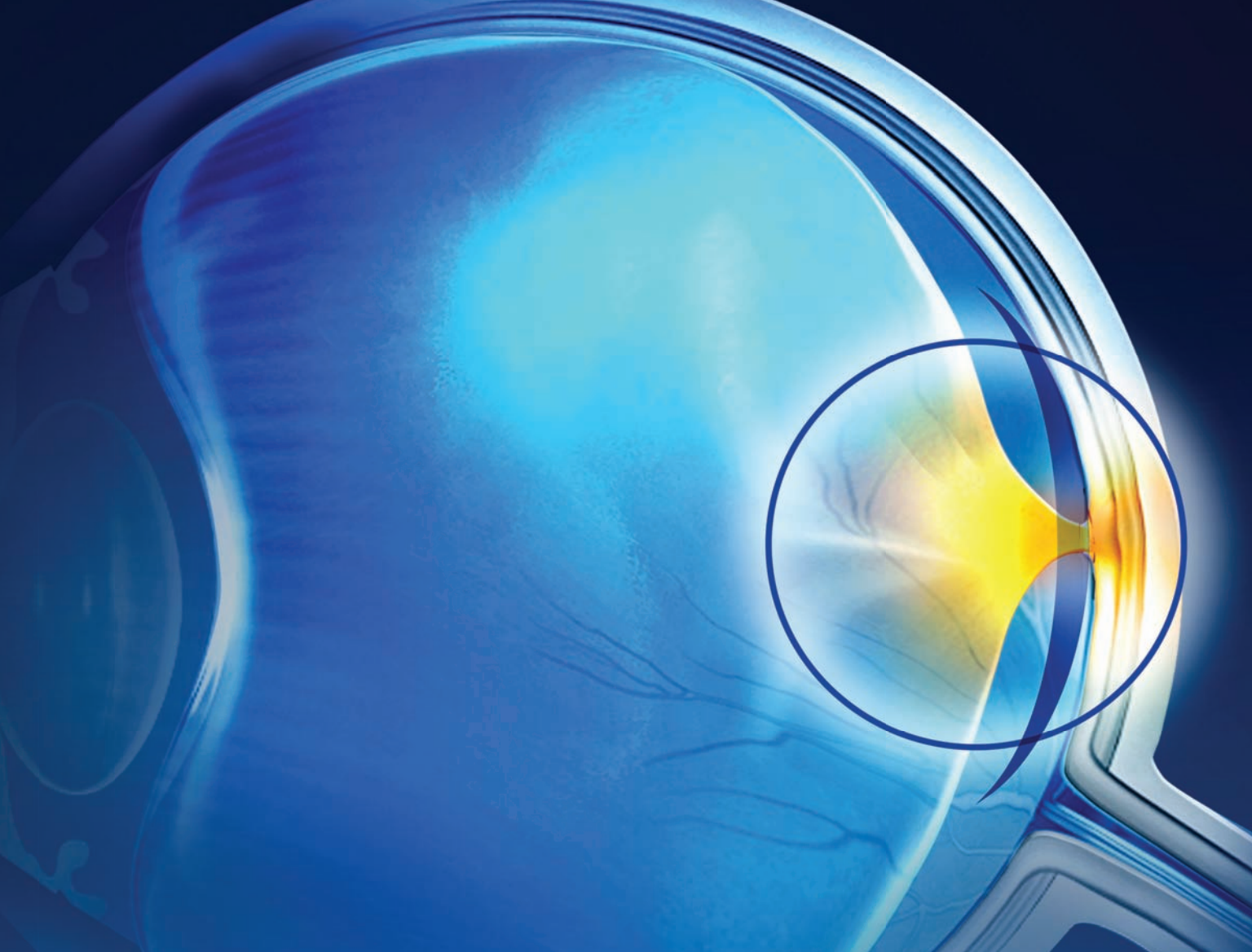

- Potential for lens subluxation.
- In the controlled trials, the incidence of retinal detachment was 0.9% in the JETREA group and 1.6% in the vehicle group, while the incidence of retinal tear (without detachment) was 1.1% in the JETREA group and 2.7% in the vehicle group. Most of these events occurred during or after vitrectomy in both groups.
- Dyschromatopsia (generally described as yellowish vision) was reported in 2% of all patients injected with JETREA. In approximately half of these dyschromatopsia cases there were also electroretinographic (ERG) changes reported (a- and b-wave amplitude decrease).

Adverse Reactions

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

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BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

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

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

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

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

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

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

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

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

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

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

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

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

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

After injection, any unused product must be discarded.

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

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

4 CONTRAINDICATIONS
None

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

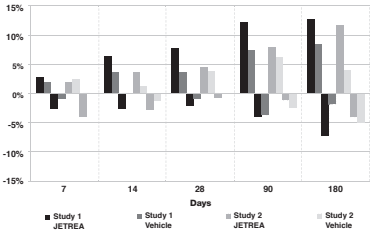
Patients were treated with a single injection of JETREA or vehicle. In both of the studies, the proportion of patients who achieved VMA resolution at Day 28 (i.e., achieved success on the primary endpoint) was significantly higher in the ocriplasmin group compared with the vehicle group through Month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

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

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

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

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



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

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

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

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

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

U.S. License Number: 1866

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

04/13 OCRVMA0072 PI A

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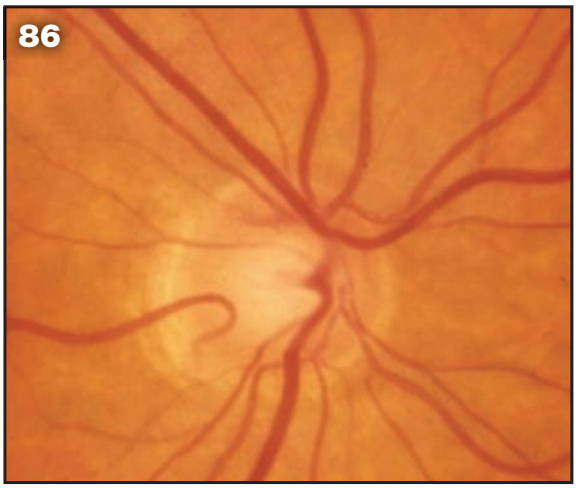

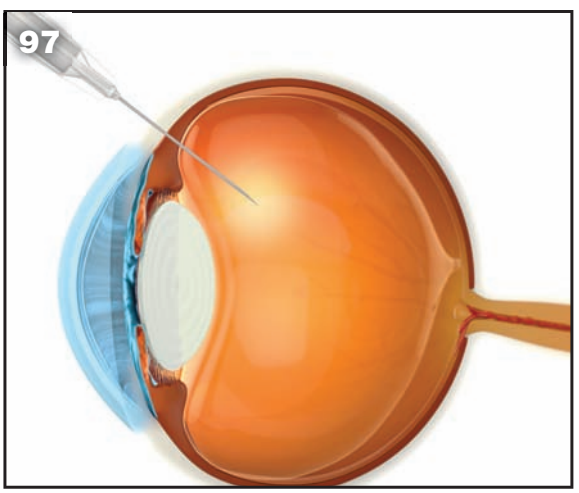

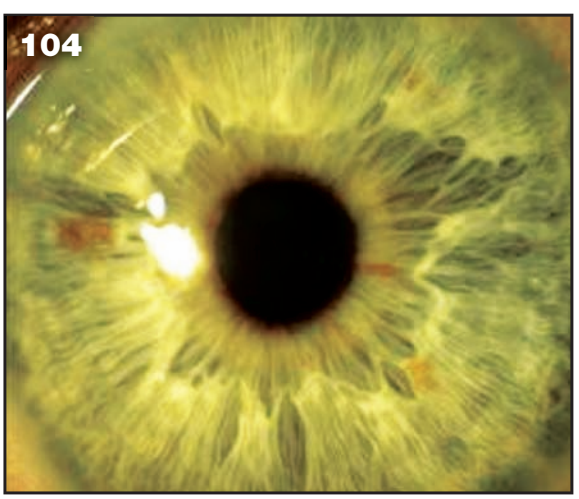

Proof positive for more eyes

- Proven therapeutic utility in a variety of superficial ocular infections—including blepharitis, conjunctivitis, and others
- Profound activity against common gram-positive pathogens—Streptococci, Staphylococci,[1] and MRSA[2,3]
- A sensitivity and resistance profile that's remained virtually unchanged over time[4]
- Unsurpassed safety profile—allergenicity and side reactions are practically non-existent[1]
- Convenient dosing—1-3 times daily[1]
- Tier 1 co pay vs. leading brands[5]

Please see adjacent page for full prescribing information

Important Safety Information

Bacitracin ophthalmic ointment should not be used in deep-seated ocular infections or in those that are likely to become systemic.

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

www.ferapharma.com

References: 1. Bacitracin Ophthalmic Ointment [Package Insert]. Locust Valley, NY; Fera Pharmaceuticals, LLC;2009. **2.** Kowalski RP, Karenchak LM, Romanowski EG. Infectious disease: changing antibiotic susceptibility. *Ophthalmol Clin N Am* 2003;16:1-9. **3.** Freidlin J, Acharya N, Lietman TM, Cevallos V, Whitcher JP, Margolis TP. Spectrum of eye disease caused by methicillin-resistant *Staphylococcus aureus*. *Am J Ophthalmol* 2007;144:313-315. **4.** Recchia FM, Busbee BG, Pearlman RB, Carvalho-Recchia CA, Ho AC. Changing trends in the microbiologic aspects of postcataract endophthalmitis. *Arch Ophthalmol* 2005;123:341-346. **5.** http://fingertipformulary.com/drugs/Bacitracinopthalmicointment/

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BACITRACIN OPHTHALMIC OINTMENT USP
STERILE

℞ only

DESCRIPTION: Each gram of ointment contains 500 units of Bacitracin in a low melting special base containing White Petrolatum and Mineral Oil.

ACTION: The antibiotic, Bacitracin, exerts a profound action against many gram-positive pathogens, including the common Streptococci and Staphylococci. It is also destructive for certain gram-negative organisms. It is ineffective against fungi.

INDICATIONS: For the treatment of superficial ocular infections involving the conjunctiva and/or cornea caused by Bacitracin susceptible organisms.

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

PRECAUTIONS: Bacitracin ophthalmic ointment should not be used in deep-seated ocular infections or in those that are likely to become systemic. The prolonged use of antibiotic containing preparations may result in overgrowth of nonsusceptible organisms particularly fungi. If new infections develop during treatment appropriate antibiotic or chemotherapy should be instituted.

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

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

HOW SUPPLIED: 3.5 g (1/8 Oz) sterile tamper proof tubes, NDC 48102-007-35.

FERA

Manufactured for:
Fera Pharmaceuticals, LLC
Locust Valley, NY 11560
FPBC00N Rev. 08/09

REVIEW® of Ophthalmology

REVIEW Editor's Page

Christopher Glenn, Editor in Chief

Want to Feel Better? Go See a Doctor

Some clearly coincidental placement of our smaller feature articles this month, with a look at eight ways the Affordable Care Act may impact your practice (p. 78), followed by a look at physician burnout (p. 82). A poll published this month by medscape.com just happens to rank "present and future impact of the ACA" as the second leading cause of burnout among its surveyed physicians. (The leading cause, "too many bureaucratic tasks," seems unlikely to find much relief as ACA rolls out.)

The good news in the medscape survey is that ophthalmology ranked 22nd of 24 specialties for the percentage of doctors identifying themselves as burned out, defined as experiencing at least one symptom including loss of enthusiasm for work, feelings of cynicism and a low sense of personal accomplishment. The bad: That percentage was still better than 30 percent.

Researchers are quick to point out that no single stress-relief strategy or set of behaviors works for everyone, physician or otherwise. But the relatively new effort to study "physician resiliency" has gained momentum in recent years and is making some interesting connections between lifestyle choices and avoiding burnout.

A 2012 study of more than 7,000 members of the American College of Surgeons reported that "surgeons placing greater emphasis on finding meaning in work, focusing on what is important in life, maintaining a positive outlook, and embracing a philosophy that stresses work/life balance were less likely to be burned out."[1]

A troubling finding in the study is the revelation that "although approximately 70 percent of surgeons reported having a primary-care provider, less than half had seen their provider in the last 12 months and more than 20 percent had not seen a primary care provider in the last four years."

Surgeons who had seen their primary-care provider in the last 12 months "were more likely to be up to date with all age- and sex-appropriate health screening guidelines and ... had higher overall and physical quality of life scores."

The study identified three specific measures associated with lower rates of burnout and improved quality of life among surgeons: 1) increasing weekly aerobic exercise and weight training to recommended levels; 2) annual visits to their primary-care provider; and 3) age-appropriate preventive testing.

In an interview with the *Canadian Medical Association Journal*, the lead author of the surgeon study referred to the "physician personality" that's characterized by hard work, perfectionism and an exaggerated sense of responsibility to patients. "Part of what makes us good at what we do also puts us at risk," he said.

1. Shanafelt TD, et al. Annals of Surgery 2012;255:625-632.


Using Low Tech To Assess Low Vision

Accurately measuring very limited vision and identifying scotomas can now be accomplished with inexpensive hand-held cards.

Christopher Kent, Senior Editor

Although we live in a world of high-tech wonders, sometimes a low-tech alternative can be a powerful tool. Here are two recently developed simple tests that help measure functionality in patients with low vision.

Testing Rudimentary Vision

When a patient's visual acuity is very poor, most eye-care practitioners use "count fingers" or "hand motion" to categorize it. Recently, a simple new system has made it possible to measure very low vision with much greater precision in two to three minutes using a series of handheld cards. The system was developed by Ian L. Bailey, OD, MS, FAAO, and colleagues. Dr. Bailey is a clinician and researcher at the University of California, Berkeley, where he is also professor of optometry and vision science.

The Berkeley Rudimentary Vision Test adds 13 increments between the lowest acuity level measureable with a standard eye chart and "light perception only." The test consists of three pairs of hinged cards, 25 cm^2, held in front of the patient at prescribed distances. The cards display four single tumbling E optotypes (145 mm, 92 mm, 58 mm and 36 mm); four grating acuity targets (290 mm, 184 mm, 116 mm and 72 mm); a white field projection test; and a black/white discrimination test. Angular size is increased by using short viewing distances.

Dr. Bailey notes that count fingers and hand motion are non-standardized. "People who use count fingers frequently don't specify the distance, the background or whether the hand is moving or not," he points out. "Also, its not encouraging for the patient, because the clinician has given up using measurement in the usual way." Dr. Bailey adds that increased precision matters. "If the patient's undergoing treatment, you'd like to know whether it's having an effect or not," he says. "Count fingers and hand motion can't identify anything other than very large changes."

Dr. Bailey says two experiences inspired him to create the new system. First, the World Blind Cricket Council asked for help classifying the severity of visual impairment of their athletes. Shortly thereafter, he attended a think-tank meeting at which scientists working with the latest bionic retinal implants were judging the increase in vision produced by the implants in terms of count fingers and hand motion.

"After that meeting I came up with the fundamental idea for the system," he says. "Initially I developed it on computer, but I wanted this to be portable, non-technological and very simple to administer, even by people who don't have a lot of training."

Dr. Bailey acknowledges that some computer-based low-vision tests, such as the Freiburg Visual Acuity and Contrast Test, the Grating Acuity Test and the Basic Assessment of Light and Motion test, are even more accurate, making them ideal for use in research and clinical trials. "However, they require a computer, take more time to administer, and each one only covers a part of the low-vision range," he says. "With our test, the patient doesn't even have to get out of the examination chair.

"Our cards are simpler than a standard eye chart because the patient is looking at isolated test targets," he continues. "If the person can't read the top row of the letter chart at one meter, the tumbling E test is

For allergic conjunctivitis[1]

THE POWER TO CALM THE ITCH

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INDICATION AND USAGE

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

IMPORTANT RISK INFORMATION

BEPREVE® is contraindicated in patients with a history of hypersensitivity reactions to bepotastine or any of the other ingredients. BEPREVE® is for topical ophthalmic use only. To minimize risk of contamination, do not touch the dropper tip to any surface. Keep the bottle closed when not in use. BEPREVE® should not be used to treat contact lens–related irritation. Remove contact lenses prior to instillation of BEPREVE®.

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

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

Please see the accompanying prescribing information for BEPREVE® on the following page.

Reference: 1. BEPREVE [package insert]. Irvine, CA: ISTA Pharmaceuticals, Inc; 2012.

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

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(bepotastine besilate ophthalmic solution) 1.5%

BEPREVE® (bepotastine besilate ophthalmic solution) 1.5%

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

----------INDICATIONS AND USAGE----------

BEPREVE® is a histamine H_1 receptor antagonist indicated for the treatment of itching associated with allergic conjunctivitis. (1)

----------DOSAGE AND ADMINISTRATION----------

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

--------DOSAGE FORMS AND STRENGTHS---------

Solution containing bepotastine besilate, 1.5%. (3)

----------CONTRAINDICATIONS----------

Hypersensitivity to any component of this product. (4)

----------WARNINGS AND PRECAUTIONS----------

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

----------ADVERSE REACTIONS----------

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

To report SUSPECTED ADVERSE REACTIONS, contact ISTA Pharmaceuticals, Inc. at 1-877-788-2020, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION
Revised: 12/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

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

2. DOSAGE AND ADMINISTRATION

Instill one drop of BEPREVE® into the affected eye(s) twice a day (BID).

3. DOSAGE FORMS AND STRENGTHS

Topical ophthalmic solution containing bepotastine besilate 1.5%.

4. CONTRAINDICATIONS

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

5. WARNINGS AND PRECAUTIONS

5.1 Contamination of Tip and Solution

To minimize contaminating the dropper tip and and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use.

5.2 Contact Lens Use

Patients should be advised not to wear a contact lens if their eye is red. BEPREVE® should not be used to treat contact lens-related irritation. BEPREVE® should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of BEPREVE®. The preservative in BEPREVE®, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of of BEPREVE®.

5.3 Topical Ophthalmic Use Only

BEPREVE® is for topical ophthalmic use only.

6. ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

6.2 Post Marketing Experience

Hypersensitivity reactions have been reported rarely [two (2) possibly related cases for an incidence of 0.00006%] during the post-marketing use of BEPREVE®. Because this reaction is reported voluntarily from a population of unknown size, the actual incidence cannot be verified. The hypersensitivity reactions include itching, body rash, and swelling of lips, tongue and/or throat.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: Teratogenicity studies have been performed in animals. Bepotastine besilate was not found to be teratogenic in rats during organogenesis and fetal development at oral doses up to 200 mg/kg/day (representing a systemic concentration approximately 3300 times that anticipated for topical ocular use in humans), but did show some potential for causing skeletal abnormalities at 1000 mg/kg/day. There were no teratogenic effects seen in rabbits at oral does up to 500 mg/kg/day given during organogenesis and fetal development (>13,000 times the dose in humans on a mg/kg basis). Evidence of infertility was seen in rats given oral bepotastine besilate 1000 mg/kg/day, however, no evidence of infertility was observed in rats given 200 mg/kg/day (approximately 3300 times the topical ocular use in humans). The concentration of radiolabeled bepotastine besilate was similar in fetal liver and maternal blood plasma following a single 3 mg/kg oral dose. The concentration in other fetal tissues was one-third to one-tenth the concentration in maternal blood plasma.

An increase in stillboms and decreased growth and development were observed in pups born from rats given oral doses of 1000 mg/kg/day during perinatal and lactation periods. There were no observed effects in rats treated with 100 mg/kg/day.

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

8.3 Nursing Mothers

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

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

8.4 Pediatric Use

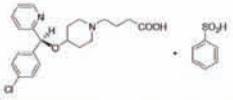
Safety and efficacy of BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% have not been established in pediatric patients under 2 years of age. Efficacy in pediatric patients under 10 years of age was extrapolated from clinical trials conducted in pediatric patients greater than 10 years of age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

8.5 Geriatric Use

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

11. DESCRIPTION

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



Bepotastine besilate is a white or pale yellowish crystalline powder. The molecular weight of bepotastine besilate is 547.06 daltons. BEPREVE® ophthalmic solution is supplied as a sterile, aqueous 1.5% solution, with a pH of 6.8.

The osmolality of BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% is approximately 290 mOsm/kg.

Each mL of BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% contains:
Active: Bepotastine besilate 15 mg (equivalent to 10.7 mg bepotastine)
Preservative: benzalkonium chloride 0.005%
Inactives: monobasic sodium phosphate dihydrate, sodium chloride, sodium hydroxide to adjust pH, and water for injection, USP.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Bepotastine is a topically active, direct H_1 receptor antagonist and an inhibitor of the release of histamine from mast cells.

12.3 Pharmacokinetics

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

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

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

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

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

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

Long term dietary studies in mice and rats were conducted to evaluate the carcinogenic potential of bepotastine besilate. Bepotastine besilate did not significantly induce neoplasms in mice receiving a nominal dose of up to 200 mg/kg/day for 21 months or rats receiving a nominal dose of up to 97 mg/kg/day for 24 months. These dose levels represent systemic exposures approximating 350 and 200 times that achieved with human topical ocular use.

The no observable adverse effect levels for bepotastine besilate based on nominal dose levels in carcinogenicity tests were 18.7 to 19.9 mg/kg/day in mice and 9.6 to 9.8 mg/kg/day in rats (representing exposure margins of approximately 60 and 20 times the systemic exposure anticipated for human topical use).

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

When oral bepotastine was administered to male and female rats at doses up to 1,000 mg/kg/day, there was a slight reduction in fertility index and surviving fetuses. Infertility was not seen in rats given 200 mg/kg/day oral bepotastine besilate (approximately 3300 times the systemic concentration anticipated for topical ocular use in humans).

14. CLINICAL STUDIES

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

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

16. HOW SUPPLIED/STORAGE AND HANDLING

BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% is supplied in a white low density polyethylene plastic squeeze bottle with a white controlled dropper tip and a white polypropylene cap in the following sizes:

5 mL (NDC 67425-007-50)
10 mL (NDC 67425-007-75)

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

17. PATIENT COUNSELING INFORMATION

17.1 Topical Ophthalmic Use Only

For topical ophthalmic administration only.

17.2 Sterility of Dropper Tip

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

17.3 Concomitant Use of Contact Lenses

Patients should be advised not to wear a contact lens if their eye is red. Patients should be advised that BEPREVE® should not be used to treat contact lens-related irritation. Patients should also be advised to remove contact lenses prior to instillation of BEPREVE®. The preservative in BEPREVE®, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of BEPREVE®.

Manufactured for: ISTA Pharmaceuticals, Inc.
Irvine, CA 92618

By: Bausch & Lomb Incorporated
Tampa, FL 33637

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

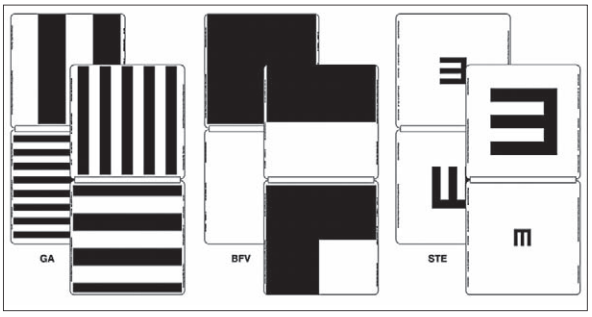
U.S. Patents: 6,307,052; 6,780,877

BRV957-2/12

introduced. If the biggest E, about 15 cm high, can't be seen at one meter, it's moved to 25 cm from the face. If the person can't see this, we change to gratings, a more basic visual target. The lowest visual acuity we can specify is 20/16,000."

To test the system, they assembled 37 individuals with 54 eyes known to be severely visually impaired. "We showed that these people could be quickly measured," he says. "We were able to subdivide those who would have been categorized as count fingers or hand motion according to descending visual capability." Median testing time was 2.5 minutes. Ongoing studies are now examining test-retest variability and comparing the results to other computerized low-vision tests, such as the FrACT tests.

Dr. Bailey says the test is now in use by a number of low-vision and retinal specialists who see patients with severe visual impairment, as well as by the International Paralympics Committee and the International Blind Sports Association. The test is not currently reimbursable, although it is easy to administer and inexpensive to purchase (around $200 at precision-vision.com). The University of California, Berkeley receives royalties for any sales, which are used to support low-vision research at the university.



The Berkeley Rudimentary Vision Test uses hand-held cards to quickly measure very low vision with far greater precision than simply labeling it "count fingers" or "light perception."

The SKread Test

The SKread test is another handheld-card test, designed to help doctors evaluate a patient's functional visual status by providing key information about the location of scotomas that are interfering with the patient's ability to recognize words. The test was developed at the Smith-Kettlewell Eye Research Institute in San Francisco.

The test features two handheld charts, each with 14 paragraphs consisting of the same number of words and letters displayed in three lines, using the same format as the commonly used MNread test. The text is high-contrast black type on a white background; type sizes range from eight times larger than newsprint down to 0.4 M (less than half the size of newsprint). In contrast to standard reading tests, the SKread uses a series of common, random words that do not form sentences with meaning. The words and letters are chosen to be easily confused, which facilitates errors that can reveal the location of a scotoma. For example, the inclusion of single letters facilitates misidentification of two-letter words as a single letter, and many words can be read as other words if the reader fails to see the first or last letter (e.g., swing or theme). The subject can take the test using a magnifier if necessary.

"When the text the patient is reading makes sense, the patient can fill in anything he's not actually seeing, just based on grammar or context," says neurophysiologist Manfred MacKeben, PhD, who worked with Donald C. Fletcher, MD, to design the SKread test. (Dr. MacKeben has worked in vision for 42 years and low-vision research since 1990. He has no financial interest in the test.) "Here, patients have to use their eyesight and nothing else." He notes that scotomas can cause functional problems not revealed by a visual acuity test.

"The number and type of errors reveal a pattern," he continues. "If the patient drops a letter at the beginning or end of the word, that implies that the patient has a dense scotoma to the left or right of whatever location in the retina he uses to fixate—the fovea, or a preferred retinal locus." Dr. MacKeben says the person giving the SKread test can mark errors on a score sheet while the patient is reading because patients read it much more slowly than normal text.

The test quickly reveals a patient's functional status and can be used to monitor the patient's progress and can guide treatment choices. (If a patient has a scotoma, simply providing magnification or new glasses won't solve the problem.) The test can also help patients by explaining the reason they're having difficulty with tasks such as reading.

To check the viability of the test, Drs. Fletcher and MacKeben performed monocular tests on 305 eyes (patient ages 16 to 97), of which 227 had diagnosed pathology and 136 had dense scotomas. Test-retest reliability was good (coefficient of repeatability: 0.543). Reading speed was much slower than in a test such as the MNread, and the number of errors was far greater, especially among patients with maculopathies. (Speed and errors did not correlate strongly with age, educational level or visual acuity.)

Finally, Drs. Fletcher and MacKeben used scanning laser ophthalmoscopy to see whether the scotomas were located where the test predicted. "We were able to verify objectively where the scotoma was in 111 patients," says Dr. MacKeben. "We found a very high correlation with the results of the SKread test."

The SKread test costs less than $150, available at precision-vision.com. REVIEW

In This Section

Leaving the warm Atlantic breezes of Ft. Lauderdale behind, the Association for Research in Vision and Ophthalmology this year ventures to the Great Northwest and Seattle, for the Annual ARVO meeting, May 5 to 9. The theme of this year's meeting: Life-changing Research.

That theme is well-reflected in the thousands of abstracts submitted by researchers, clinicians and surgeons from around the world. As we have done for many years, this year's ARVO report attempts to collect what we feel are representative trends and research initiatives that will be of interest to the practicing ophthalmologist. Some may be early in their development; others may be well-established. We encourage the reader to explore the abstracts that we report here and others that interest you at the ARVO website, arvo.org. After each abstract you'll find a citation representing the abstract number, which you can use to locate the original report. (Where there was financial support or other commercial relationship reported, we so indicate with each abstract.)

We want to thank our board members and medical editors who have helped us prepare this year's report, and the researchers who have cooperated with us to bring you the latest data in the six subspecialties shown on the left. Enjoy.

This article has no commercial sponsorship.

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Glaucoma: Slow but Steady Strides Forward

Peter A. Netland, MD, PhD, and Kuldev Singh, MD, MPH, Section Editors

Though a cure remains elusive, our ability to manage the disease continues to improve.

Researchers and clinicians continue to break new ground in glaucoma management. This year, ARVO studies have made inroads into nonstandard approaches to detecting glaucoma (and demonstrated the limits of some familiar approaches); tested new approaches to drug delivery, ciliary body coagulation, and nutritional supplementation; provide more data showing the value of combining structure and function to monitor the disease; and provide new insights into risk factors, surgery and selective laser trabeculoplasty.

Detecting Signs

Researchers at two Chicago universities and a clinic in Denver have found that low-tension glaucoma patients have microhemorrhages detectable in capillaroscopic scans of their fingers, seldom found in normal subjects, suggesting the presence of a systemic vascular dysfunction.

Researchers performed nailfold video capillaroscopy on seven low-tension primary open-angle glaucoma patients and seven age-matched controls. Videos were made of the third and fourth fingers of the nondominant hand, and analyzed to determine capillary morphology. The data showed that all seven low-tension glaucoma patients had detectable microhemorrhages; only one of the control subjects did ($p<0.001$). *(See images, p. 28.)*

The study authors note that the cause of the microhemorrhages remains undetermined. Possible explanatory factors would include capillary growth regulation, breakdown of support matrix, blood flow velocity and neurogenic dysfunction. They conclude that POAG has systemic features characteristic of connective tissue diseases.[1881]

Researchers at Wills Eye Institute and Jefferson Medical College in Philadelphia conducted a study to compare the ability of the RAPDx pupillograph (Konan) and the swinging flashlight method (both with and without magnification) to detect afferent pupillary defects, indicative of asymmetric glaucomatous damage.

Separate examiners blinded to the patient's clinical information gave full clinical examinations to 118 patients; they conducted APD testing using the SFM, MA-SFM and RAPDx device. With the flashlight, a positive APD was defined in terms of immediate or delayed pupillary dilation. With the RAPDx, a positive APD was defined by a calculated index of defect. An APD was considered "corroborated" when there was a difference of

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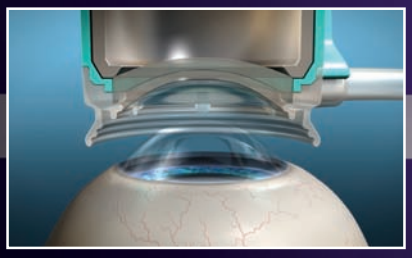

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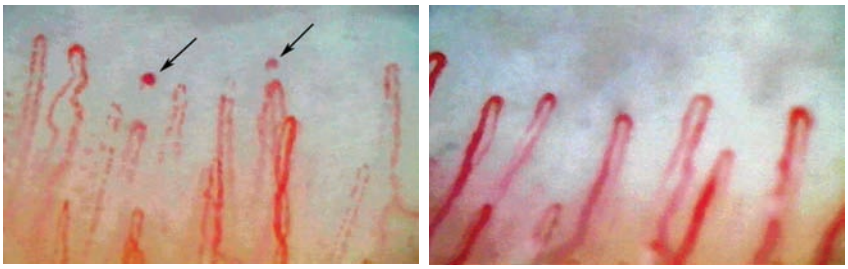


A study found that low-tension glaucoma patients have microhemorrhages detectable in capillaroscopic scans of their fingers (left), seldom found in normal subjects (right).[1881] (Copyright 2013, University of Illinois Board of Trustees. Used with permission.)

either a) one or more units on the Disc Damage Likelihood Scale between both eyes, or b) a cup/disc ratio ≥0.1 between the eyes. Sixty-one patients were excluded for a variety of reasons that interfered with testing. Of the 57 patients who were testable:

• Apparent APDs were detected in 15 patients using SFM (26.3 percent); in 35 patients using MA-SFM (61.4 percent); and in 35 patients using the RAPDx device (61.4 percent).

• "Corroborated" APDs were found in nine patients using SFM (15.8 percent); in 21 patients using MA-SFM (36.8 percent); and in 22 patients using RAPDx (38.6 percent).

• Clinically detected asymmetry in disc damage was missed in 28 patients using SFM (49.1 percent); in 12 patients using MA-SFM (21.1 percent); and in 12 patients using the RAPDx (21.1 percent).

The authors conclude that the RAPDx pupillograph and MA-SFM method are both useful for the detection of asymmetric glaucomatous damage, and both detect apparent and "corroborated" APDs more often than the non-magnified SFM.[4811]

Researchers at the Wilmer Eye Institute and Johns Hopkins University in Baltimore conducted a prospective, case-control study to assess the relationships between the pupillary light reflex, as measured by a pupillometer, and visual field defects and retinal nerve fiber layer thickness. They analyzed pupillary responses to various stimulus patterns in 157 patients with glaucoma (mean age 67 ±11, 50 percent female) and 71 controls (mean age 60 ±10, 69 percent female). They compared the responses between the two eyes and to superonasal and inferonasal stimuli within each eye, and calculated the absolute PLR value for each individual eye. The data showed:

• Glaucoma patients had a more asymmetric pupil response between the two eyes (p<0.001), and between the superonasal and inferonasal fields within the same eye (p=0.014).

• Glaucoma patients had a smaller amplitude, slower velocity and longer latency of pupil response than controls (all p<0.001).

• For every difference of 0.3 log units in between-eye asymmetry of PLR there was an average 2.3-dB difference in visual field mean deviation (R2=0.62, p<0.001) and a 3.7-µm difference in RNFL thickness between the two eyes (R2=0.34, p<0.001).

• Greater visual field damage and a thinner RNFL were associated with a smaller response amplitude, slower velocity and longer time to peak constriction and dilation (all p<0.001 after adjusting for age and gender).

• Asymmetry of PLR between superonasal and inferonasal stimulation within a given eye was not associated with differences in visual field or RVFL in those locations.

The authors conclude that carefully measured pupillary light reflex is strongly correlated with visual field functional testing and measurements of RNFL thickness, indicating that

quantitative pupillography may have a role in the diagnosis and management of optic neuropathies.[2261]

A study conducted at the Prasad Eye Institute in Hyderabad, India, used spectral domain optical coherence tomography to evaluate the optic nerve head, RNFL and ganglion cell complex in 261 eyes of 197 recently referred glaucoma suspects, to see how well current SD-OCT technology and algorithms could diagnose preperimetric glaucoma. (Visual fields were normal in all eyes.)

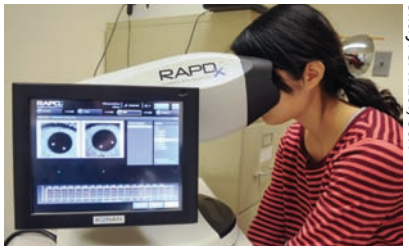
Two glaucoma experts masked to the patient's data independently classified the optic nerves into glaucoma and non-glaucoma groups based on digital optic disc photographs. Sixty-eight eyes of 60 patients were classified as glaucomatous; 193 eyes of 137 subjects were classified as controls.

Although age and visual field characteristics were comparable between the groups, all SD-OCT parameters were significantly different. Inferior neuroretinal rim area (area under the receiver operating characteristic curve: 0.708), inferior quadrant RNFL thickness (AUC: 0.713) and global loss volume (AUC: 0.702) had the best AUCs for differentiating preperimetric glaucoma from control eyes. Sensitivities at a fixed specificity of 95 percent for all these parameters were below 27 percent. Likelihood ratios of the outside-normal-limits category of the RNFL and GCC parameters were between 2.2 and 5.9; for the within-normal-limits category they were between 0.6 and 0.8; for the borderline category they were between 1 and 2.

The authors conclude that the ability of the ONH, RNFL and GCC parameters of SD-OCT to diagnose preperimetric glaucoma is poor, indicating a need for improvements in the current analysis algorithms.[4828]

New Treatment Approaches

Surgeons at nine glaucoma centers in France participated in a prospective, non-comparative interventional clinical study to test the safety and efficacy of a new high-intensity focused ultrasound procedure called Ultrasonic Circular Cyclo Coagulation.



Sheryl S. Wizov, COA

Several studies suggest that quantitative pupillography may have a role in the diagnosis and management of glaucoma.

Forty-two eyes of 42 patients with primary open-angle glaucoma were treated. Subjects had an IOP>21 mmHg, an average of 1.65 failed previous surgeries and were using an average of 3.2 medications. Eighteen patients (Group 1) received four-second exposures for each shot; 24 patients (Group 2) received six-second exposures. Complete ophthalmic examinations were performed before the procedure and at one day, one week, and one, two , three, six and 12 months after. Primary outcomes were surgical success (defined as an IOP reduction from baseline ≥20 percent and IOP>5 mmHg) at the last follow-up visit, and vision-threatening complications. Secondary outcomes were the mean IOP at each follow-up visit compared to baseline, medication use, complications and re-interventions.

The data showed that mean IOP was significantly reduced in both groups ($p<0.05$). Group 1 dropped from 28.6 ±4.7 mmHg to 16.1 ±2.8 mmHg at last follow-up; Group 2 dropped from 28.1 ±8.6 mmHg to 16.7 ±4.4 mmHg. An IOP reduction >20 percent was achieved in 12 of 18 eyes in Group 1 (67 percent) and 17 of 24 eyes in Group 2 (71 percent). Four patients had to be retreated. No major intra- or postoperative complications occurred. The authors conclude that Ultrasonic Circular Cyclo Coagulation appears to be an effective and well-tolerated method to reduce IOP in patients with POAG.[4775]

Because previous studies had found a decrease of the magnesium content in aqueous humor, anterior sclera and tear fluid of patients with various stages of POAG, a group of researchers in Moscow conducted a study to determine whether a magnesium-containing supplement might have a beneficial effect on IOP, visual fields and retinal nerve fiber layer thickness.

In the study, 22 POAG patients (mean age 61.1 ±2.5 years; r: 42 to 72) received hypotensive therapy supplemented by Magnerot (Wörwag Pharma, Germany) daily for six weeks: two tablespoons three times a day for one week, then one or two tablespoons two to three times a day for five more weeks. As a control, 16 POAG patients (63.7 ±2.7 years) received hypotensive therapy without Magnerot. The group assessed the optic nerve before treatment and at one, two, three and five months post-treatment. In addition to perimetry and retinal tomography, the ORA (Reichert) was used to measure corneal-compensated IOPcc, IOP equivalent to Goldmann (IOPG) and corneal hysteresis.

The treatment group showed almost twice as many improved visual field results as the control group. IOPG dropped by 3.3 ±0.4 mmHg after adding the magnesium supplement; IOPcc dropped by 4.1 ±0.3 mmHg (both $p<0.05$). Perimetry showed a significant increase in total functional visual field (from 426.5 ±7.8 to 452.5 ±8.8 degrees, $p<0.05$), mainly in patients with moderate glaucoma, and analysis of the MD index showed reduction in the total depression of sensitivity from an average of -5.8 dB to -3.9 dB ($p>0.5$). Furthermore, the average thickness of the RNFL tended to grow in patients in the early stages of glaucoma (from 0.25 ±0.02 mm to

Morgan V. Fedorchak, PhD

Researchers have developed a patient-administered drop, made of hydrogel and microparticles, that delivers a drug for a full month. Above: A drop is placed in the fornix of a rabbit eye. It quickly gels into a form-fitting shape and remains in place, exuding the medicine. After a month it can easily be removed with tweezers (right).[4294]

0.27 ±0.01 mm) and moderate stage (0.19 ±0.03 mm to 0.21 ±0.02 mm) following treatment.

The authors believe these results suggest that a magnesium-containing supplement may have a stabilizing effect on the course of glaucoma, and recommend further study.[759]

In an effort to surmount glaucoma medication patient compliance issues, researchers at the University of Pittsburgh, McGowan Institute for Regenerative Medicine and UPMC Eye Center in Pittsburgh have developed a new way to deliver brimonidine tartrate to the eye for about one month noninvasively, without daily eye drops or periodic implants or injections. (One researcher has an interest in the patent.) The new method consists of a patient-administered drop made of hydrogel and microparticles that provides sustained release of the drug. The amount of drug released is within the calculated therapeutic range of topical brimonidine drops.

To test the formulation *in vivo*, a single drop was administered to the inferior fornix of New Zealand white rabbits. IOP was measured periodically and histology was used to assess the biocompatibility of the system. Testing showed that the gel/microparticle drop could be easily administered, and that it formed a stable, opaque gel *(See images, above)*. The gel eye drop was easily removed, leaving no evidence of gel or microparticles. Cytotoxicity testing demonstrated no significant effect on conjunctival cell viability.

The authors believe this new system will provide a simple way for patients to achieve adequate IOP reduction without the issues surrounding injections or compliance with daily eye drop instillation.[4294]

Structure & Function

Researchers at Bascom Palmer Eye Institute in Miami have demonstrated that in glaucoma suspects, pattern electroretinogram may reveal loss of function years before an equivalent loss is seen in retinal nerve fiber layer thickness loss, as measured by OCT.

Researchers compared progressive losses measured by pattern electroretinogram and those indicated by retinal nerve fiber layer thickness loss over time in 201 eyes of 107 glaucoma suspects. Subjects were monitored with PERG and OCT every six months for at least four years. Longitudinal PERG amplitudes and peripapillary RNFL thicknesses were normalized based on the difference between the values in normal subjects and advanced stages of the disease. The researchers calculated the time required for PERG and OCT to lose 10 percent of their baseline value.

The data showed that in eyes that had an abnormal PERG amplitude at baseline (50 to 90 percent below normal, n=99), pooled PERG amplitude slopes took 1.9 to 2.5 years to lose 10 percent of their initial amplitude. In contrast, measured RNFL thickness took 9.9 to 10.4 years to show the same level of loss ($p<0.05$). Thus, it appears that it may take eight years longer for retinal nerve fiber layer thickness to reveal this level of loss.[796]

Using data from the Diagnostic Innovations in Glaucoma Study and the African Descent and Glaucoma Evaluation Study, researchers at multiple universities and clinics in the United States, Brazil and Taiwan sought to determine whether a combination of structural and functional data (from SAP and OCT—the CSF index) could predict conversion to glaucoma in 345 glaucoma suspect eyes.

Subjects were followed for an average of 74.8 months; all had normal standard automated perimetry at baseline. Time domain OCT was used to assess RNFL thickness. Data models were adjusted for age, IOP and central corneal thickness. Conversion to glaucoma was defined as repeatable abnormal SAP or progressive optic disc changes during follow-up.

Fifty-eight eyes (16.8 percent) con-

Ability of Different Factors to Predict Conversion to Glaucoma[1887]

Predictive Factors	c-index*	R^2 (95% CI)*
SAP mean deviation	0.699	28 (14-51)
SAP pattern standard deviation	0.648	15 (6-34)
SAP visual field index	0.688	26 (13-49)
OCT RNFL average thickness	0.718	39 (24-60)
Number of RGCs (weighted estimate)	0.742	47 (29-66)
CSFI (combined structure & function index)	0.770	55 (39-72)

* adjusted for baseline age, baseline IOP and central corneal thickness.

A predictive model including the Combined Structure and Function Index was superior to models using standard visual field parameters and retinal nerve fiber layer thickness.

verted to glaucoma. Mean baseline CSFI was 14.1 percent in those who developed glaucoma, and 0.2 percent in those who did not. In the multivariable model, higher CSFI was predictive of conversion (adjusted hazard ratio=2.08 per 10 percent higher; 95 percent CI: 1.70 to 2.56; $p<0.001$). The model that included CSFI had better predictive ability than models including standard visual field parameters and OCT average RNFL thickness. (*See table, facing page*).

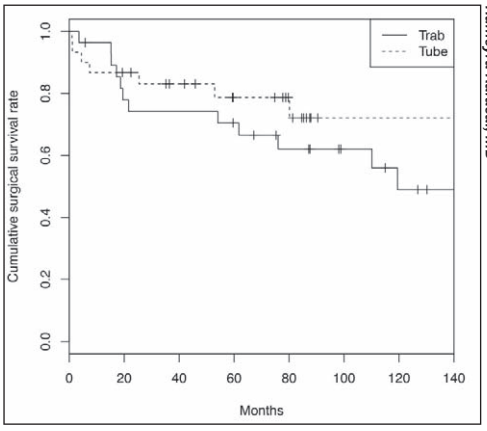
The authors conclude that baseline CSFI values were predictive of conversion to glaucoma and performed significantly better than conventional approaches for risk stratification.[1887]

Researchers in Pittsburgh and Boston followed 60 eyes of 31 subjects (four healthy, 34 glaucoma suspect and 22 glaucoma) for an average of 7.4 ±2.3 years to evaluate glaucoma progression in terms of the relationship between structure and function (using visual field mean deviation and OCT RNFL thickness) over the long term. Visual field progression was defined as a decline in MD ≥2 dB from baseline; for OCT, progression was defined as RNFL thinning ≥20 µm. Subjects had a median of 12 visual field and 27 OCT scans. The data showed:

- A total of 41 eyes (68.3 percent) progressed; 46.7 percent according to OCT criteria; 10 percent according to visual field criteria; and 11.7 percent according to both criteria.
- Of the seven eyes that progressed by both criteria, three progressed in terms of structure and function simultaneously; in three eyes OCT showed progression before visual field; and in one eye the visual field showed progression before OCT.
- Using the same progression criteria after four, five, six and seven years of follow-up, there was a gradual increase in the number of progressors with all criteria. The agreement between both devices increased from 6 percent to 14 percent.

• Fifty-three percent of eyes that were defined as OCT rapid progressors were also labeled as visual field rapid progressors.

The authors note that although they expected to find improved agreement between structure and function over extended follow-up, that increase was marginal. Thus even over the long term there may be limited detectable correspondence between structural and functional progression.[1898]



In eyes with glaucoma associated with ocular inflammation, tube shunts had a significantly lower risk of failure than trabeculectomy.[4767]

Humeyra Karacal, MD

Glaucoma Surgery

Researchers at the North Shore LIJ Department of Ophthalmology in New Hyde Park, N.Y., conducted a retrospective study of 195 Descemet's Stripping Automated Endothelial Keratoplasty grafts performed between January 2007 and August 2012, to assess the incidence of medical or surgical escalation of IOP management after DSAEK in patients with or without pre-existing glaucoma, and whether such escalation was associated with graft failure.

Seventy-one grafts were performed in eyes that had required surgical or medical management of elevated IOP prior to DSAEK; 22 were performed in eyes that had previous glaucoma surgery (including trabeculectomy and/or tube implant). One graft was performed concomitantly with a tube implant. The study found:

• Eleven eyes with preexisting glaucoma required a glaucoma valve implant within 24 months after DSAEK; only one eye without preexisting glaucoma did (p<0.0003).

• Thirty-one eyes with preexisting glaucoma that received grafts (46.5 percent) required drops for IOP management after DSAEK; only 23 eyes without pre-existing glaucoma that received grafts (18.5 percent) required drops (p<0.0002).

• Graft failure occurred in 17 out of 71 eyes with pre-existing glaucoma (23.9 percent); seven of these had glaucoma surgeries prior to DSAEK, and three of them had had a tube revision performed concomitantly with DSAEK. Four of the seven required rebubbling and one had hypotony postoperatively. Five required subsequent glaucoma tubes after DSAEK, and three of those five had intra- or postoperative complications during tube placement (including choroidals in two eyes and malignant glaucoma in one eye).

• In contrast, of the 124 eyes without glaucoma, only six DSAEKs failed, all without adjuvant IOP management following DSAEK. Five of the 124 (4 percent) required rebubbling, and of these, two went on to failure.

The authors conclude that adjuvant medical or surgical therapy is more likely to be needed after DSAEK in patients with a pre-existing history of glaucoma and that prior glaucoma surgery may be a risk factor for failure of DSAEK grafts.[3093]

Researchers at Washington University in St. Louis retrospectively reviewed the charts of 58 eyes of 42 patients (mean age 55 years) with a diagnosis of uveitic or steroid-induced glaucoma, in order to compare the surgical outcomes of tube shunts versus trabeculectomy (with antimetabolites) in patients with glaucoma associated with ocular inflammation.

All patients had uveitis or steroid use prior to glaucoma onset, underwent a primary tube shunt or trabeculectomy surgery and had three or more months of follow-up after surgery. (Median follow-up was 85 months.) Surgical failure was defined as IOP >21 mmHg at two or more consecutive postoperative visits; any additional glaucoma procedures; loss of light perception; and complications secondary to hypotony. Covariates included were age, race, gender, preoperative IOP, preoperative number of glaucoma medications, perioperative use of steroids or systemic immunosuppressants, anterior-segment-involving uveitis and combined surgery with cataract extraction.

In this group there were 30 cases of tube shunt implantation (53 percent), 16 Ahmed, 14 Baerveldt; and 28 cases of trabeculectomy with mitomycin (47 percent), two receiving Ex-Press shunts. The most common etiologies of ocular inflammation were idiopathic (33 eyes, 55.9 percent), followed by sarcoidosis (12 eyes, 20.3 percent).

After controlling for covariates, tube shunts trended towards a 44.4 percent lower risk of surgical failure (HR: 0.56 95 percent CI: 0.21 to 1.49). Shunts also had a lower sustained risk of time to failure compared to the trabeculectomy group.[4767]

Risk Factors

A study at the University of Washington, Seattle and Duke Eye Center in Durham, N.C., partly retrospective and partly prospective, found that longer axial length is a risk factor for glaucoma, regardless of refractive status.

Retrospective data was collected from patients who had undergone biometry (IOLMaster) prior to elective cataract surgery at the University of Washington or Harborview Medical Center from 2009 to 2011; prospec-

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INDICATIONS AND USAGE

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

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

WARNINGS AND PRECAUTIONS

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

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

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

DRUG INTERACTIONS

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

DRUG INTERACTIONS

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

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

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

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

OVERDOSAGE

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

NONCLINICAL TOXICOLOGY

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

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

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

PATIENT COUNSELING INFORMATION

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

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

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

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

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Based on package insert 71816US15C

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tive data was collected from patients at the University of Washington Eye Institute Glaucoma Clinic who agreed to have ocular biometry. (They excluded patients with secondary causes of glaucoma and those classified as glaucoma suspects.) Of 901 eyes of 901 subjects, 281 had glaucoma; 620 did not. Average age was 67.16 ±12.38; corneal curvature was 43.87 ±1.67 D; axial length was 24.38 ±1.76 mm.

The data showed:

• Eyes with glaucoma had longer axial lengths (24.88 ±1.91 mm vs. 24.16 ±1.65 mm, $p<0.001$) and flatter corneas (43.62 ±1.73 D vs. 43.98 ±1.64 D, $p=0.002$) than eyes without glaucoma.

• In a multivariate analysis, age and axial length were significant independent risk factors for glaucoma.

• For any given refractive error, subjects with glaucoma had longer axial lengths than controls (0.218 ±0.882 mm vs. -0.099 ±0.82 mm, $p<0.001$).

The authors note that this suggests that increased axial length might be the pathophysiologic mechanism underlying the association between myopia and OAG, rather than strictly refractive error.[3524]

A study at the University of California, San Francisco and Stanford University was conducted to investigate possible associations between myopia and glaucoma risk in 115 young, healthy adults (mean age, 24.63; 61.74 percent female). The participants were categorized into two groups: 56 subjects with emmetropia or mild myopia (0.99 to -2.99 D) comprised Group A; 59 subjects with moderate to severe myopia (>-3.00 D) made up Group B. Anyone who had previously undergone LASIK was excluded.

Subjects underwent a comprehensive ophthalmic examination including visual acuity, refraction, slit lamp exam, ophthalmoscopy, IOP measurement, A-scan biometry, automated perimetry and optic nerve and anterior segment optical coherence tomography. Outcome variables included IOP, RNFL thickness, visual field mean deviation and pattern deviation. In addition to comparing the mean value of each outcome variable, a multivariate linear regression model was used to examine independent associations between spherical equivalents and outcome variables.

The data showed that mean IOP in group A was significantly lower than in Group B (13.13 mmHg vs. 14.68 mmHg, $p=0.0064$); mean RNFL thickness was greater in Group A (110 µm vs. 104.24 µm, $p=0.0016$); and mean visual field mean deviation and pattern deviation were significantly more suspicious for abnormality in Group A (-0.34 dB vs. -1.29 dB, $p<.0001$; and 1.46 dB vs. 1.71 dB, $p= 0.02$).

After adjusting for age, gender and ethnicity, the relationship between spherical equivalent and each of the outcome variables remained statistically significant.

The authors conclude that the association between greater myopia and higher IOP, thinner RNFL thickness and more suspicious visual field mean deviation and pattern deviation may represent greater glaucoma risk among young myopes, consistent with previous findings of increased risk in older myopic populations.[3499]

SLT Update

A retrospective study involving 79 eyes of 56 patients, conducted at the Massachusetts Eye and Ear Infirmary and Tufts University School of Medicine, sought to determine the repeatability of selective laser trabeculoplasty in patients with pseudoexfoliation glaucoma. (One researcher has a commercial relationship with Lumenis.) The subjects (24 males, 32 females) were PXFG patients who had undergone initial and/or repeat SLT between January 2001 and March 2012. (Anyone with prior laser or incisional surgery was excluded.)

The authors compared IOP, percent of IOP reduction and number of glaucoma medications before and after the first and subsequent laser treatments. The data showed:

• Of the 79 eyes that underwent an initial SLT, 21 eyes (27 percent) underwent a second SLT; five eyes (6.3 percent) underwent a third SLT.

• Of the eyes that did not have a second or third SLT, 43 (59 percent) had controlled IOP, while 15 (19 percent) underwent surgery.

• Of the eyes that had a second SLT but not a third, 11 (out of 21) had controlled IOP; five (21 percent) underwent surgery.

• Of eyes that had a third SLT, two (out of five) had controlled IOP; the other three underwent surgery.

• Time between SLT #1 and #2 was 29 ±24 months. Time between SLTs #2 and #3 was 17 ±11 months.

• Percent of IOP reduction was 39 ±18 percent after SLT #1, 33 ±14 percent after SLT #2, and 36 ± 19 percent after #3. In all three procedures, the reduction was statistically significant.

• There was no significant change in the mean number of medications before and after SLT #1 or SLT #3. However, the mean number of medications significantly increased after SLT #2 (from 2.19 to 2.67 meds, $p<0.05$).

The authors conclude that SLT was effective in reducing IOP in both initial and repeat treatments in eyes with pseudoexfoliation glaucoma. The percentage of eyes maintaining IOP control without additional SLT (about 50 percent) and those requiring surgery (about 20 percent) were similar after SLT #1 and #2. Although a small group, 60 percent of eyes after SLT #3 required surgery.[1857] REVIEW

Dr. Netland is a professor and chairman of the department of ophthalmology at the University of Virginia; Dr. Singh is a professor of ophthalmology and director of the Glaucoma Service at Stanford University School of Medicine.

Retina Surgeons Drill Deeper into Anti-VEGF

Carl Regillo, MD, Section Co-editor

An inside look at the latest advances in medical and surgical management of retinal conditions.

Retinal surgeons and clinical investigators have long been impressed with the results of using anti-vascular endothelial growth factor in various retinal diseases; now they're analyzing it more closely to see how it works over the long term and when it's combined with other therapies. At this year's ARVO, research groups will share their results from these anti-VEGF studies, as well as provide more insight into retinal surgery outcomes.

AMD Investigations

Investigators from the Regeneron/Bayer-sponsored VIEW studies have performed a long-term analysis of retreatment with aflibercept and ranibizumab for neovascular age-related macular degeneration.

In the studies, the researchers randomized 2,412 patients with wet AMD to monthly ranibizumab 0.5 mg (Rq4), monthly intravitreal aflibercept injection 2 mg (2q4), monthly IAI 0.5 mg (0.5q4), or IAI 2 mg every other month (2q8) following three initial monthly doses. They evaluated the primary outcomes at week 52. Between weeks 52 and 96, the physicians administered injections at 12-week intervals, but they could be given as frequently as every four weeks for any of the following: increased central retinal thickness ≥100 µm compared to the lowest previous value; loss of five or more ETDRS letters from best previous score with recurrent fluid; new onset classic neovascularization or hemorrhage or new or persistent fluid on optical coherence tomography; or leak on fluorescein.

Between weeks 52 and 96, all of the patients received an average of 4.1 to 4.7 injections, and there was a small overall trend of acuity loss at week 96. The researchers say that subgroup analysis found that the slight loss was mainly caused by approximately a fifth of patients in all groups who lost at least five letters between weeks 52 and 96 in spite of p.r.n. retreatment. The physicians report that this group was stable from baseline until week 52, but lost on average more than 11 letters with either drug when switched to reactive treatment, and that CRT didn't change. The subgroup received a number of injections similar to the full study population.

The investigators performed a separate subgroup analysis on patients who lost five or more letters between two consecutive treatments and subsequently received reactive treatment for weeks 52 through 64. At 96 weeks, acuity in these patients decreased from gains at Week 52 (+8.5 to 10.3 letters),

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to a VA of -2.5 to -3.8 letters below baseline, with no obvious changes in CRT. They add that frequent ocular adverse events were conjunctival hemorrhage, eye pain, retinal hemorrhage and reduced VA.

The researchers say that there seems to be a subset of patients in whom reactive treatment won't recover vision that's lost, and that proactive treatment results in better vision.[3171]

The researchers from the Comparison of Age-related Macular Degeneration Treatment Trials have done an analysis of the results to determine risk factors for developing geographic atrophy. Two of the researchers receive financial support from, or are consultants to, makers of anti-vascular endothelial growth factor drugs.

The researchers looked at the 1,020 CATT patients who had no GA visible on digital color photos or FA at the time of enrollment. The patients had been randomly assigned to treatment with ranibizumab 0.5 mg or bevacizumab 1.25 mg and to a two-year-long regimen of either monthly or p.r.n. dosing, or monthly injections for a year and p.r.n. the following year.

The investigators report that GA developed in 187 (18.3 percent) of the patients by two years. In multivariate analysis, poor baseline visual acuity, presence of retinal angiomatous proliferation, absence of blocked fluorescence on FA, presence of GA in the fellow eye, ranibizumab treatment and a monthly treatment regimen, thinner subretinal fluid, decreased sub-RPE height and intraretinal fluid in the foveal center were independently associated with increased risk of GA. The researchers also looked at possible genetic connections in 770 patients who took part in the CATT genetic study. They found that the ARMS2 and HTRA1 risk alleles were associated with an increased incidence of GA.[3658]

Researchers from the European-based Inhibit VEGF in Age-related choroidal Neovascularization study have performed an analysis of the relationship between hemorrhage and OCT signs and the likelihood of neovascular AMD being active during follow-up. Some of the doctors receive financial support from, or are consultants to, Bayer and Novartis.

In the analysis, the Network of Reading Centres UK prospectively graded image sets from the IVAN study for presence or absence of hemorrhage and intraretinal fluid cysts, neuroretinal foveal thickness and height of subretinal fluid at the fovea. FA was graded for the presence or absence of leakage, which was the reference standard for activity. Feature discrimination between presence or absence of activity was quantified by the area under the receiver operating characteristic curve.

The researchers say that at 12 months there was leakage in 41 percent of the patients (183/449 angiograms), and at 24 months 38 percent (168/436 angiograms) had leakage activity. At 12 months, hemorrhages were present in 11 percent of the patients and intraretinal fluid cysts were present in 36 percent. At two years, 8 percent showed hemorrhage and 35 percent had evidence of cysts. The median neuroretinal foveal thickness height was 150 µm at 12 months and 140 µm at two years. The investigators say that 14 percent of OCTs at 12 months and 15 percent at two years showed subretinal fluid, and that the median height of SRF, when present, was 70 µm at both follow-up points. The positive/negative likelihood ratios for the features (the number of times more likely a positive test comes from someone with the disease vs. someone without it/the number of times more likely a negative test comes from someone with the disease vs. someone without it) were as follows:

- hemorrhage: 4.38/0.84 at 12 months, 5.51/0.87 at 24 months;
- fluid cysts: 1.72/0.72 at 12 months, 1.25/0.88 at 24 months; and
- any SRF: 5.47/0.76 at 12 months, 8.1/0.71 at 24 months.

The areas under the receiver operating curve were ≤ 0.7 for neuroretinal foveal thickness and SRF, or a combination of features.

The investigators say that none of the features they studied does a good job of diagnosing FA-classified active

Selected Risk Factors for Geographic Atrophy from CATT[3658]

	Number of subjects	Percent with geographic atrophy in two years	Adjusted hazard ratio (95-percent CI)	*p*-value
Baseline VA in study eye				
20/25-40	355	14.1	1.0	0.006
20/50-80	349	20.6	1.7 (1.2, 2.5)	
20/100-160	188	22.9	1.7 (1.1, 2.6)	
20/200-320	53	28.3	2.7 (1.4, 4.9)	
RAP Lesion				
No	839	16.8	1.0	0.008
Yes	106	36.8	1.7 (1.2, 2.4)	
Intraretinal Fluid				
None	254	10.2	1.0	0.006
Fluid, not in foveal center	249	17.7	1.8 (1.1, 3.0)	
Fluid, in foveal center	442	24.9	2.1 (1.3, 3.3)	

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*United States Census Bureau, *"2010 Census Briefs – Age and Sex Composition: 2010, Table 2"* (2011).

Emixustat's Suppression of ERG b-wave Rod Recovery[4506]

	Placebo	2 mg a.m. dose	5 mg a.m. dose	5 mg p.m. dose	7 mg a.m. dose	10 mg a.m. dose
Rate of recovery (slope)	2.68	1.77	0.99	0.96	0.89	0.28
Percent suppression		34	63	64	67	90

By demonstrating the ability to suppress ERG b-wave rod recovery, researchers say emixustat's mechanism of action works as intended.

disease well. They say that though hemorrhage and any SRF have high specificity, and can help rule in the presence of activity, most of the FAs classified with active disease didn't have those features. As a result, they think that physicians should consider adopting OCT-guided treatment for neovascular AMD.[3660]

Researchers have completed a proof-of-concept study of Acucela's orally administered emixustat HCl for the treatment of geographic atrophy associated with non-exudative AMD. Most of the researchers are either consultants for Acucela or receive financial support from the company.

Emixustat HCl is a rod visual cycle modulator that inhibits isomerase (RPE65) activity and reduces retinal toxins that damage the retinal pigment epithelium and the overlying photoreceptors. In the prospective, double-masked, Phase II study, researchers randomized 72 patients to receive 2-, 5-, 7-, or 10-mg emixustat HCl to be given before noon (a.m. dosing) or 5 mg to be given after noon (p.m. dosing); or oral placebo daily for up to 90 days in a 3:1 ratio. To assess the drug, after 30 minutes of dark adaptation, researchers recorded electroretinograms. They then photo-bleached the eyes and recorded the ERGs immediately, then again at 10, 20 and 30 minutes. Rod b-wave amplitudes were expressed as a percentage of the pre-bleach dark-adapted rod amplitude from baseline. The investigators compared the rate of rod recovery (slope) for each emixustat HCl group to the placebo group.

The researchers say that the drug suppressed ERG b-wave rod recovery after light exposure in a dose-related fashion. Suppression plateaued by day 14 of dosing, and reversed within seven to 14 days after cessation. There were no systemic adverse events, and chromatopsia and delayed dark adaptation were the most common ocular AEs. Two subjects had a treatment-related serious AE, moderate chromatopsia at the 5-mg dose level. The study doctors say that all ocular AEs resolved upon drug cessation, and that the common events were explainable based on the drug's mechanism. A long-term, Phase II/III study is under way.[4506]

The AMD Gene Exome Chip Consortium, sponsored by the National Institutes of Health, is gradually putting together some of the pieces of the genetic puzzle behind AMD, and will share results of their first round of analysis at this year's meeting.

Researchers from the United States and Germany designed a custom genotyping array consisting of 250,000 common and rare coding variants discovered in large-scale sequencing experiments (and enriched for variants discovered in sequencing experiments targeting patients with AMD), and an additional set of 250,000 common variants distributed evenly across the genome. Then, working with the NIH Health Center for Inherited Disease Research, they began to genotype all available samples using this custom array. They ultimately curated and organized DNA samples for more than 48,000 people, consisting of 48.25 percent AMD cases with the rest acting as non-AMD controls.

The researchers say that, among the AMD cases, 46.25 percent had CNV, 14.7 percent had GA and 9 percent had GA in one eye and neovascular disease in the other (resulting in 70.2 percent of cases having advanced disease). In the remaining cases, 16.5 percent had large drusen and 13.3 percent had earlier signs of disease. The researchers say that they expect an 80-percent power level in detecting variants with a frequency of >0.1 percent that lead to greater than a 2.45-fold increase in disease risk.[4977]

Researchers in the Age-Related Eye Disease Study 2 say that visual acuities in AMD patients improve significantly after cataract surgery, despite the retinal issues.

AREDS2 is a five-year, multicenter, randomized, controlled trial of nutritional supplements for AMD that has enrolled 4,203 patients with different degrees of AMD. In assessing secondary outcomes, researchers analyzed pre- and postoperative characteristics of participants who underwent cataract extraction during the five-year trial, using both clinical data and standardized lens and fundus photographs obtained at baseline and yearly thereafter. A centralized reading center graded photographs for lens opacities and severity of AMD.

In this particular subset of the study, the researchers analyzed visual acuity results for 1,232 eyes (793 patients) that had cataract surgery during AREDS2. After adjustment for age at surgery, gender, and type and severity of cataract, the mean changes in visual acuity were as follows: Eyes with mild AMD (AREDS AMD Scale 1 to 3, n: 31) gained 10.7 letters ($p<0.0001$)

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compared to preoperative acuity; eyes with moderate AMD (AAS 4 to 6, n: 346) gained 11.2 letters ($p<0.0001$); eyes with moderate AMD (AAS 7 to 8, n: 464) gained 8.8 letters ($p<0.0001$); eyes with non-central geographic atrophy (AAS 9, n: 70) gained nine letters ($p<0.0001$); and eyes with advanced AMD (AAS 10 to 11, n: 321) gained seven letters ($p<0.0001$). The mean time from measurement of preoperative acuity to cataract surgery was 5.9 ±3.6 months, and the mean time from surgery to measurement of postoperative acuity was 7.0 ±3.6 months.[243]

Ophthotech has released the Phase IIb data from its study of its anti-platelet derived growth factor drug Fovista, in combination with ranibizumab, compared to ranibizumab monotherapy in neovascular AMD.

In the prospective, controlled study, a physician randomized 449 patients with wet AMD to receive one of the following every four weeks for 24 weeks: Fovista 0.3 mg in combination with ranibizumab 0.5 mg; Fovista 1.5 mg in combination with ranibizumab 0.5 mg; or sham in combination with ranibizumab.

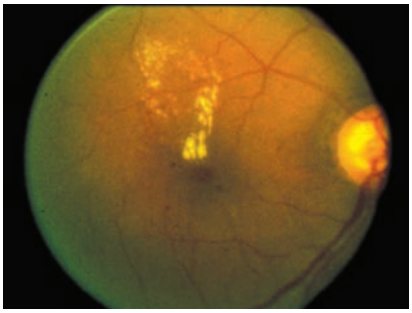
The researcher reports that the combination using Fovista 1.5 mg met the primary endpoint of superiority in mean visual acuity gain compared to ranibizumab alone (10.6 ETDRS letters gained at week 24 vs. 6.5 letters, $p=0.019$). There was an additional 62 percent benefit from baseline in the Fovista 1.5 mg combination therapy arm over ranibizumab monotherapy, and there was a classic dose-response curve. The researcher notes that the relative magnitude of visual benefit increased over time, and that the superiority of Fovista 1.5 mg combination therapy over ranibizumab monotherapy was consistent across all subgroups, including those based on baseline vision, lesion size and central retinal thickness. Fovista 1.5 mg combination was superior to ranibizumab monotherapy across multiple treatment endpoints including three, four and five lines of vision gain. OCT and fluorescein angiography analysis showed patients receiving Fovista 1.5 mg combination therapy had greater reduction in neovascular size compared to those receiving ranibizumab monotherapy. No significant safety issues were observed for either treatment group in the trial.[2175]

Diabetic Retinopathy

Researchers from the Genentech-sponsored RISE and RIDE trials analyzed the trial data to determine the effect of intravitreal ranibizumab on diabetic retinopathy severity.

To recap the trials' structure, 759 patients with diabetic macular edema were randomized in a 1:1:1 ratio to receive monthly 0.3-mg or 0.5-mg ranibizumab or sham injections. The sham patients were able to receive 0.5-mg ranibizumab during the third year. Everyone was eligible for macular laser starting at month three, and panretinal photocoagulation was also available.

The researchers report that a higher percentage of eyes in the ranibizumab arms had a regression of their DR of at least two or three steps on the ETDRS severity scale compared to the sham/0.5-mg crossover group at three years. Fifteen percent of the 0.3-mg eyes and 13.2 percent of the 0.5-mg patients experienced three steps or more of improvement, compared to just 3.3 percent of the sham/0.5-mg crossover patients. Through 36 months, 33.9 percent of eyes originally randomized to sham developed proliferative DR as measured by a composite outcome that included photographic changes and clinically important events such as occurrence of vitreous hemorrhage or application of PRP. Only 12.8 percent of the 0.3-mg group and 15.1 percent of the 0.5-mg group progressed to PDR. However, in the third year, the investigators say that the proportions of patients exhibiting DR progression were similar in all three treatment arms.



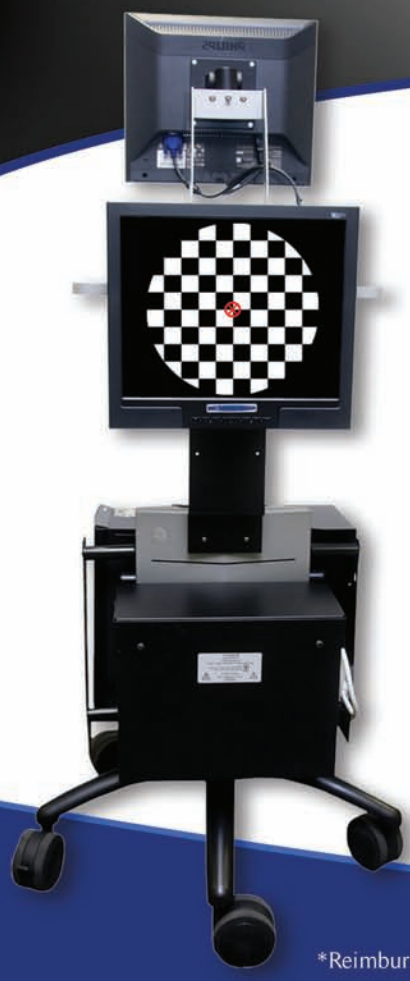
Delaying ranibizumab reinjections may stunt their effect in diabetic retinopathy, say researchers.[4028]

The physicians say that the data provides strong evidence that ranibizumab is effective in reducing DR severity and inhibiting its progression to PDR, but add that delays in starting ranibizumab therapy may stunt this therapeutic effect.[4028]

Researchers from a large-scale, randomized study supported by Novartis Pharmaceuticals Canada share their results from treating DME with ranibizumab alone and with laser.

The researchers randomized 241 patients in a 1:1:1 ratio; 78 received a combination of ranibizumab and laser, 81 received ranibizumab alone and 82 received only laser. The protocol consisted of administering three consecutive monthly injections to patients, then following them for 10 months during which further injections could be given based on retreatment criteria. For patients receiving it, laser was administered according to ETDRS guidelines at intervals no shorter than three months. The mean best-corrected acuity and central retinal thickness for the intention-to-treat group (n: 212) were 63.7 ±10 letters and 437 ±141 µm, respectively.

The investigators say the mean change in BCVA and CRT from baseline to a year was +8 letters (95-percent CI: 5.5, 10.5) and -144 µm (95-percent CI: -182, -106), respectively, for the combination arm (n: 60); +8.3 letters



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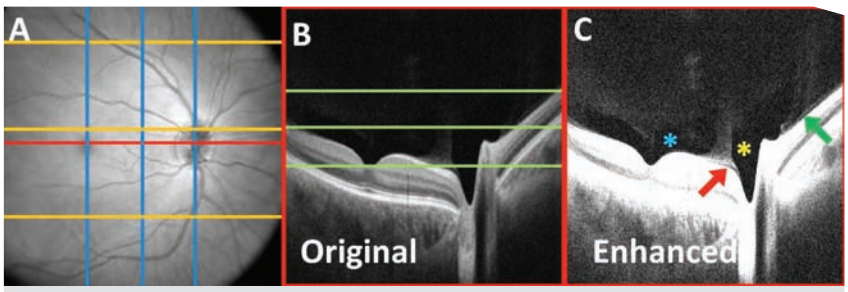
(95-percent CI: 6.5, 10.1) and -135 µm (95-percent CI: -170, -100), respectively, for the ranibizumab arm (n: 62) and +1.1 letters (95-percent CI: -2.5, 4.6; n: 46) and -112 µm (95-percent CI: -157, -68; n: 45), respectively, for the laser arm. During the trial, the mean number of injections received was 8.5 ±3 for the combination arm (n: 71) and 8.6 for the ranibizumab arm (n: 74). The average number of laser sessions was 1.6 ±1 for the combination arm (n: 69) and 2.5 ±1 sessions for laser arm (n: 69). The most common reason for discontinuation was an unsatisfactory effect in 11 percent of the laser arm (n: 82), 3 percent of the combination arm (n: 78) and 1 percent of the ranibizumab arm (n: 81).[4025]

A group of researchers from France, one of whom receives financial support from Allergan, has performed a retrospective, multicenter study of the intravitreal dexamethasone implant dubbed the Multicenter Ozurdex Assessment foR diabeTic macular edema, or MOZART.

The researchers placed the implant in 69 eyes of 59 patients with DME and followed them for at least six months (mean: 9.8 months). The patients' mean age was 65 years. The mean systolic blood pressure was 138 mmHg and the mean HbA1c was 7.2 percent. Seventeen patients (24 percent) were naive to any macular treatment.

At baseline, the patients' mean central retinal thickness was 540 µm. Postop, the average CRT decrease was: 188 µm at month one (M1); 235 µm at month two (M2); 117 µm at month four (M4); and 77 µm at month six (M6). The initial BCVA letter score was 54.4 letters, and the mean BCVA improvement postop was: 2.1 letters at M1; 5.4 at M2; 2.4 at M4; and 1.6 at M6. For treatment-naive patients this gain was higher: 5.8 letters at M1; 6.7 at M2; 8.7 at M4 and 6.7 at M6. During the follow-up, 28 percent of patients had a BCVA better than 20/40 (73 letters), vs. only 6 percent at baseline.



Researchers say that a new approach to OCT called swept-source may enable enhanced vitreal imaging, and reveal more detail than current methods. One of the investigators holds a patent related to the technology.

In the study of 22 normal eyes, EVI enabled researchers to see features such as vitreous separation from the retina and hyaloid detachment near the optic nerve head. They say that SS-OCT's main advantages are its high sensitivity over a long imaging range, and that its high speed combined with its motion correction and image merging enables wide-field volumetric imaging. Appearing above are a wide-field OCT (A), a standard OCT image (B) and EVI (C). EVI shows a posterior precortical vitreous pocket (blue asterisk), hyaloid adhesion at the optic nerve (red arrow), space of Martegiani (yellow asterisk) and vitreous separation (green arrow).[3167]

Researchers noted a gain in BCVA greater than 15 letters in 28 percent of patients, while a loss greater than 15 letters occurred in 6 percent. The mean number of implant injections was 1.2 at six months, with an average of 4.9 months before reinjection. The mean initial intraocular pressure was 15 mmHg. Ocular hypertension greater than 25 mmHg, managed by topical treatment, was observed in 7 percent of patients. Cataract progressed in 4 percent of patients, vitreous hemorrhage occurred in 1.5 percent and there were no cases of endophthalmitis.

Overall, the investigators say that the implant showed anatomical and functional effectiveness, but note that patient follow-up must be adapted to the implant's duration of action, with a visit before the second month to detect pressure spikes and one before the fourth month to detect DME recurrence.[2387]

Surgeons in the RELATION study of ranibizumab and/or laser for DME report good results from combining the treatments.

RELATION is a multicenter, 12-month, two-armed, double-masked, parallel-group, active-controlled clinical trial in which patients with visual impairment due to DME were randomized 2:1 to ranibizumab in combination with focal/grid laser photocoagulation (combined group) or focal/grid laser photocoagulation combined with sham injections (laser group). After initial treatment starting at baseline with laser and four monthly ranibizumab/sham injections, treatment was given as needed. Also, a subgroup of patients with concomitant PDR was included, and this group received additional panretinal laser photocoagulation at baseline, then treatment as randomized.

Out of 128 patients, the investigators randomized 85 to the combined group and 43 to the laser group. They note that BCVA in the combined group was significantly better than BCVA in the laser group at final follow-up (mean change from baseline +6.5 letters for combined vs. +1.4 letters for laser, p=0.001). Eighty percent of centers used SD-OCT instruments, and reported that the reduction of total retinal volume (within a 6-mm^3

ETDRS grid) on OCT was significantly higher in the combination group than in the laser group (mean change from baseline was -1.174 mm^3 for the combination therapy vs. -0.501 mm^3 for the laser group).

For the subgroup analysis, 27 patients had PDR at baseline (20 in the combined and seven in the laser group). Presence of PDR had no significant effect on BCVA outcome. Eight patients (40 percent) with PDR in the combined group, but none of the PDR patients in the laser group, showed regression of PDR during follow-up. The researchers say that the adverse event profile was similar to previous studies in NPDR and PDR patients.[1239]

Surgical Studies

In a study sponsored by ThromboGenics, researchers say that the company's new drug ocriplasmin was effective in patients with symptomatic vitreomacular adhesion who would usually be candidates for vitrectomy.

The study included symptomatic patients with OCT-confirmed VMA who were randomized to receive a single intravitreal injection of 125 µg ocriplasmin (n: 464) or placebo (n: 188). Clinical criteria for consideration for vitrectomy was visual acuity of 65 ETDRS letters (20/50) or less (n: 301) or full-thickness macular hole (equivalent to stage II) at baseline (n: 153). A total of 127 patients met both criteria. In patients without baseline FTMH, the investigators evaluated the rate of VMA resolution at 28 days post-injection. In patients with baseline FTMH, they evaluated VMA resolution and FTMH closure at day 28.

The researchers report that pharmacologic VMA resolution at day 28 was observed in a significantly larger proportion of eyes in the ocriplasmin group compared to placebo. Among patients with a baseline VA of 65 letters or fewer, 33.2 percent of eyes treated with ocriplasmin achieved VMA resolution compared with 11.5 percent in the placebo group ($p<0.001$). Half of the patients with a baseline FTMH had VMA resolution vs. 25.5 percent in the placebo group ($p=0.006$). This correlated with a FTMH closure rate of 40.6 percent in the ocriplasmin group and 10.1 percent in the placebo group ($p<0.001$).

In terms of vision, the researchers say they saw greater changes in mean BCVA in both the VMA and FTMH ocriplasmin groups, +6.6 and +6.8 ETDRS letters, respectively, compared to placebo. At six months, 43 percent of the VMA patients treated with ocriplasmin had a gain of two or more lines of best-corrected acuity, as did 44.3 percent of the FTMH ocriplasmin group. In the placebo groups, only 28.7 percent of the VMA patients ($p=0.018$) and 30.4 percent of the FTMH ($p=0.104$) gained two or more lines. Also, 25.2 percent of the VMA patients treated with ocriplasmin and 27.4 percent of the FTMH treatment group had an improvement of three or more lines. For placebo patients, this gain was 10.3 percent in VMA cases and 13 percent for macular hole patients ($p=0.003$ and $p=0.063$, respectively). The study doctors say that most suspected treatment-related adverse events were mild, non-serious and occurred within seven days post-injection.[1942]

Researchers from Los Angeles' Doheny Eye Institute say a little creative procrastination may help improve outcomes with reoperations for macular pucker and macular hole.

The researchers evaluated 10 pseudophakic eyes undergoing reoperation for MP or MH using visual acuity as an outcome measure. They excluded eyes with a history of prior vitreoretinal surgery, retinal detachment, vein occlusion, wet AMD or diabetic retinopathy. The surgeons used 25-ga. vitrectomy in all cases, and performed chromodissection with doubly diluted indocyanine green dye in all primary MH surgeries and in all reoperations for MH and MP. VA was correlated with immunohistochemistry for neurofilament and transmission electron microscopy of excised tissue in six out of 10 cases.

The investigators report that VA improved by more than three lines in six cases and worsened by more than three lines in three cases. All cases with a six-month or larger interval before reoperation (six cases) showed VA improvement (>3 lines), while three out of four with less than a six-month interval had VA worsening (>3 lines; $p=0.03$). The average postoperative logMAR VA was 1.59 ±1.07 (20/800) for patients with an interoperation interval shorter than six-months, with positive neurofilament staining and retinal cell debris present on the peeled membrane in 2/2 eyes. The surgeons say that waiting six months or more before reoperating resulted in logMAR VA of 0.42 ±0.25 (20/50) ($p=0.03$) and resulted in no evidence of neurofilament staining or retinal elements on the peeled membranes (0/4 eyes).

The researchers theorize that if repeat vitrectomy with membrane peeling is performed too early, there may not be adequate time for Müller cells to reform a layer of endplates over the denuded retinal nerve fiber layer, exposing it to damage during the second operation with resultant poor vision. Waiting longer than six months before reoperating, they say, may allow enough time to reform normal tissue planes, enabling a better surgical plane of dissection, which seems to be associated with less inner retinal damage and superior final vision.[2147] REVIEW

Dr. Regillo is director of the Retina Service of Wills Eye Institute, and a professor of ophthalmology at Thomas Jefferson University School of Medicine.

Cataract Continues to Change with the Times

Mark H. Blecher, MD, Chief Medical Editor

The aging population, the evolution of technology and the changing health-care system are all reflected in this year's ARVO abstracts.

As the surgery itself continues its evolution to a refractive surgical procedure, an aging population and changes in our health-care system are contributing to a cataract surgery picture that is in flux. This year's ARVO abstracts encapsulate some of that activity.

Lens Studies

Surgeons in Glasgow, Scotland, report that an aspheric intraocular lens significantly reduces certain higher-order aberrations. They conducted a prospective, observational study of 50 patients who underwent uncomplicated cataract extraction to evaluate the effectiveness of an aspheric IOL in reducing monochromatic higher-order aberrations (MHOA). They measured whole-eye, corneal and internal MHOA before and four weeks after surgery. Pre- and postoperative data was compared to 300 eyes of 167 age-matched patients with no visually significant cataract. MHOAs were measured over a 5-mm dilated pupil diameter using the iTrace aberrometer. Zernike coefficients were obtained to the 6th order. *(See results, below.)* There was a significant reduction in total root mean square MHOA following surgery ($p<0.001$). The RMS of total internal 3rd ($p<0.001$), 4th ($p<0.001$), 5th ($p=0.033$) and 6th ($p=0.006$) orders also showed a significant reduction postoperatively. Postoperative whole-eye MHOAs (mean 0.484 µm) were found to be significantly less ($p<0.001$) than age-matched controls (mean 0.648 µm). Postoperative whole eye (mean 0.133 µm) and internal SA (mean 0.071 µm) were found to be significantly less than control cases (mean 0.223 µm; $p<0.001$ and mean 0.133; $p=0.022$ respectively).

Implantation of an aspheric IOL during cataract surgery significantly reduces both internal and whole eye MHOA. Postoperative MHOAs in patients with an aspheric IOL are significantly less than age matched

Monochromatic HOAs with an Aspheric Intraocular Lens[842]

	Preop	Postop	P Value
Whole-eye mean MHOA	0.729 µm	0.484 µm	$p<0.001$
Mean internal MHOA	0.681 µm	0.475 µm	$p<0.001$
Internal spherical aberration	0.172 µm	0.071 µm	$p=0.004$

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INDICATIONS AND USAGE: DUREZOL® Emulsion is a topical corticosteroid that is indicated for the treatment of endogenous anterior uveitis.

Dosage and Administration

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.

Adverse Reactions

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.

Reference: 1. DUREZOL® Emulsion Package Insert.

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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
Safety and effectiveness in pediatric patients have not been established.

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

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.

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Refractive Outcomes of Alcon AcrySof Toric IQ IOL[1848]

Outcome Group	Postop UDVA	Mean Residual Astigmatism
Good (n=75)	20/22	0.14 ±0.22 D
Fair (n=22)	20/28	0.38 ±0.33 D
Poor (n=36)	20/44	0.79 ±0.31 D

controls with clear optical media and no visually significant cataract, they write, and these changes may contribute to greater patient satisfaction and improved visual function.[842]

French surgeons compared the visual performance of two multifocal diffractive intraocular lenses, AcrySof ReSTOR SN60D3 (Alcon) and Acri.LISA 376D (Carl Zeiss Meditec), two years after cataract surgery.

The prospective, comparative study included patients between 50 and 80 years of age; 20 eyes (10 patients) that received the ReSTOR intraocular lens and 24 eyes (12 patients) that received the Acri.LISA IOL, with bilateral implantation by a single surgeon.

There was no statistically significant difference (α=5 percent) between the two lenses in terms of visual acuity for far and near vision, for monocular and binocular vision, for contrast sensitivity and glare test. There was a statistically significant difference in favor of the Acri.LISA group for intermediate visual acuity, especially for monocular uncorrected VA (p=0.03), binocular uncorrected VA (p=0.041) and binocular corrected VA (p=0.004). The analysis of quality of life questionnaire did not find any statistically significant difference between the two groups nor any correlation between visual discomfort during night driving and glare test.

While both IOLs have similar visual performance (good level of satisfaction without eye glasses), the better intermediate vision in the Acri.LISA group may be explained by the asphericity of the lens increasing the depth of field, the authors surmise. This two-year follow-up data confirms the results of previous studies reported in the literature (six months and one year follow-up).[846]

A group in Massachusetts sought to establish criteria for determining quality of refractive outcomes after toric IOL implantation and assess whether toric IOLs with higher cylindrical power are associated with inferior refractive outcomes. Reviewing the charts of patients implanted with the Alcon AcrySof Toric IQ lens over three years, they recorded cylindrical power of the IOL; postop uncorrected distance VA (UDVA); postop corrected distance VA (CDVA); postop residual astigmatism by manifest refraction; and presence of ocular comorbidities. Eyes were assigned to groups based on outcomes defined as good (UDVA 20/25 or better with ≤ 0.5 D residual astigmatism), fair (either UDVA 20/30 with ≤ 0.5 D residual astigmatism, or UDVA 20/25 or better with 0.75 D residual astigmatism), and poor (UDVA 20/30 or worse with ≥ 0.75 D residual astigmatism).

Of 133 eyes of 96 patients included, with 56.4 percent in the good outcome group, 16.5 percent in the fair group, and 27.1 percent in the poor group; 13.5 percent of eyes (n=18) had ocular comorbidities (corneal or retinal pathology) that limited postop CDVA; all met criteria for the poor outcome group; 38.4 percent (n=51) of eyes received the lowest cylindrical power toric IOL (T3), and 61.6 percent (n=82) of eyes received the higher cylindrical power toric IOLs (T4 to T9). There was no significant difference in postoperative UDVA between the T3 and the T4 to T9 groups (20/26 versus 20/28, p=0.3537). Residual astigmatism was lower in the T3 group than in the T4 to T9 group (0.24 ±0.33 D versus 0.43 ±0.46 D, p=0.0115).

Establishing criteria for determining quality of refractive outcomes with toric IOLs can be helpful in counseling patients before cataract surgery, they conclude. Implantation of higher cylindrical power toric IOLs is associated with slightly more residual astigmatism, but there is no association with inferior postop UDVA.[1848]

A group in Mexico City assessed the safety and effectiveness of the AcrySof Cachet Phakic angle-supported IOL for the correction of high myopia. The study evaluated 14 eyes of nine patients, age 22 to 53 years, mean 34.1 years; 66.6 percent were female; mean follow-up was 29 months (r: nine to 38 months). The mean preop spherical equivalent was -14.39 (r: -10.25 to -19.25); mean postop SE was -0.5 (r: -3.25 to +0.62). The mean postoperative UCVA was 20/30 (logMar 0.17) or better and the BCVA 20/25 (logMar 0.098) or better. The contrast sensitivity was measured with CDVA, considering the low (6.28 cycles per degree), medium (5.07 cpd) or high (3.78) mean spatial frequencies. The change of the mean preop endothelial cell density (2,763.4 cells) to mean postoperative cell density (2,626.9) was statistically significant (p=0.013). Only one patient was a steroid hyper-reactor; the pressure normalized after the drug was suspended. None of the patients showed IOP rise or other adverse effects.

The group says its results are consistent with other published reports of phakic IOLs, where the UCVA and BCVA were excellent. However endothelial cell loss over time was statistically significant, which has been attributed to the proximity of the anterior chamber IOL to the endothelium, the surgery itself and physiologic decrease with aging.[3134]

Surgical Issues

Researchers from nine U.S. institutions collected data for the Veterans Administration's Ophthalmic Surgical Outcomes Data Project to assess the impact of intraoperative floppy iris and the use of pupillary expansion devices on intraoperative complication rates in cataract surgery.

The retrospective analysis recorded the use of alpha-blockers (both selective and non-selective), intraoperative floppy iris, intraoperative iris trauma, intraoperative iris prolapse, posterior capsular tear, anterior capsule tear, intraoperative vitreous prolapse, and use of pupillary expansion devices.

Of 4,923 total cataract surgeries included, 1,294 patients, (26.3 percent) took alpha-blockers preoperatively (selective 627, non-selective 667). Of these 1,294 patients, 428 patients (33.1 percent) had documented IFIS. However, 75.2 percent of patients with IFIS had taken alpha-blockers preoperatively ($p<0.00001$); 430 patients of the total studied (8.7 percent) had a pupillary expansion device used during their cataract surgery, of which 186 patients had IFIS (43.3 percent, $p<0.0001$). Seventeen patients had anterior or posterior capsule tears (3 percent); five patients had both. Of patients with posterior capsule tear, 88.2 percent (15/17) had vitreous prolapse that required vitrectomy; only four of these involved the use of a pupillary expansion device (23.5 percent). Thirty-eight patients with IFIS had at least one intraoperative complication, and 18 patients with IFIS had more than one intraoperative complication ($p<0.00001$). Of these 18 patients with IFIS and more than one intraoperative complication, 27.8 percent (five of 18) had pupillary expansion devices used.

The use of alpha-blockers preoperatively demonstrated a significant risk of IFIS. Less than half of IFIS patients had pupillary expansion devices used during their cases. Approximately half of patients with intraoperative surgical complications and IFIS incurred more than one complication. A prospective trial could be conducted looking at whether the increased use of pupillary expansion devices in high-risk VA patients could decrease intraoperative surgical complication rates.[1826]

With complete removal of lens epithelial cells recognized as a common strategy to prevent posterior capsule opacification, surgeons in Norfolk and London, U.K., investigated how total LEC loss affects IOL stability within the capsular bag.

Capsular bags were generated from human donor eyes by capsulorhexis and lens extraction followed by implantation of a single-piece Acrysof IOL. Capsular bags with associated zonules and ciliary body were removed from the eye and secured by pinning the ciliary body to a silicone ring. One bag of each pair was treated with 1µM thapsigargin, a calcium ATPase inhibitor, to destroy all LECs. Observations of LEC growth were captured by phase contrast microscopy, and IOL stability was assessed by video microscopy. At end-point, the bags were examined using scanning electron microscopy and immunocytochemistry.

LECs in control capsular bags could be observed to migrate centrally, closing the bag and fixating the IOL between the anterior and posterior capsules, as seen clinically. In addition a firm seal was formed at the rhexis edge between the anterior capsule and the underlying IOL. Application of thapsigargin to the capsular bags prevented cell growth and led to a complete loss of viable cells. Consequently, thapsigargin-treated preparations did not exhibit adhesion between anterior and posterior capsules nor adhesion to the IOL surface. These observations were confirmed by SEM and immunocytochemistry. Following a period of controlled orbital movement, the positioning within the capsular bag was unaffected in each test group. However, the IOLs in the control group stabilized more quickly than in the thapsigargin-treated bags.

They conclude that LECs appear to aid stabilization of current IOL designs in the capsular bag. This study has important clinical implications for IOL design and for strategies to prevent posterior capsule opacification.[2975]

Scleral fixation of IOLs with fibrin glue has been reported in a few case series in the literature. Potential advantages include relative surgical ease, minimal intraoperative complications and stability of the IOL at follow-up. Surgeons at the University of Ottawa Eye Institute, Ontario, Canada have incorporated this technique into their practice predominantly as a secondary IOL implant procedure in aphakes and as an IOL exchange procedure for patients destined for endothelial keratoplasty. The procedure involves the creation of two partial thickness scleral flaps, 3 mm from the limbus at 180 degrees from each other. A three-piece IOL is inserted, with each haptic being externalized through a sclerotomy under the flap and tucked into an intrascleral tunnel. The flaps are then closed with fibrin glue.

The retrospective review of their first 10 consecutive patients assessed outcomes including complications, centration of IOL, visual acuity, manifest refraction and endothelial cell count. The 10 eyes of nine patients (mean age 63) included eight edematous, pseudophakic bullous keratopathy eyes with poor visibility through the cornea, which had an IOL exchange procedure in which the offending primary anterior chamber IOL was replaced by a glued IOL, later followed by EK. The remaining two eyes were treated for traumatic lens subluxation. There were no intraoperative complications, and pain

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Percentage of Eyes Achieving Emmetropic Target Based on 'Back-calculated' IOL Equation[3004]

	All Eyes ≤0.5 D ≤1 D emmetropia		Post-LASIK/PRK ≤0.5 D ≤1 D emmetropia		Post-RK ≤0.5 D ≤1 D emmetropia	
Implanted IOL	66%	77%	94%	94%	25%	50%
ORA predicted IOL	53	70	72	89	25	42
ASCRS calculator predicted IOL	43	63	33	61	58	77
Conventional formula predicted IOL	23	47	17	50	33	41

symptoms resolved within one week postoperatively. At one-month follow up, nine of 10 eyes had a centered IOL, with the remaining patient having inferior subluxation. One eye with preexisting glaucoma had an IOP rise to 54 mmHg, which was managed with topical therapy.[2991]

Combined use of the ORA intraoperative aberrometer, the ASCRS calculator and conventional formulas to predict IOL power allows cataract surgeons to achieve better refractive outcomes in post-refractive cataract patients than any one method alone, according to a study at Rush University Medical Center, Chicago.

The study reviewed outcomes of 30 eyes of 24 patients. Twelve had a history of RK and 18 had previous myopic/hyperopic LASIK/PRK. Biometry measurements were obtained preoperatively. The IOL power was calculated using the SRK/T or Holladay 1 formula and the ASCRS Post Keratorefractive IOL calculator. The ORA-recommended IOL power, the actual implanted IOL power, and the postoperative UCVA and manifest refraction were recorded. IOL back-calculation for emmetropia was done using previously published formulas.

Mean postop UCVA was 20/40. Mean postop SE was 0.07D (r: -1.75 to +4.5 D). There was a significant difference between the mean postoperative SE in the LASIK/PRK and RK groups (-0.31 and 0.63 respectively, p=0.039). *(See other outcomes above.)*

The ORA's ability to predict IOL power was significantly better in LASIK/PRK patients than in RK patients (p=0.0064).[3004]

Surgeons at Chicago's Northwestern University used spectral domain anterior segment optical coherence tomography to analyze the morphology of clear corneal incisions performed in patients undergoing femtosecond laser-assisted cataract surgery (Catalys, Optimedica).

An intended triplanar incision was programmed into the Catalys. The first plane was at 90 degrees to the corneal surface and extended to 40 percent corneal depth, the second was an angled intrastromal plane and the third plane was at 45 degrees to the posterior corneal surface and reached the second plane at 70-percent depth. The intended incision width was 2.85 mm and length was 1.8 mm. AS-OCT was performed on the first postop day. The clear corneal incision length, incision depth, angles of the tri-planar corneal incision, and wound gaping were measured using software calipers. The variability in wound length, depth and angle were calculated and compared to the programmed software settings. Five architectural features were used to describe the clear corneal incisions: gaping of the wound at the epithelial side; gaping of the wound at the endothelial side; within-wound gape; misalignment of the roof and floor of the incision at the endothelial side; and local Descemet's membrane detachment. This study is ongoing and will include 30 eyes.

At one day postop, two of three eyes had endothelial side wound gape; one of three had epithelial wound gape, two of three eyes had a within-wound gape; and three eyes had a focal DM detachment. All three eyes had visible three-plane profile on AS-OCT. The clear corneal incision length was within 100 µm of the intended length. The incision depth was within 8 percent of the intended depth.

While initial results suggest that CCIs using the femtosecond cataract laser were close to the intended size and depth, a significant proportion of eyes had marginal and stromal wound gape and focal DM detachment.[563]

Femtosecond cataract surgery appears to be safe and effective in high-risk cases of lens exfoliation syndrome, and may hold an intrinsic advantage of less surgical zonular weakening associated with capsulorhexis and lens fragmentation, according to a group from New York University.

In 65 eyes of 48 consecutive patients with LES, the group recorded preoperatively and three months postoperatively: age; UCVA; BSCVA; refraction; cylinder; capsulorhexis diameter; topographic cylinder change; endothelial cell count; and possible complications. (An endocapsular tension ring was used in five cases.)

The mean age was 71 years. The mean pre- and postop values were as follows:

Femto Cataract in High-Risk Cases[1818]

	Preop	Postop
UCVA	20/100	20/25
BSCVA	20/40	20/22
SE reduction	3.7	0.5 D
Cylinder	-2.25 D	-0.55 D
ECC	1,850	1,650
Capsulorhexis Diameter	5.0 mm	
Topographic cylinder change	-0.45D	

Demographics, Miscellaneous

A Duke University study concludes that white patients and those with private insurance tend to present with better preoperative best-corrected visual acuity, on average, than their respective counterparts at the time of cataract surgery. The findings may represent a disparity in access to care or utilizing the care based on insurance and race variables. Larger studies are needed to confirm these preliminary findings.

Over the four-year study, the researchers collected data on visual acuity, race, gender, health insurance plans, systemic and ocular comorbidities, body mass index and smoking history on 430 candidates for cataract surgery.

Insurance (uninsured, public, private) and race (white, black, other) were the two sociodemographic variables with significant differences between groups ($p<0.0001$ and $p=0.0005$, respectively). Significant differences in mean preop BCVA were found for private (Snellen~20/55) versus public (20/75, $p=0.0001$); private versus uninsured (20/150, $p=0.0003$); white (20/60) versus black (20/75, $p=0.0008$); and white versus other race (20/105, $p=0.0138$). There was no significant difference in BCVA between public and uninsured, black and other race, or men and women, and no strong correlations between BCVA and BMI or smoking pack-years. In a multivariate regression model adjusting for age, significant comorbidities from univariable analyses (diabetes, age-related macular degeneration and hypertension), and other vision-impairing conditions, insurance and race remained significant ($p=0.0056$, 0.0038).[857]

Incident cataract surgery steadily has increased over the last three decades, and second-eye surgery is performed sooner and more frequently, based on data from the Rochester Epidemiology Project collected and analyzed by researchers at Minnesota's Mayo Clinic.

The data came from 8,012 cataract surgeries from 2005 through 2011. During this time, incident cataract surgery significantly increased ($p<0.001$), peaking in 2011 with an overall incidence rate of 1,100 per 100,000 residents. The probability of second-eye surgery was 60 percent at three months after first-eye surgery, 76 percent at 12 months and 86 percent at 24 months; this was an increase of >30 percent when compared to the same time intervals in the previous seven-year period, 1998 to 2004 ($p<0.001$). When merged with previous REP data, incident cataract surgery steadily increased over the last three decades ($p<0.001$).[1819]

A group at the University of Michigan, Ann Arbor, has found dramatic variability in the age of first cataract surgery in different communities throughout the United States.

The group reviewed health-care claims data from a nationwide managed-care network to identify all enrollees age >40 who underwent one or more cataract surgeries between 2001 and 2011, recording the age of first cataract surgery and comparing the median age of first cataract surgery in 306 different communities throughout the United States.

Of the 1,052,277 enrollees diagnosed with cataracts, 243,467 (23.1 percent) underwent ≥1 cataract surgery. Large differences were noted in the median age of first cataract surgery among the different communities: those with the lowest median age of first cataract surgery (Lansing, Mich.—59.9 years, and Aurora, Ill.—60.1 years) differed considerably from those with the highest median age (Marquette, Mich.—77 years, Rochester, N.Y.—78.4 years and Binghamton, N.Y.—79.6 years). Differences in the age-standardized rates of cataract surgery varied five-fold across communities, ranging from 7.5 percent in Honolulu to 37.3 percent in Lake Charles, La. Some communities exhibited variability in age of first cataract surgery of as little as six to seven years (Lawton, Okla.—6.4 years and Yakima, Wash.—7.2 years) while others had large variability in the age of first cataract surgery (Bloomington, Ill.—12.7 years and Santa Cruz, Calif.—12.7 years).

The authors recommend that efforts be directed at understanding the extent to which these differences are due to patient-related factors, the supply of ophthalmologists or optometrists in a given community, and the impact of the timing of cataract surgery on patient outcomes.[4384]

Canadian researchers make an economic case for same-day bilateral cataract surgery as a cost-effective procedure and suggest that population and practice trends may make the need for it greater as time goes on.

Cost-effectiveness of cataract surgery will become increasingly important, they say. More than 2.5 million Canadians are currently suffering from cataract and this is likely to double by 2031. They project an increasing senior population to make up 23 percent of the population of Canada by 2031, with a resulting increase in cataract surgeries performed per year. Moreover, one in three Canadian ophthalmologists are over the age of 55 and are due to retire in the next decade; it is expected that the ratio of ophthalmologists to people over 65 will drop about 43 percent over the next 15 years.

They compared immediately sequential bilateral cataract surgery (ISBCS) and delayed sequential bilateral cataract surgery (DSBCS) using an analytic model based on data consisting of the cost of the surgery, intravitreal injections, medications and drops. The effectiveness was measured by the utility values

(Continued on page 114)

Cross-linking Leads the Way in a Busy Year

Natalie Afshari, MD, FACS, San Diego

Expanding the base of patients who may benefit from cross-linking and refining the procedure lead the way in a busy year of cornea research.

Corneal collagen cross-linking continues to be a mainstay of research reports in this year's ARVO Cornea selections. Expanding the pool of patients who may potentially benefit from the procedure and improving various aspects of the technique are a big emphasis for researchers. Along with a look at dry eye, transplant techniques and other traditionally rich areas of corneal research, here are just a few of the representative abstracts from this year's offerings.

Cross-linking—Technique

Italian researchers report that a new riboflavin formulation increased corneal penetration in pig eyes by 852 percent vs. the commercial riboflavin-5-phosphate (RFP). The new complex, riboflavin MDV1224, and commercial riboflavin-5-phosphate were placed in donor chambers with excised porcine cornea at 37 C for 360 minutes. The receiver chamber contained an isotonic phosphate buffer saline solution. Samples were collected from the receiver chamber every 60 minutes and quantitatively analyzed by high-performance liquid chromatography.

Trans-corneal permeability, cm/sec, was calculated by plotting the amounts ($\mu g/cm^2$) of riboflavin in MDV1224 or RFP that permeated through the corneal cells over time (minutes). Riboflavin stability in MDV1224 was also monitored for six months in dark conditions and compared to RFP.

Trans-corneal permeability of MDV1224 (45.7×10^{-6} cm/sec) was almost tenfold greater compared to that of RFP (4.8×10^{-6} cm/sec). After six months, stability data at 40 C and 25 C showed high degradation values for both riboflavin in MDV1224 and RFP formulations, while at 2 to 8 C riboflavin in MDV1224 and RFP showed only 3 percent degradation.

The group call for *in vivo* studies to confirm that the higher delivery of MDV1224 vs. RFP is able to guarantee a correct corneal cross-linking in the intact human cornea.[5259]

Two surgeons in New Jersey compared the effect of concurrent vs. sequential corneal collagen cross-linking (CXL) and Intacs on visual and topographic outcomes in patients with keratoconus and corneal ectasia.

The prospective, randomized clinical trial analyzed 41 eyes with KC and ectasia. All patients were initially treated with symmetric 350-µm Intacs segments. Patients were randomized into one group that received standard CXL immediately following the Intacs procedure (concurrent group, n=23), and a second group that received the identical CXL treatment three months

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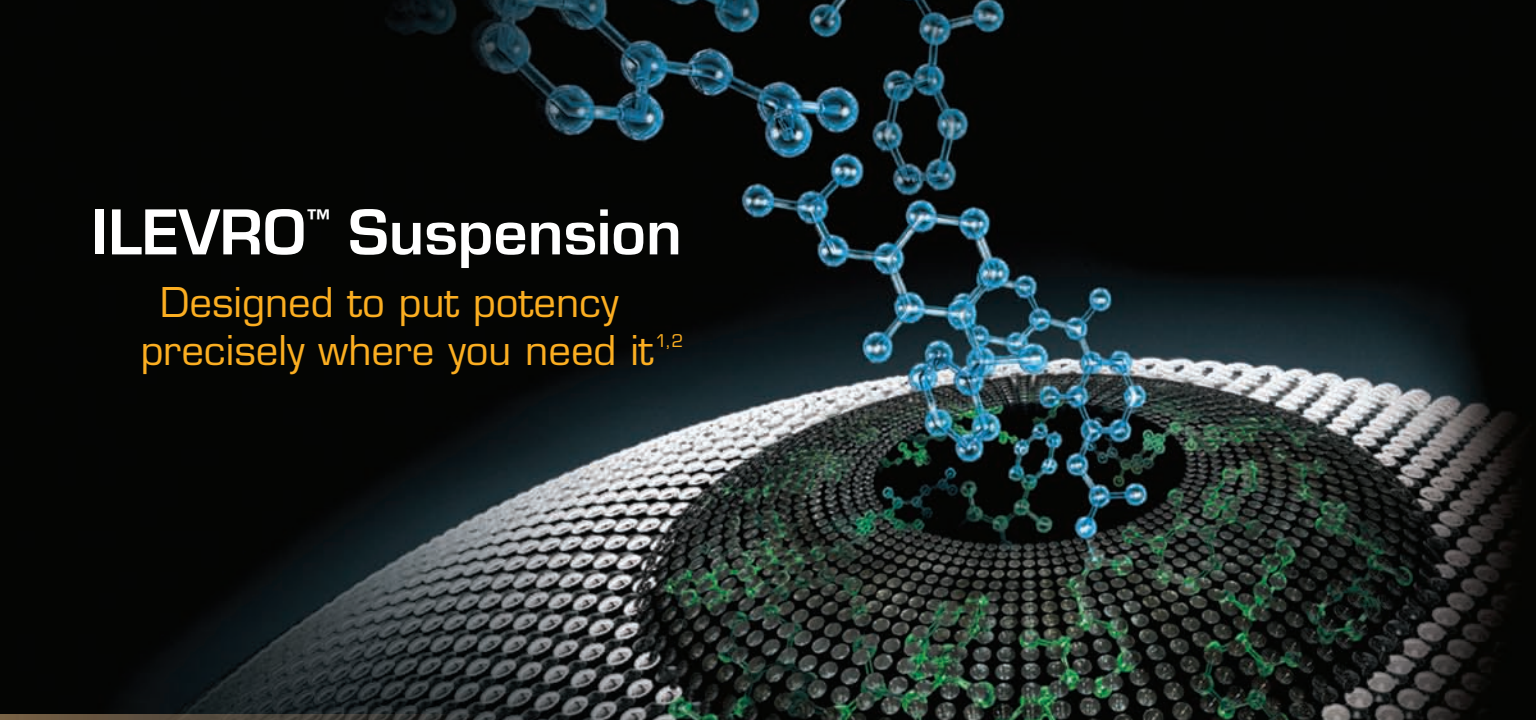

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One drop should be applied once daily beginning 1 day prior to surgery through 14 days post-surgery, with an additional drop administered 30 to 120 minutes prior to surgery[3]

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

INDICATIONS AND USAGE

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

Dosage and Administration

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

IMPORTANT SAFETY INFORMATION

Contraindications

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

Warnings and Precautions

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

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

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

Adverse Reactions

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

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

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

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ILEVRO™

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

USE IN SPECIFIC POPULATIONS
Pregnancy
Teratogenic Effects.
Pregnancy Category C: Reproduction studies performed with nepafenac in rabbits and rats at oral doses up to 10 mg/kg/day have revealed no evidence of teratogenicity due to nepafenac, despite the induction of maternal toxicity. At this dose, the animal plasma exposure to nepafenac and amfenac was approximately 70 and 630 times human plasma exposure at the recommended human topical ophthalmic dose for rats and 20 and 180 times human plasma exposure for rabbits, respectively. In rats, maternally toxic doses ≥10 mg/kg were associated with dystocia, increased 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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Concurrent vs. Sequential Corneal Collagen Cross-linking[5264]

	Concurrent	P Value	Sequential	P Value
	logMar gain		logMar gain	
UCVA	0.96 ±0.31 to 0.82 ±0.31	p=0.03	1.03 ±0.19 to 0.85 ±0.31	p=0.01
BCVA	0.36 ±0.17 to 0.34 ±0.21	p=0.7 (NS)	0.29 ±0.23 to 0.21 ±0.15	p=0.06 (NS)
	K reading		K reading	
Kmax	61.9 ±8.2 D to 61.0 ±7.8 D	p=0.15	58.2 ±9.3 D to 58.4 ±8.8 D	p=0.9
Kavg	51.5 ±5.2 D to 50.1 ±5 D	p<0.01	49.7 ±5.3 D to 48.8 ±5 D	p=0.02
Kf	49.2 ±4.7 D to 48.3 ±4.6 D	p=0.01	47.6 ±5.1 D to 47.3 ±4.8 D	p=0.5
Ks	54.0 ±6.1 D to 52.2 ±5.8 D	p<0.01	50.3 ±5.4 D to 52.2 ± 5.8 D	p<0.01

after the initial Intacs procedure (sequential group, n=18). All outcomes were analyzed one year after CXL therapy. Outcomes included UCVA and BCVA, and maximum (Kmax), flat (Kf), steep (Ks) and average (Kavg) keratometry as measured by the Pentacam *(See results, above)*. When the sequential vs. concurrent groups were compared at one year, there were no statistical differences between the changes in any of the visual or topographic outcomes except for Kflat. All patients who were treated with symmetric Intacs and CXL therapy experienced an improvement in corneal topography and UCVA one year after therapy. There was no meaningful difference between sequential vs. concurrent treatment at one year.[5264]

Epithelial thickness appeared to be greater in keratocones, possibly as a reaction to ectasia, researchers in New York City and Athens, Greece, say of their study that used imaging from anterior-segment optical coherence tomography and high-frequency ultrasound biomicroscopy.

Thickness mapping was studied in eyes in a normal group, keratoconic group (KCN) and keratoconic eyes treated with collagen cross-linking group (K CXL).

Substantial topographic variation in epithelium thickness was seen in the KCN group, however, there was an overall thickening of the epithelium, particularly over the pupil center onthe order of +3 µm, while the mean epithelial thickness was on average +1.1 µm compared to normals. No statistically significant difference was found between the normals and the K CXL group in terms of overall epithelium thickness. This finding was more pronounced among younger patients, and in agreement with HF ultrasound epithelial thickness imaging.

This researchers say the method may aid in sub-clinical screening, particularly among young patients.[5294]

Cross-linking—Pediatric

Surgeons in Switzerland conclude that cross-linking is very effective in stabilizing keratoconus in children. They evaluated tomographies (Pentacam) and topographies (TMS) of prospectively collected data after CXL in children younger than 18 years. Examinations were conducted prior to surgery at regular intervals during the first postoperative year, and at two, three and four years after the procedure. Twenty-five patients (33 eyes) were included (mean age, 14.9 years) with a mean follow-up of 27.3 months, and minimum follow-up one year. Progression was defined as an increase in Kmax (Pentacam) of at least 1 D in one year.

The researchers made 669 KMax comparisons, resulting in four cases of progression identified. In one case, the keratoconus was extremely advanced prior to CXL (Kmax 78.2 D preop, and 79.3 D at one year). One case showed marked steepening of 3.4 D in the Pentacam between three and four years after CXL, but the TMS parameters were unchanged. Because of this discrepancy, the Pentacam exam was repeated and showed that Kmax was actually stable, i.e., no progression after all (50.8 D at three years and 50.7 D at four years). Two children with active limbal vernal keratoconjunctivitis worsened dramatically (46.4 D at one year and 48.3 D at two years; 53.6 D at one year and 54.9 D at two years). This progression was also seen in topography. After resolution of the limbal inflammation, the Kmax values returned to 46.3 D and 54.2 D, respectively.

True progression after CXL could only be verified in one out of 33 eyes, but that eye had already progressed to such an extreme extent prior to CXL that it was probably unrealistic to expect that CXL could arrest progression at such a late stage. Further, in assessing possible progression, the use of two different measuring devices can help detect discrepancies and thus prevent false conclusions. Moreover, limbal vernal changes can present a clinical picture of progression. However, this is actually a pseudo-progression that can be reversed with anti-inflammatory treatment.[5262]

Two-year results of cross-linking in pediatric patients with progressive keratoconus come from another group of Swiss and Italian surgeons.

Forty-eight eyes of pediatric patients (mean age 13.7 ±1.9 years, r: 4 to 18 years) with topographically and tomographically documented progressive keratoconus were treated with cross-linking. The standard treatment procedure was used, applying riboflavin 0.1% following epithelial abrasion. The corneas were then irradiated with UVA light. The eyes were monitored for a minimum of 24 months. CDVA, UDVA, refraction, topography, tomography and aberrations

were documented at one, three, six, 12 and 24 months.

At 24 months after CXL, mean logMAR UDVA had significantly ($p<0.05$) improved from 0.81 ±0.25 to 0.61 ±0.23. Mean CDVA improved from 0.43 ±0.14 to 0.21 ±0.13 ($p<0.05$). Mean SE refraction had improved from -3.65 D ±3.49 D to -2.14 D ±2.26 D. Accordingly, mean SE refraction showed a significant decrease of 1.51 D, in line with the statistically significant reduction of both sphere and cylinder. Topography maps exhibited a statistically significant ($p<0.05$) reduction of mean simulated keratometry in the flattest meridian from 46.35 D to 45.28 D, and a near-significant decrease in the steepest meridian from 51.53 D to 50.20 D. Mean pachymetry, after an initial decrease, recovered by 12 months and remained stable through the follow-up period. There was a significant ($p<0.05$) decrease in total, corneal and higher-order aberrations at 24 months, but no significant change in endothelial cell counts at any time during the follow-up. Abrasion-related discomfort was reported by most patients in the immediate postoperative period, but there were no significant vision-related adverse effects.

The group concludes that CXL appears to stabilize keratoconus even long term in pediatric patients, the age group that shows the most dramatic progression when left untreated. The procedure further improves UDVA and CDVA. This improvement is likely due to the significant reduction of corneal asymmetry and corneal as well as total wavefront aberrations.[5267]

Surgeons in Rio de Janeiro, Brazil, studied a slightly older group of teenagers with progressive keratoconus, and report one-year outcomes of epithelium-off corneal collagen cross-linking.

The prospective, non-randomized, interventional clinical study enrolled 51 KC patients (84 eyes).

Mean patient age was 16.50 ±1.68 years (r: 13 to 18 years). The UCVA improved from 0.65 ±0.41 to 0.55 ±0.42 ($p=0.34$) and the CDVA, from 0.26 ±0.21 to 0.16 ±0.16 ($p=0.74$). The flat K value decreased from 46.68 ±2.65 D to 46.31 ±2.6 D ($p=0.61$), and the steep K value decreased from 49.83 ±3.19 D to 49.45 ±3.09 D ($p=0.74$). The mean preoperative corneal pachymetry at the thinnest point was 456.26 ±52.50 µm. This value decreased to 393.26 ±76.96 µm at six months ($p<0.001$) and to 423.79 ±72.41 µm at 12 months ($p<0.001$).[5266]

Cross-linking—Miscellaneous

Ultrasound treatment may facilitate the entry of topical riboflavin into the corneal stroma, achieving clinically useful concentrations of riboflavin without removing the corneal epithelium and reducing the risk profile of cross-linking procedures, based on a study at the University of California, San Francisco.

Rabbit eyes had a cup with riboflavin 0.1% placed over the central cornea and were treated with ultrasound 1 W/cm^2 at 880 Khz for six minutes followed by the removal of the cup and the application of two drops of riboflavin solution every three minutes for 39 minutes. In the control eyes (no ultrasound), two drops of riboflavin solution were applied every three minutes for 45 minutes. The excised corneas were examined by confocal microscopy to detect the presence of riboflavin.

Fluorescence intensity was significantly higher in the treated corneas ($p<0.05$). At a depth of 200 µm, average fluorescence intensity of riboflavin was 216.24 in treated eyes (n=7), and 6.55 in control eyes (n=6).[5269]

Researchers at Avedro Inc. suggest that both pulsing UVA and performing the UVA irradiation in an oxygen-rich environment increased the amount of cross-linking achieved for the same energy dose. When combined, the two have an additive effect.

Pig eyes were brought to 37 degrees C in a humidity chamber, epithelium was removed, and an intraocular pressure of 15 mmHg was applied using a water column. Drops of 0.1% riboflavin in 0.85% saline were applied in a humidity chamber for 20 minutes. Eyes in oxygen groups had 100 percent oxygen pumped into the chamber for the final five minutes of pre-soak. Eyes were then placed under a UVA and irradiated at 30 mW/cm^2 either with constant irradiance or pulsed at a rate of 1.5 seconds on, 1.5 seconds off, either in the ambient atmosphere or in the oxygen-enriched chamber, for a total UVA dose of 5.4 J/cm^2. A central 9-mm diameter, 200-µm thick flap was cut by femtosecond laser from the anterior surface of the cornea. The corneal flaps stretched until either a maximum load of 5N was applied or the sample failed. Flaps were then removed and digested in papain. Papain solutions were excited at 360 nm in a fluorometer.

Mechanical analysis showed an increase in corneal stiffness and fluorometric analysis showed a higher response at 450 nm for cross-linking performed in an oxygen-rich environment. The result was the same for pulsed UVA. The combination of pulsed UVA and an oxygen-rich environment produced the most corneal stiffening and the highest fluorometric response.[5281]

Dry Eye, Tears, Ocular Surface

Researchers at the Wilmer Eye Institute at Johns Hopkins, Baltimore, evaluated the prevalence of associated inflammatory systemic diseases in patients with dry eye. They reviewed the records of 264 patients with a primary diagnosis of dry eye over two years and divided them into two groups: patients with clinically significant dry-eye disease (Schirmer test result without topical anesthesia ≤10 mm at five minutes

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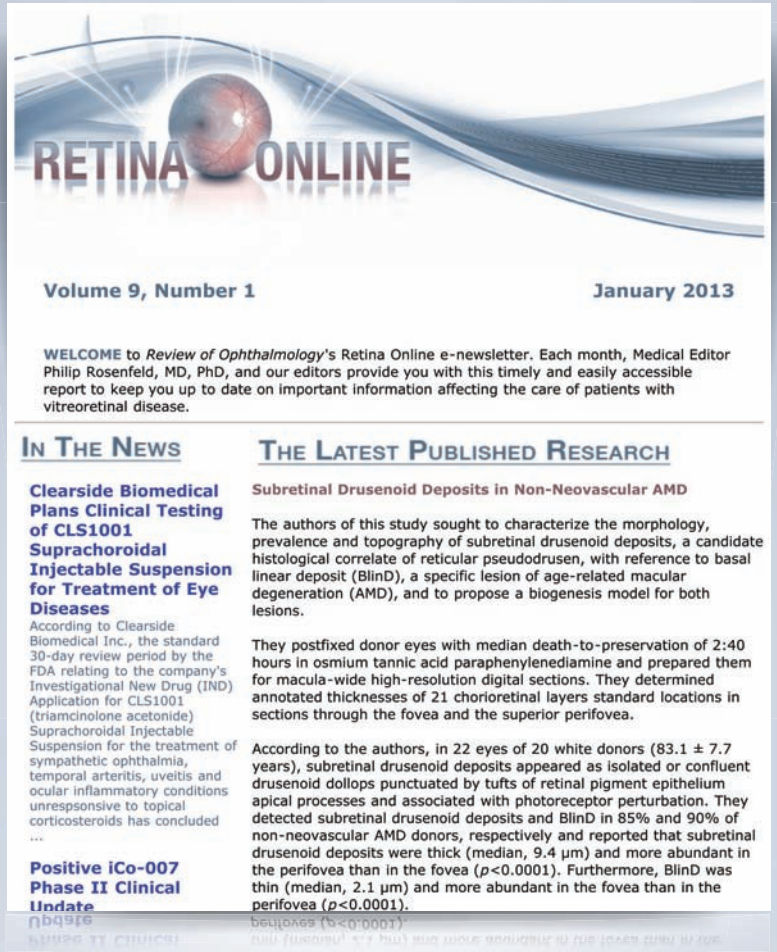

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WELCOME to *Review of Ophthalmology*'s Retina Online e-newsletter. Each month, Medical Editor Philip Rosenfeld, MD, PhD, and our editors provide you with this timely and easily accessible report to keep you up to date on important information affecting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

IN THE NEWS

Clearside Biomedical Plans Clinical Testing of CLS1001 Suprachoroidal Injectable Suspension for Treatment of Eye Diseases

According to Clearside Biomedical Inc., the standard 30-day review period by the FDA relating to the company's Investigational New Drug (IND) Application for CLS1001 (triamcinolone acetonide) Suprachoroidal Injectable Suspension for the treatment of sympathetic ophthalmia, temporal arteritis, uveitis and ocular inflammatory conditions unrespsonsive to topical corticosteroids has concluded ...

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THE LATEST PUBLISHED RESEARCH

Subretinal Drusenoid Deposits in Non-Neovascular AMD

The authors of this study sought to characterize the morphology, prevalence and topography of subretinal drusenoid deposits, a candidate histological correlate of reticular pseudodrusen, with reference to basal linear deposit (BlinD), a specific lesion of age-related macular degeneration (AMD), and to propose a biogenesis model for both lesions.

They postfixed donor eyes with median death-to-preservation of 2:40 hours in osmium tannic acid paraphenylenediamine and prepared them for macula-wide high-resolution digital sections. They determined annotated thicknesses of 21 chorioretinal layers standard locations in sections through the fovea and the superior perifovea.

According to the authors, in 22 eyes of 20 white donors (83.1 ± 7.7 years), subretinal drusenoid deposits appeared as isolated or confluent drusenoid dollops punctuated by tufts of retinal pigment epithelium apical processes and associated with photoreceptor perturbation. They detected subretinal drusenoid deposits and BlinD in 85% and 90% of non-neovascular AMD donors, respectively and reported that subretinal drusenoid deposits were thick (median, 9.4 µm) and more abundant in the perifovea than in the fovea ($p<0.0001$). Furthermore, BlinD was thin (median, 2.1 µm) and more abundant in the fovea than in the perifovea ($p<0.0001$).

Once a month, Medical Editor Philip Rosenfeld, MD, PhD, and our editors provide you with timely information and easily accessible reports that keep you up to date on important information affecting the care of patients with vitreoretinal disease.

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in either eye, or bulbar conjunctival staining with lissamine green scored based on Oxford scale ≥1 in either eye) and patients with dry-eye symptomatology but without the clinical findings.

The majority of the patients (81.4 percent) were female; 217 (82.2 percent) had clinically significant dry eye. About half of the patients (45.8 percent) had an underlying inflammatory systemic disease on presentation; 109 of these (90.1 percent) had a clinically significant dry eye. Thirty one patients (11.7 percent) had primary Sjögren's syndrome; 38 (14.4 percent) had thyroid disease; 13 (4.9 percent) had rheumatoid arthritis; 42 (15.9 percent) had other rheumatic diseases.

In 50 patients without a previously known systemic disease (regardless of the severity of the dry eye) a further workup was performed based on review of systems. In 12 of those patients (24 percent) a diagnosis based on the workup was established: 10 patients (20 percent) were diagnosed with thyroid eye disease; two patients (4 percent) were diagnosed with Sjögren's syndrome or presumed Sjögren's syndrome; and one (2 percent) was diagnosed with a mixed connective tissue disease.

Based on clinical suspicion and review of systems, further diagnostic testing might uncover some of these previously undiagnosed conditions, the authors say.[931]

Higher circulating plasma levels of sex hormones appear to play a role in increased symptoms of dry eye in females without ocular surface disease, but not in males, and appear not to be influenced by age, says a group of researchers in Germany and Australia.

The study involved 74 subjects without ocular surface disease, including 52 females (mean age 35.3 ±13.4 years, r: 18.8 to 70.3) and 22 males (mean age 34.2 ±13.8 years, r: 20.2 to 75.3). Subjects completed the Dry Eye Questionnaire (DEQ5) and numerical ratings of discomfort, dryness, foreign body sensation, burning and watering. Tear osmolarity and volume (Phenol Red Thread) were assessed. Venous blood was collected and plasma concentrations of oestradiol (E2) and total testosterone (TT) were determined using ELISA.

Mean group E2 concentration was 65.2 ±50.9 pg/ml in females and 40.7 ±23.8 pg/ml in males; TT concentration was 0.49 ±0.29 and 4.3 ±1.6 ng/ml respectively. All symptom measures were higher in females ($p<0.05$). Tear volume was reduced in females ($p=0.02$); there was no difference in tear osmolarity. In females, increased ocular symptoms correlated with higher levels of E2 (DEQ5 Rho=0.36, $p=0.01$; dryness Rho=0.36, $p=0.01$; FB Rho=0.37, $p=0.01$). Higher TT in females correlated with more FB sensation (Rho=0.30, $p=0.03$) and lower tear volume (Rho=-0.30, $p=0.04$). No association was found between tear osmolarity and hormone levels in females. In males, no evidence of a relationship between hormone levels and ocular symptoms or tear parameters was apparent. Although concentrations of E2 and TT were reduced with age in females (E2 Rho=-0.36, $p=0.01$; TT Rho=-0.37, $p=0.01$), there was no association between age and ocular symptoms in either males or females.

The group looks for more detailed analysis and exploration of factors such as levels of free testosterone to further explore these relationships in the pathophysiology of dry eye.[969]

Two Boston researchers developed the Korb-Blackie Lid Light Test to investigate the possibility that apparently normal, closed lids fail to create the necessary protective seal to prevent ocular surface dessication during sleeping. The test results, they report, are correlated with symptoms of eye discomfort upon awakening.

The subject rests his head against the head rest of a semi-reclined exam chair and closes his eyes as if falling sleep. A transilluminator is lightly placed against the closed outer upper eyelid of each eye. The apparently closed lids are examined for the presence of any light emanating from the lid area between the lashes. The examiner positions his eye level inferiorly in order to be looking up to optimize viewing of three regions of the lid: temporal; central; and nasal. The amount of visible light in each section was quantified on a scale of 0 to 3 where 0=no light, 1=minimal, 2=moderate and 3=severe. Eye discomfort upon awakening was quantified on a scale of 0 to 2 where as 0=no discomfort, 1=mild and 2=significant discomfort.

They studied 148 patients, mean age 53.9 ±16.2 years (50 males; 98 females), with no lid abnormalities or history of lid surgery, no current ocular disease and no ocular surgery within six months. The mean light score for each lid region was: temporal=0.3 ±0.5; central=1.0 ±1.0; nasal=0.5 ±0.7, indicating the central region is the least likely to close completely. The level of eye discomfort upon awakening was significantly correlated with the number of lid sections (0-3) emanating light during the test ($p<0.0001$).[942]

Researchers in Rome, Italy and Philadelphia collaborated to quantify the variability of tear osmolarity measurements in dry-eye patients and controls. Using the TearLab system, they studied 74 eyes of 37 subjects (18 Sjögren's syndrome, 10 blepharitis and nine controls with no history of symptoms or signs of dry-eye disease); 94 percent of Sjögren's patients and 80 percent of blepharitis patients were on systemic or topical dry-eye medications on enrollment. For all subjects, three consecutive osmolarity measurements were taken at one-minute intervals in each eye to assess the within-session variability. For 15 subjects, three measurements were taken at each of three time points throughout the day to examine the inter-session variability over

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the course of a day. The within-session and inter-session variability were assessed based on the standard error of measurement (SEM), calculated from the analysis of variance.

Among all subjects, the within-session variation for a single osmolarity measurement was 14.4 mOsm/l (13.8 for SS, 8.8 for blepharitis, and 16.2 for controls). When the average of the three consecutive measurements in a single session was used, the variability of osmolarity measurement was 8.3 mOsm/l. Between-session variability was 17.2 mOsm/l for a single osmolarity measure, and 10.4 mOsm/l for an averaged measurement. The variability of osmolarity measurements between two eyes of the same subject was not correlated.[959]

A group in Houston has identified what it calls Zone A Posterior Lid Margin Vascularization and says it may be a helpful clinical sign of early ocular surface disease.

Their retrospective analysis included 49 patients >20 years old seen in a tertiary care center who completed the Ocular Surface Disease Index questionnaire and had a complete ocular surface evaluation, including anterior blepharitis, vascularization of the inferior lid margin, meibomian gland obstruction and turbidity. Previous surgery or current topical anti-inflammatory treatment were exclusions. Basal tear test, lissamine green staining and quantification of the Zone A (ZA) was graded based on the degree of vascularization noted on the everted posterior inferior lid margin. OSDI scores were grouped as normal: ≤12 vs. dry eye: >12; ZA was grouped normal and severe. Lower lid biopsy was obtained for histology.

Of 49 charts reviewed, 14 patients had normal OSDI and 35 had dry-eye OSDI. There was no significant statistical difference between OSDI groups and all OSD findings. Basal tear test and lissamine green staining were not statistically different between the two OSDI groups. Comparing the ZA groups, 10 patients had normal grading and 39 had severe grading. No significant statistical differences were found between ZA groups and OSD findings; basal tear test and lissamine green staining were not statistically different between the ZA groups. Patients with severe ZA grading were found to have normal to mild OSD findings (anterior blepharitis=84.2 percent, vascularization=82.1 percent, MG obstruction=56.4 percent, turbidity=32.4 percent), in contrast to patients with severe ZA grading that had severe OSD (AB=15.8 percent, V=18 percent, O=43.6 percent, T=67.6 percent). Histology showed inflammatory response and increased number of dilated vessels in the posterior lid margin.

The OSDI questionnaire did not correlate with any ocular surface disease clinical signs. ZA grading was noted to be severe even in the cohort with mild disease.[968]

Portland, Ore. researchers report that there is still a wide range of refractive outcomes with two current endothelial keratoplasty techniques in combination with cataract surgery. They evaluated refractive error after combined Descemet stripping automated endothelial keratoplasty or Descemet's membrane endothelial keratoplasty coupled with cataract surgery to determine whether the intended target refraction was achieved.

In 117 eyes with Fuchs' endothelial dystrophy and cataract that underwent combined DSAEK (n=88) or DMEK (n=29) with cataract surgery, the surgeons targeted emmetropia by choosing a lens power from IOLMaster that provided a refraction of -1.25 to -1.5 D for DSAEK and -0.3 to -0.6 D for DMEK. Postop best spectacle-corrected visual acuity and SE were measured pre- and one to six months postop. The difference in actual versus targeted SE was calculated.

After DSAEK, mean BSCVA was 20/26 (r: 20/20 to 20/70), and the mean SE was -0.44 D (r: -3.125 D to +1.625 D). After DMEK, mean BSCVA was 20/26 (r: 20/20 to 20/50), and mean SE was -0.37 D (r: -2.5 D to +2.125 D). Mean postoperative SE was not significantly different between DMEK and DSAEK (p=0.691).

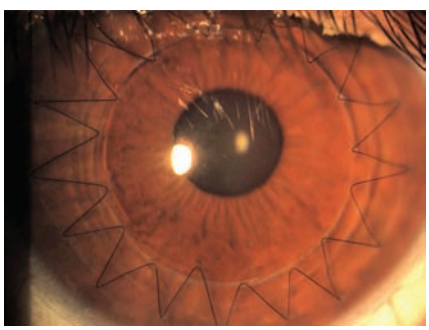
DMEK appeared to have slightly more reliable results, though the sample size was small, the surgeons say. The results suggest the need for further study of the hyperopic shift and IOL selection in this population.[3081]

Keratoplasty

Italian surgeons offer a new anvil-like trephination pattern in penetrating keratoplasty assisted by femtosecond laser.

Thirty eyes underwent the procedure, in which anvil-shaped penetrating cuts are made with an IntraLase femtosecond laser on both donor and recipient corneas. A diode laser welding procedure was performed in order to improve the healing process.

All surgeries were successful and without any intraoperative complications. This profile enables a safe and easy to perform suturing procedure, with an immediate closure effect evidenced during surgery. The large interface between donor and recipient tissue supports the laser welding procedure. Six months follow-up showed that the anvil-shaped flap provided a better VA recovery and a reduction



An anvil-like trephination profile in a human patient six months postop.

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* Average training time. Actual training time may vary.

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in the number of rejections. Mean postoperative BSCVA (logMAR, mean ±SD) was 0.50 ±0.24 at one month, 0.32 ±0.19 at three months, and 0.19 ±0.14 at six months. Mean pachimetry was 537 ±56 µm at one month, 550 ±77 µm at three and 528 ±70 µm at six. Mean preoperative endothelial cell density was 2,300; postoperative results were 1,945 ±363 at one month, 1,881 ±401 at three and 1,781 ±393 at six months.

They consider the short-term visual results and refractive results to be encouraging compared with those of conventional PK studies. Longer term follow-up and comparative studies are necessary to determine precise advantages of this technique.[3077]

Citing previous reports that avoiding overlap of the donor DMEK graft with the host Descemet's membrane may promote graft adherence, surgeons at the Devers Eye Institute, Portland, Ore., retrospectively analyzed their results for a difference in the rate of rebubbling procedures and primary graft failure between overlapped and non-overlapped cases.

They studied 52 DMEK cases performed for Fuchs' dystrophy eyes; in 28 eyes, the host was stripped smaller than the graft, resulting in overlap of the graft and the host DM; in 24 eyes, the host was purposely stripped wider than the size of the graft to avoid overlap of the DMEK graft and host DM. The incidence of graft replacement and frequency of rebubbling was compared between the groups.

Fifteen of 28 (53.5 percent) grafts that overlapped with the host DM required rebubbling, significantly more than the 6/24 (25 percent) grafts without overlap of the host DM that required rebubbling (p=0.036). There was no significant difference in the rate of primary graft failure. There was a 10.7 percent PGF rate for the overlap group and 8.3 percent for the non-overlap group (p=1.0).

Avoiding overlap of the DMEK graft with the host DM appears to promote adherence of the graft and decrease the rate of rebubbling procedures. They call for a prospective, randomized study with a greater sample size to further validate this finding.[3079]

Air fluid exchange in DSAEK does not introduce a significant change in graft-host interface separation compared to the separation present after corneal sweeping, according to a group at the Cole Eye Institute, Cleveland.

DSAEK was performed by a single surgeon on 23 eyes in 23 patients, 18 with Fuchs' endothelial dystrophy, two previously failed PK, and one each previously failed DSAEK, pseudophakic bullous keratopathy, and Brown-McLean syndrome. Intraoperative spectral domain OCT (iOCT) was executed after corneal sweeping and after air fluid exchange. Graft-host interface separation was digitally quantified in the axial and transverse dimensions and compared after corneal sweeping and after air fluid exchange using a paired t-test.

Average axial length of the graft-host interface was 34.6 +28.5 µm post-sweep and 59.6 +92.7 µm post-air fluid exchange (p=0.24). Average transverse length of the graft-host interface was 1.16 +1.15 mm post-sweep and 1.29 +1.65 mm post-air fluid exchange (p=0.62). No visible interface fluid was present in four eyes after corneal sweeping and in five eyes after air fluid exchange. iOCT, the group concludes, can evaluate the efficacy of surgical techniques in DSAEK by quantifying graft-host interface separation and confirming graft adherence in real-time.[3083]

For phakic and pseudophakic patients with bilateral Fuchs' endothelial dystrophy, contrast sensitivity and BCVA were significantly improved in DMEK eyes compared to the untreated fellow eye, in a study from the Netherlands and Spain. Improvement of those parameters after surgery influenced the subjective perception of patients' visual quality.

A total of 29 patients with a history of bilateral FED and unilateral DMEK were identified and divided into three groups, 12 phakic, 17 pseudophakic and 11 controls. Unilateral cataract, unilateral IOL, previous anterior segment surgery or any other concurrent ocular condition that may limit BCVA were exclusions. Pelli Robson contrast sensitivity test and Fansworth Munsell 100 Hue color vision test were used to assess contrast sensitivity and color vision. A specific questionnaire consisting of 11 questions was developed to measure the subjective visual quality. Individual variability was taken into account by measuring all visual parameters for the untreated (FED) and the treated eye (DMEK) of each subject. All parameters were compared between the phakic, pseudophakic and the control groups.

Comparing the eyes of each patient, statistically significant differences in BCVA and contrast sensitivity were found for the phakic and pseudophakic groups between FED and DMEK eyes. Contrast sensitivity of DMEK eyes in the phakic group did not significantly differ from the control group, while it differed significantly between the DMEK eyes of the pseudophakic group and the control group. No statistically significant difference was observed in the mean color vision of the FED and the DMEK eyes for the phakic and the pseudophakic groups. Subjective vision quality was rated significantly higher for the DMEK eye than for the FED eye in both the phakic and the pseudophakic groups.[3092]

Subtle, clinically undetectable residual interface fluid may be present at the end of DMEK surgery, possibly representing a risk for postoperative

(Continued on page 112)

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Brien Holden Vision Institute is one of the largest and most successful social enterprises in the history of eye care. By applying commercial strategies to vision research and product development the Institute has generated income for research and public health programs that provide quality eye care solutions and sustainable services for the most disadvantaged people in our world.

The concern for the devastating shortfall in eye care education in developing communities, especially for correction of refractive error, became action in 1998 for those at the Institute. The lack of training institutes and educational opportunities was creating a human resource gap and a critical eye care shortage for hundreds of millions of people in need of services. The concern and willingness to address the issue gave rise to the International Centre for Eyecare Education (ICEE).

Almost 15 years later, and acknowledging that 640 million people are still without access to permanent eye care, concern has galvanised into action again. To advance the process of addressing the challenge, both ICEE and Brien Holden Vision Institute will more closely align, share one common purpose and one name.

Together, we believe if we harness our efforts and broaden our scope we can achieve much more.

Together, we aim to drive, innovate, educate, collaborate, advocate and negotiate what is needed so that hundreds of millions of people worldwide can enjoy the right to sight.

Whether it's research to develop the technology to slow the progress of myopia, investment in new systems for diagnosis of disease, delivery of sustainable access to services or provision of eye care education in the most marginalised and remote communities in the world, the Institute will focus on the quality of vision people experience and equity in eye care access worldwide.

We believe in vision for everyone...everywhere.

The Durban community in South Africa arrives in hundreds to support the Brien Holden Vision Institutes initiative Drive for Sight, part of the World Sight Day celebrations in October 2012. All attendees were offered free eye examinations, access to free or affordable low cost spectacles and referrals for further eye care where necessary. ***Photo by Graeme Wyllie.***

Brien Holden Vision Institute

Education Research Technology Public Health

Brien Holden Vision Institute Foundation (formerly ICEE) is a Public Health Division of Brien Holden Vision Institute

Refractive Surgeons Continue to Innovate

Louis B. Probst, MD, Chicago

A look at the latest research on screening refractive surgery patients and getting the best outcomes with their surgeries.

Year after year, the annual meeting of the Association for Research and Vision in Ophthalmology demonstrates that even though LASIK and PRK have been approved in the United States for more than a decade, surgeons are still developing new ways to improve their outcomes with the procedures. In this year's refractive surgery section of the meeting, you'll see studies on how to get the best results with laser procedures, as well as the latest data on cutting-edge techniques such as intrastromal ablations and corneal inlays.

Techniques and Outcomes

Surgeons from Mexico City say that the actual post-LASIK corneal tissue ablation depth may be greater than that predicted by the Abbott Medical Optics/Visx Star S4, and that this should be taken into account in patients with thin corneas.

The researchers retrospectively analyzed 36 eyes of 19 patients. They excluded seven patients who were lost to follow-up and excluded two eyes due to surgical complications. Their mean preoperative spherical equivalent was -4.07 ±1.92 D, which was decreased to 0.18 ±0.73 D postop. The researchers performed corneal ultrasonic pachymetry (Accupach V 24-5000; Accutome, Malvern, Pa.) before surgery and one month afterward in order to obtain the postsurgical corneal tissue ablation by subtraction. The mean predicted ablation depth was 49.11 ±28.07 µm, but the actual postoperative depth was 61.64 ±28.07 µm. The surgeons say this potential disparity should be considered in order to avoid residual stromal beds of less than 300 µm.[3128]

Researchers from AMO say that, after evaluating the data from controlled clinical refractive surgery studies, it may be possible to estimate the amount of aberration induced by the LASIK flap and then adjust the procedure's treatment target.

The researchers say that flap-induced aberrations aren't dependent on the amount of treatment, but instead can differ among surgeons, tools used and surgery sites. *(See bar graph, p. 68.)* They add that flap-induced aberrations can be measured directly or estimated statistically, pointing out that in the trend line for induced spherical aberration, with SA vs. preop spherical equivalent, SA usually crosses the axis SE=0 at some non-zero level. They say that this value quantifies the change in SA when the flap is created but no ablation is done. They add that the flap-induced aberrations may also be derived from

a flap-creation model that accounts for site-specific parameters.

In practice, the researchers say that flap-induced aberrations may be taken into account during treatment planning, when surgeons can apply treatment target adjustments to compensate for them. These adjustments, the investigators say, can be derived statistically for each site, surgeon or tool. They say that the site-specific SA can be readjusted so that the adjusted scatter plot will become more compact, with tighter correlation and R2 values, allowing a better fit for the nomogram adjustment and more precise modeling of corneal healing.[3120]

Surgeons from Denmark, one of whom receives financial support from Carl Zeiss Meditec, have provided a long-term look at outcomes from the intrastromal refractive procedure known as small-incision lenticule extraction, which is performed using the CZM VisuMax laser.

In the study, 90 patients underwent normal LASIK, femtosecond lenticule extraction or SMILE, and were followed for over a year. The mean preoperative spherical refractive error was -7 D (r: -4.5 to -11 D), with a mean spherical equivalent of -7.28 D. Three months postop, the average spherical refraction was -0.32 ±0.63 D for the LASIK group, 0.00 ±0.38 D for the FLEX group and 0.06 ±0.51 D for the SMILE group. The average SE refraction was -0.49 ±0.71 D for the LASIK group, -0.13 ±0.45 for the FLEX group and -0.10 ±0.49 D for the SMILE group. An analysis of variance showed no significant change in the SE over the long term after the three-month visit. *(Outcomes appear in Tables 1 and 2.)* The uncorrected vision in the FLEX and SMILE, but not LASIK, patients improved significantly over the longer period, surgeons say. They add that best-corrected vision didn't show any significant difference over the long term.[3131]

Table 1. Three-month Results: LASIK, FLEX and SMILE[3131]

	Sphere	Cylinder	Spherical equivalent	UCVA LogMAR	BCVA LogMAR
LASIK	-0.32 ±0.63 D	-0.33 ±0.35 D	-0.49 ±0.71 D	0.11 ±0.18	0 ±0.04
FLEX	0 ±0.38 D	-0.27 ±0.45 D	-0.13 ±0.45 D	0.06 ±0.12	-0.01 ±0.07
SMILE	0.06 ±0.51 D	-0.32 ± 0.51 D	-0.10 ±0.49 D	0.07 ±0.16	-0.02 ±0.11

A group of surgeons from Mexico City are also sharing their experience with the learning curve of the new SMILE procedure for the treatment of myopia. One of the surgeons receives some financial support from Carl Zeiss Meditec.

The study consisted of 120 eyes of 76 patients with a mean SE of -5.37 D. The surgeons say that the patients achieved refractive stability within six weeks postop and that at six months the SE was +0.17 D. A year after the surgery, 87 percent of the eyes see 20/25 or better without correction, and the best-corrected vision is the same or better than the preoperative BCVA in all of the eyes. Less than 5 percent of the eyes lost any lines of BCVA, and eight eyes experienced complications, which the surgeons didn't specify in the description of their study.[3712]

Investigators from several research facilities and ophthalmology practices in Texas say that CustomVue LASEK is accurate in high myopia, but that surgeons need to make appropriate preoperative adjustments to the surgical plan or risk having to do an enhancement.

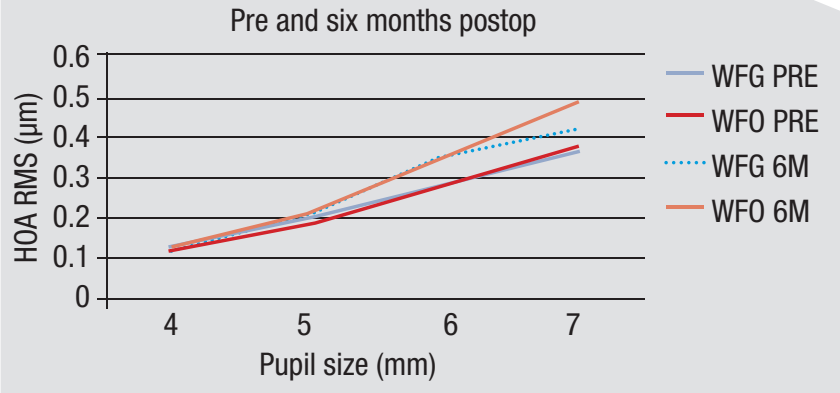
The investigators performed a retrospective analysis of 113 eyes of 69 LASEK patients who had either a standard or a CustomVue ablation. The standard ablation group, in which the physicians used the system's ability to make adjustments to the target refraction, included 63 eyes with an average error of -7.49 D and an average cylinder of -1.41 D. The CustomVue group, in which they also used the adjustments, was composed of 50 eyes with an average sphere of -6.56 D and an average astigmatism of -0.63 D. The researchers say that the use of mitomycin-C was slightly higher in the standard group (74 percent of patients vs. 54 percent) but wasn't different between the preoperative <0.1 µm normalized polar Zernike coefficient and the >0.1 µm NPZE CustomVue spherical aberration groups.

The group says that the mean postop SE wasn't significantly different between the two groups (standard group mean: +0.07 ±0.62 D; CustomVue mean: +0.15 ±0.58 D). When they removed the preop physician adjustments from the treatment, the researchers found that 32 percent of the CustomVue LASEK eyes would have had a final result of ±0.5 D or greater. Twenty-three of the 50 eyes had a preop positive spherical aberration >0.1000 µm NPZE, and without a physician adjustment these 23 eyes would have been responsible for 69

Table 2. Changes from Three Months to a Year[3131]

	Change in Sph. Equivalent	Change in UCVA LogMAR	Change in BCVA LogMAR
LASIK	-0.04 ±0.99 D	0 ±0.14	-0.09 ±0.06
FLEX	0 ±0.53 D	-0.03 ±0.10	-0.06 ±0.08
SMILE	-0.02 ±0.39 D	-0.07 ±0.12	-0.06 ±0.09

Postop LASIK Higher-order Aberrations[3114]



HOAs that result from wavefront-guided and wavefront-optimized LASIK.

percent of the eyes with a postop refraction of ±0.5 D or more.

The researchers say that, though their results using physician adjustment factors for the ablations were good, patients with preop spherical aberration greater than 0.1 µm NPZE are at higher risk of needing an enhancement if a physician doesn't use an adjustment in the surgical planning.[3139]

Surgeons from the U.S. Army Warfighter Refractive Surgery Research Center in Virginia, the Walter Reed Military Medical Center in Maryland, and the Wilmer Eye Institute say a small-scale, randomized study of wavefront-guided vs. wavefront-optimized LASIK shows little difference between the two in terms of quality of vision as defined by higher-order aberrations and patient satisfaction.

The surgeons randomized 18 patients, all around 30 years old, to WFG surgery and 17 to WFO. The average preop refraction was -2.96 ±0.97 D for WFG patients and -3.62 ±1.57 D for WFO. They analyzed the root mean square value of HOAs at four different pupil sizes, and administered a questionnaire to the patients preoperatively and at six months postop.

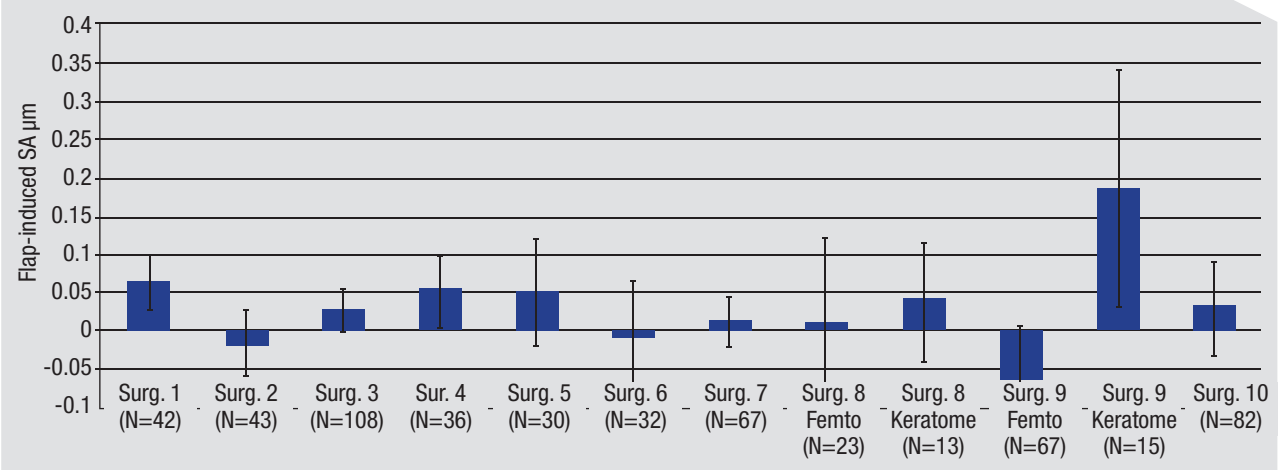
At six months postoperatively, the patients' manifest spherical equivalent refraction was 0.04 ±0.27 D for WFG vs. -0.02 ±0.26 D for WFO (p=0.33). *(The HOA results appear in the graph at left.)* The researchers say there was no significant difference in RMS HOA when comparing WFG vs. WFO LASIK, and that the questionnaire didn't show any differences in terms of the patients' expected visual outcomes vs. what they achieved.[3114]

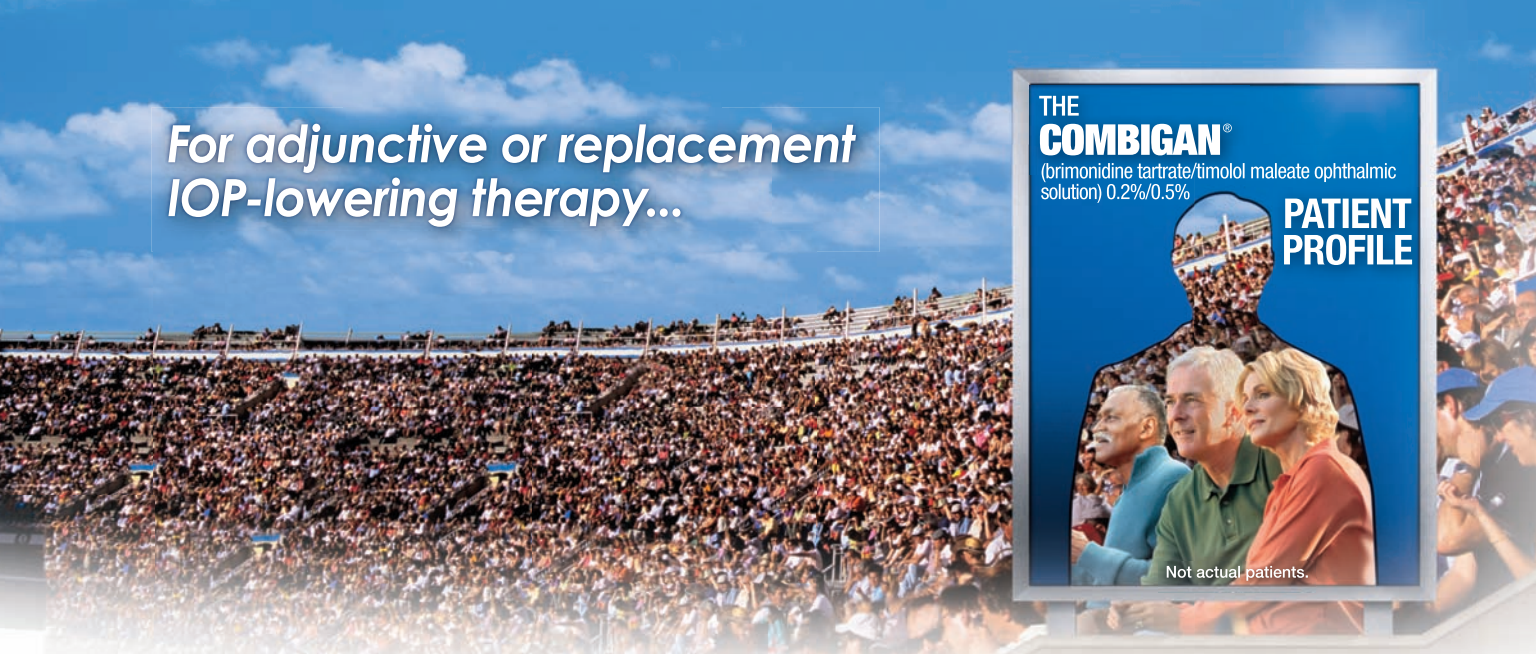
Surgeons from the same facilities also compared aberrations in PRK. In the study, they randomized 52 patients to receive either WFG or WFO PRK. Preoperatively, the WFG patients had an average spherical equivalent of -3.49 ±1.88 D vs. -3.31 ±1.79 D. At six months, the average SE was 0.09 ±0.38 D vs. -0.02 ±0.31 D for WFO (p=0.09). In terms of HOA RMS, however, there were significant differences between the two procedures over time, the surgeons say. They add that even though there was a significant increase in HOA RMS of WFO PRK patients, results from a questionnaire showed no significant difference in daily activities, glare, halo or satisfaction with the procedure compared to WFG PRK.[3135]

Implant Rundown

Employees of and consultants to ReVision Optics have provided an update on the company's treatment for

How Flap-induced Spherical Aberration Can Vary by Surgeon and Surgery Center[3120]





Can More of Your Patients Benefit From the Power of COMBIGAN®?

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® 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; in neonates and infants (under the age of 2 years); in patients with a hypersensitivity reaction to any component of COMBIGAN® in the past.

WARNINGS AND PRECAUTIONS: COMBIGAN® contains timolol maleate. COMBIGAN® is administered topically, but can be absorbed systemically. The adverse reactions with systemic administration of beta-adrenergic blocking agents may occur with topical use (eg, severe respiratory reactions including death due to bronchospasm in patients with asthma have been reported with systemic or ophthalmic administration of timolol maleate).

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 beta-blocking agents, including 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 accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

Beta-adrenergic blockade can potentiate muscle weakness with myasthenic symptoms (eg, diplopia, ptosis, and generalized weakness). Although rare, timolol can increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

Beta-adrenergic receptor blocking agents 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 to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Carefully manage patients that may develop thyrotoxicosis to avoid abrupt withdrawal of beta-adrenergic blocking agents 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-adrenergic receptor blocking agents due to impairment of beta-adrenergically mediated reflexes during surgery. If necessary during surgery, the effects of beta-adrenergic blocking agents 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: COMBIGAN® may reduce blood pressure. Use caution in patients on antihypertensives and/or cardiac glycosides.

Observe patients receiving a beta-adrenergic blocking agent orally and COMBIGAN® for additive effects of beta-blockade, both systemic and on intraocular pressure. Concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Use caution in the co-administration of beta-adrenergic blocking agents (eg, COMBIGAN®) and oral or intravenous calcium antagonists due to possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. Avoid co-administration in patients with impaired cardiac function.

Observe patients closely when a beta-blocker is administered to patients receiving catecholamine-depleting drugs (eg, reserpine) due to possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

Specific drug interaction studies have not been conducted with COMBIGAN®, but consider the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics).

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

Potentiated systemic beta-blockade (eg, decreased heart rate, depression) has been reported with combined use of CYP2D6 inhibitors (eg, quinidine, SSRIs) and timolol.

Tricyclic antidepressants (TCAs) can blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of TCAs with COMBIGAN® in humans can interfere with the IOP-lowering effect. Caution is advised in patients taking TCAs, which can affect the metabolism and uptake of circulating amines.

Monoamine oxidase (MAO) inhibitors may theoretically interfere with the metabolism of brimonidine and potentially increase systemic side effect such as hypotension. Use caution in patients taking MAO inhibitors, which can affect the metabolism and uptake of circulating amines.

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

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

Write it RIGHT DAW

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

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CONTRAINDICATIONS

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

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

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

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

OVERDOSAGE

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

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APC33KM13

ALLERGAN®

presbyopia, the Raindrop hydrogel corneal inlay.

In the study, 22 hyperopic presbyopes received bilateral inlays under a femtosecond flap in their non-dominant eyes. They then received a similar inlay in the dominant eye three to six months later. The patients averaged 0.99 D in the non-dominant eye and 0.97 D in the dominant eye (r: +0.25 to +1.75 D) preop. The average preop reading add was 1.89 D. After implantation, the investigators used a questionnaire to assess the patients' ability to perform daily tasks without correction.

After implantation, the surgeons found that, at three months, uncorrected visual acuity had improved by an average of five lines at near, three lines at intermediate and one line at distance when both eyes were measured separately. Near and intermediate vision improved in all the eyes. Eighty-six percent of the implanted non-dominant eyes and 95 percent of the implanted dominant eyes achieved at least 20/25 at near uncorrected vs. zero percent preop. At distance, the average uncorrected acuity was 20/21. Two patients lost a line of distance vision in their non-dominant eyes.

After the second inlay was implanted, at three months 95 percent saw 20/25 or better at near and intermediate uncorrected, and all saw 20/20 or better at distance. The researchers say that patients reported a significant improvement in task performance with bilateral inlays versus preop performance.[3129]

Refractive Issues

Researchers in China say that the amount of tear secretion after LASIK may depend greatly on the residual corneal nerve density at one month postop.

In the prospective study, surgeons enrolled 16 patients who were undergoing bilateral myopic LASIK, and measured the height and area of the upper and lower tear menisci using real-time anterior segment optical coherence tomography before surgery, and then at one week, one month and three months. They also measured central, temporal and nasal subbasal nerve densities with confocal microscopy preop and at one month and three months postop. The investigators didn't specify the technology that was used to create the flap in the LASIK procedures.

The researchers say that tear menisci parameters and nerve densities all decreased significantly after LASIK ($p<0.05$). *(The values appear in Table 3, p.72.)* The researchers found it interesting that the temporal and nasal nerve densities increased between one and three months postop while the central nerve density decreased. They also found that the lower tear meniscus area at one month was statistically significantly correlated with the nasal nerve density (r value: 0.380, $p=0.032$), but the LTMA at three months was significantly correlated with the one month postop central nerve density value (r value: 0.360, $p=0.043$).

The investigators say that the study suggests that lower tear menisci recover continuously between one week and three months after LASIK surgery, accompanied by increased temporal and nasal corneal nerve densities. They note that the residual corneal nerves at the one month follow-up point seem to play a large role in tear secretion during the rest of the postop period.[3142]

Researchers from the Federal University of São Paulo and São Paulo Hospital in Brazil say that it pays to determine the quality of the water used to feed steam sterilization devices in order to avoid infection after refractive surgery.

The investigators collected water samples in three different surgery centers that each used the same model of steam sterilizer for their cases. Two of the centers used tap water that underwent filtration and distillation and was stored in non-sterile gallon containers. At those two facilities, samples were collected from the tap, filter hose, distillation outlet and collector, and the stored gallons. The third center used sterile water, so the researchers took a sample from the water bag.

In samples from the first center, the study doctors found *Mycobacterium chelonae* in the distilled water gallons and the steamer reservoir. From the tap water they found *Mycobacterium mucogenicum*. The researchers say that all the *M. chelonae* isolated colonies showed the same pulsed-field gel electrophoresis pattern, meaning that a single strain was in both the distilled water and the storage gallons. They also found other aerobic bacteria in the storage gallons and steamer reservoir. In the second center, they found *M. chelonae* in samples from the tap and filter hose, and identified other aerobic bacteria in samples from the distillation outlet and collector, storage gallons, steamer reservoir and hose. Samples from the third center, however, which used sterile distilled water, showed no evidence of microorganism growth.[3145]

Surgeons from the Massachusetts Eye and Ear Infirmary, the Boston Foundation for Sight and Harvard Medical School say that *in vivo* confocal microscopy can help surgeons identify the mechanism behind the long-term postoperative pain that can follow refractive surgery, including LASIK.

In the study, two masked observers analyzed laser *in vivo* confocal microscopy images of 17 patients with corneal pain after refractive surgery (28 LASIK eyes and five PRK eyes), and 62 controls. The patients reported constant pain and photophobia. Ninety-four percent of the subjects had sensitivity to air and 47 percent were sensitive to chemical fumes.

Though the researchers noted minimal fluorescein staining in the patients, they did find a significant loss in

Table 3. Tear Menisci Parameters and Nerve Densities Post-LASIK[3142]

	One week postop	One month postop	Three months postop
Lower tear menisci height	207.85 ±43.94 µm	238.55 ±34.07 µm	273.33 ±44.91 µm
Lower tear menisci area	22,640 ±3730.23 µm^2	25,523.10 ±3,991.37 µm^2	27,859.86 ±3,234.15 µm^2
Temporal nerve density	N/A	1,325.35 ±286.44 µm/mm^2	1,861.44 ±143.54 µm/mm^2
Nasal nerve density	N/A	7,450.51 ±700.73 µm/mm^2	8,053.21 ±1,043.85 µm/mm^2
Central nerve density	N/A	1,866.83 ±292.63 µm/mm^2	1,694.02 ±192.83 µm/mm^2

the length of total subbasal nerves vs. controls and branches ($p<0.001$), as well as increased tortuosity ($p<0.001$). There was also a fivefold increase in dendritic cell and inflammatory cell densities ($p<0.001$). The investigators say that the decrease in total nerve length was associated with an increase in ocular surface disease index severity, and tortuosity correlated with sensitivity to fumes (both $p<0.001$). Also, inflammatory cell density correlated with OSDI severity and photophobia (both $p<0.001$). The dendritic cell density correlated with sensitivity to air ($p<0.001$).

The researchers say that, though postoperative keratoneuralgia that some patients experience after LASIK may be associated with minimal findings on clinical exam, there are also microscopy findings that correlate with its symptoms and may help physicians better understand this syndrome.[3711]

Researchers from the United States and Optical Express in the United Kingdom, with funding from the National Eye Institute, That Man May See Inc., and Research to Prevent Blindness, have shed some light on the effects of temperature and humidity on LASIK by analyzing more than 200,000 cases done at Optical Express' surgery centers in the United Kingdom and Ireland.

The study looked at the results of 202,394 eyes of 105,712 patients who had LASIK at Optical Express. The researchers found that an increase of 1 C during LASIK was associated with a refraction that was 0.003 D more hyperopic at one month postop ($p=0.0094$) and a 1-percent increase in humidity was associated with a 0.0004 D more myopic refraction ($p<0.0001$). The physicians say that the effects were considered clinically insignificant and remained the same or similar with myopic eyes, hyperopic eyes and subgroups of eyes stratified by age and the level of preop refractive error.[3110]

Researchers also analyzed 186,019 eyes of 95,523 Optical Express LASIK patients to assess the rate of microbial keratitis and any factors associated with it. In this group of patients, 16 had either culture-proven infection or a strong clinical suspicion of it (0.017 percent or 1:5,970). The investigators say that there was a higher incidence of infection in men vs. women (0.023 vs. 0.012 percent), in myopes vs. hyperopes (0.018 vs. 0.010 percent), in PRK vs. LASIK (0.032 vs. 0.015 percent) and mechanical-microkeratome vs. femtosecond laser-created flap patients (0.025 vs. 0.013 percent). However, they don't indicate whether these rates reached statistical significance.[3126]

Researchers from Fudan University in Shanghai and the New England College of Optometry found that Hartmann-Shack aberrometry may actually underestimate aberrations in post-refractive surgery eyes by measuring an effective pupil size that's smaller than the actual pupil.

In the study, 58 patients (95 eyes) who had undergone myopic LASIK were tested with manifest refraction, H-S aberrometry and Pentacam scanning. Aberrations were measured under mydriatic conditions (pupil size greater than 8 mm) and the effective pupil size was acquired from the aberrometer.

The researchers say that, in all patients, the effective pupil size in the study was smaller than the actual pupil size, with average sizes of 6.9 ±0.53 mm (mild myopia, n=15, $p<0.01$), 6.56 ±0.37 mm (moderate myopia, n=26, $p<0.0001$) and 5.84 ±0.55 mm (high myopia, n=54, $p<0.0001$). They found that the effective pupil size was correlated to the level of correction that was attempted in the surgery (correlation coefficient [r]= -0.8, $p<0.0001$), the ablation depth (r=0.65, $p<0.0001$), the optical zone (r=0.7, $p<0.0001$) and the postop corneal eccentricity (r=0.57, $p<0.0001$). They say all these attributes are independent factors in determining the effective pupil size, and that a mathematical model of the effective pupil size can be determined with the following formula: -0.81*Rx of ablation + 1.11*optical zone + 0.55*postop eccentricity value (r2 = 0.997).[3118]

Ectasia Screening Tools

Surgeons from Rio de Janeiro and São Paulo, Brazil say that an integrated analysis of clinical findings, topo-

metric and tomographic data may be better at identifying eyes at risk for postop ectasia than a "classic" ectasia risk score system. One of the surgeons is a consultant to Oculus, maker of the Pentacam, which was used in the integrated analysis.

In a retrospective, non-randomized fashion, the researchers looked at 23 eyes that developed ectasia after LASIK and 266 eyes with stable LASIK outcomes (after a minimum of a year follow-up). In all cases, the preoperative clinical and Pentacam data were available. The surgeons used the ERSS based on age, SE, residual stromal bed, central thickness and a subjective classification of corneal topography's front surface axial map. They also assessed the curvature of the front surface (topometry) and the thickness profile and front/back elevation (tomography). The researchers developed different factors that best distinguished ectasia from stable LASIK groups using Fisher's linear discriminant analysis based on clinical parameters and topometric data individually, as well as on clinical parameters combined with tomographic data. The area under the receiver operating characteristic curve, in which a value of 1.00 is considered a perfect result, was calculated for each LDA function with pairwise comparisons.

The surgeons say they found statistically significant differences among the groups for all of the study's parameters ($p<0.001$) except for preoperative SE. Using the ERSS, in which a score of 4 indicates high risk for ectasia and a zero indicates a patient at very low risk, 12 eyes from the ectasia group had a score of 3 or higher (sensitivity: 52 percent) and 48 eyes from the stable group scored a 3 or higher (specificity: 82 percent). The best parameters, using clinical and topometric indices as identified by the LDA function, used the index of height decentration, which had an area under the ROC of 0.98 (sensitivity: 100 percent; specificity: 93 percent). The best LDA function combining clinical and tomographic parameters, including the Belin-Ambrosio Deviation, which achieved 100-percent sensitivity and 97-percent specificity, had a statistically better area under the ROC of 0.994 than all individual parameters ($p<0.001$).

Researchers have found that, though postoperative keratoneuralgia may be associated with minimal clinical findings, microscopy findings can correlate with its symptoms and help physicians better understand it.[3711]

The surgeons say that the integrated analysis of clinical and objective topometric parameters was superior to the ERSS, and that tomographic data significantly enhanced the ability to screen for ectasia risk among LASIK candidates. The investigators add that clinical parameters, in turn, significantly improve the ability to detect ectasia susceptibility based on tomographic data, but that further validation is necessary for the LDA functions.[3715]

Researchers from Oregon Health & Science University and private ophthalmology practices in New York and San Diego, some of whom own patents for the technology discussed or are consultants to the companies that make the diagnostic imaging technology, say that anterior segment OCT images of corneal, epithelial and stromal thickness map patterns have potential as a screening tool for keratoconus.

The researchers developed a computer algorithm to calculate the corneal, epithelial and stromal thickness maps from the Optovue RTVue CAM OCT. In their analysis, they defined a "pattern map" as the thickness map divided by the average thickness of the map.

The surgeons designated 108 eyes of 57 patients as a "training" group (i.e., defining the pattern maps that would be considered normal), and 42 eyes of 22 patients as the "evaluation" group (i.e., they'd be used to evaluate the accuracy of the system). The OCT maps of the training group were then averaged and normalized to serve as the normal average pattern maps. The corneal, epithelial and stromal thickness map pattern standard deviation values were calculated by the RMS of the difference between the individual pattern maps and the normal average pattern maps. In the study, the accuracy of the method in distinguishing forme fruste KC eyes from normals was determined by the area under the ROC.

In terms of results, the researchers say that the PSD values for the subjects' stromal, corneal and epithelial thickness maps were all significantly higher in the FFKC eyes compared to the normal evaluation group ($p<0.001$). The area under the ROC values were 0.988 (pachymetry map PSD), 1.00 (epithelial thickness map PSD) and 0.967 (stromal thickness map PSD).

After seeing the level of accuracy displayed by pattern map analysis, the investigators say the process may be useful in the detection of early keratoconus.[2587] REVIEW

Dr. Probst is national medical director for TLC The Laser Center.

Contact Lenses: New Data, New Designs

Penny A. Asbell, MD, FACS, MBA, Section Editor

Studies are finding news ways to make the most of both familiar and less-often-used lenses.

This year, researchers have presented data on the impact and management of multifocal contact lenses; several new contact lens designs and their advantages (including a revival of interest in scleral contact lenses); the latest research on rigid gas permeables and orthokeratology; how wearing contact lenses affects the progression of myopia; and the results of a large epidemiological study of contact lens wearing habits.

Myopia Control

In a study sponsored by CooperVision, researchers at the University of Houston found that multifocal contact lenses and single-vision contact lenses produce different types of peripheral defocus, which might give clinicians a way to impact the progression of myopia in children. (Peripheral myopic defocus has been hypothesized to slow the progression of myopia.)

Twenty-five subjects (mean age 23.8 ±1.3, r: 22 to 27) with myopia (mean -3.62 ±1.56 D, r: -0.05 to -6 D) took part in the study. The researchers measured the refractive error of the right eye while wearing a Biofinity single-vision soft contact lens and while wearing a Biofinity multifocal "D" lens, a soft, center-distance lens with a +2.50-D add. They took measurements centrally and along the horizontal meridian at 20, 30 and 40 degrees from the line of sight, both while viewing a near target at 30 cm, and at distance, under cycloplegia. Lens type and measurement starting location were randomized.

The data showed:

- At distance, the single-vision spherical lens produced a peripheral mean spherical equivalent refractive error that was significantly more hyperopic than that found with the multifocal lens ($p<0.001$).
- The multifocal lens produced peripheral myopic defocus at all locations tested. The largest difference in defocus between the two types of lens was 2.35 D (temporally); the smallest difference was 1.06 D (all locations $p<0.05$).
- Regardless of lens type, accommodating to a near target caused a greater myopic shift in the periphery than closer to the center of vision ($p<0.01$).
- Compared to the spherical lens, when focused at near the multifocal produced different types of defocus at different locations tested: a more myopic defocus at three locations (r: 0.91 to 0.38 D—all $p<0.05$); a more hyperopic defocus at two locations (r: 0.27 to 0.42 D—both $p<0.05$); and no difference at two locations.

This article has no commercial sponsorship.

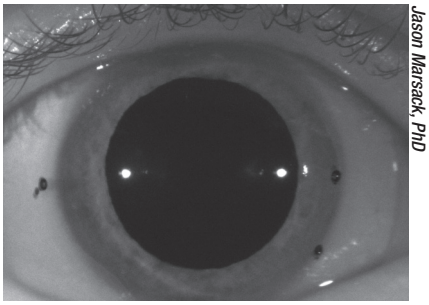
Although the peripheral defocus caused by the two types of lenses was somewhat similar when focused at near, when focused at distance the spherical lens produced peripheral hyperopia, while the multifocal lens produced peripheral myopia. The authors note that if it is confirmed that peripheral myopic defocus helps to slow axial length growth in children, wearing center-distance multifocal contact lenses could be an effective way to slow myopia progression.[5455]

A large prospective study was conducted in Yokohama, Japan, to determine how wearing glasses vs. contact lenses affected progression of myopia and/or hyperopia in different age groups over a five-year period. Approximately 270,000 eyes were included in the study; 13,977 eyes ranging in age from 4 to 88 years who were seen at the Okada Eye Clinic in Yokohama for glasses, and 273,042 eyes ranging in age from 10 to 91 years who were seen at the same clinic for contact lenses. (Anyone undergoing cataract surgery or orthokeratology, or who had had a change in refraction greater than 5 D within a one-year period during the course of the study, was excluded.)

The data showed that:

- In the 10-to-14 and 15-to-19 age groups, individuals of both sexes who wore glasses had a significantly greater shift toward myopia than those wearing contact lenses ($p<0.001$).
- In contrast, men in the 25-to-34 age group and women in the 20-to-24 age group who wore glasses showed significantly less shift toward myopia than those of the same age who wore contact lenses ($p<0.05$).
- Among those of either sex in all age groups 50 years and older who wore glasses, a shift toward hyperopia was significantly greater than among those of similar age wearing contact lenses ($p<0.05$).

The authors note that a further prospective study is needed.[5478]



Jason Marsack, PhD

Scleral lenses can be customized to correct higher-order aberrations in patients with keratoconus. (Marks are for orientation; lens border is visible on the far right.)[5466]

Managing Keratoconus

Scleral contact lenses have recently re-emerged as a potential approach for managing diseases such as keratoconus. In addition to refractive correction, the lenses serve to mitigate the higher-order aberrations caused by the surface of the diseased eye, in part by generating a tear-film lens.

Noting that this does not totally eliminate the aberration problem, researchers at the University of Houston compared the visual outcomes with scleral contact lenses that were either designed to correct lower-order aberrations alone or customized to correct both lower- and higher-order aberrations. (The rigid nature of scleral lenses makes them ideal for this type of customization.)

At the time of abstract submission, six eyes of three subjects had been tested and analyzed. A fitting lens set was used to determine the optimum lens design for each eye in terms of corneal vault, limbal clearance and blood flow at the margin of the lens. Then, two more scleral lenses were created for each eye, one designed to correct the lower-order aberrations, and one designed to correct for lower- and higher-order aberrations. After a 30-minute period to allow the lens to settle on the eye, visual acuity and residual ocular aberration through the 10th radial order were measured.

Wearing the lower-order-only lenses, four out of six eyes continued to exhibit higher-order aberrations that were worse than an age-matched mean. In contrast, when wearing the lenses designed to correct both higher- and lower-order aberrations, all six eyes surpassed the age-matched mean. The root-mean-square values of the HOAs were 0.372 ±0.128 µm with the former lenses, 0.152 ±0.049 µm with the latter, a 57-percent improvement. LogMAR visual acuity improved by seven or more letters in three of the eyes.

The study authors note that gain in vision appeared to be subject-dependent, and that given time to adjust to the lenses, the subjects' vision might improve even further.[5466]

Researchers at the Osaka University Graduate School of Medicine in Japan explored the visual performance of a new design of silicone-hydrogel soft contact lens. The lens is designed to correct a refractive vertical asymmetry in eyes with keratoconus.

Fifty eyes of 37 individuals with mild keratoconus were involved in the study. Lenses used in the study featured six different asymmetrical refractive power distributions (2, 4, 6, 8, 10 and 12 D) designed to create vertical irregular astigmatism. Eyes were measured using corneal anterior OCT, wavefront aberrometry and subjective refraction; visual acuity and visual clarity (using the visual analog scale) were also checked. A lens was chosen and fitted for each eye based on those measurements. The eye was then retested with the lens on, using wavefront aberrometry and over-refraction, and visual acuity and visual clarity were rechecked.

With the specially designed lenses, monocular visual acuity improved from -0.03 ±0.13 to -0.08 ±0.08 LogMAR ($p<0.01$); visual clarity improved from 61.2 ±20.7 to 73.8 ±18.5 ($p<0.01$); vertical coma was reduced from -0.49 ±0.36 µm to -0.35 ±0.38 µm ($p<0.05$); and overall higher-order

aberrations were reduced from 0.66 ±0.39 µm to 0.61 ±0.39 µm ($p<0.05$). The authors note that the new design's correction of refractive vertical asymmetry caused a significant improvement in visual performance.[5487]

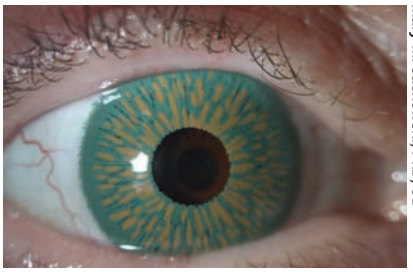
Ortho-K and RGPs

A researcher at Fudan University in Shanghai, China, conducted a study using SD-OCT to determine how orthokeratology affects the epithelium, and whether this could account for the refractive changes produced.

The study included 60 patients who had worn orthokeratology lenses for at least one night (mean age 10.6 ±2.38 years), divided into six groups based on duration of wear. Eleven eyes with no history of contact lens use served at controls. A pachymetry module measured epithelial topography in the central 6 mm of the cornea. In addition, average epithelial thickness was measured for the central 3 mm; within a ring from 3 to 5 mm in diameter; and within a ring from 5 to 6 mm in diameter. Then Munnerlyn's formula was used to determine the refractive change that would be expected as a result of these changes.

The data showed that orthokeratology caused significant epithelial thinning of the central cornea in all wearers. However, in the 3 to 5 mm ring no significant difference was found between wearers and controls. In the 5 to 6 mm ring, thickness increased for some of the groups, but only one group increased significantly (compared to controls). Notably, the refractive changes measured in wearers significantly exceeded the refractive change predicted by the formula.

The author concludes that the lenses can cause significant remodeling of the corneal epithelium, but that these are not sufficient to account for the refractive change. The author hypothesizes that changes in stromal thickness or bending of corneal tissue may also play a role.[3113]



Mary M. Jackowski, PhD, OD

Lenses that create an artificial pupil are helping reduce symptoms caused by light sensitivity.[5307]

Researchers in Germany evaluated the value and safety of rigid gas permeable contact lenses for correcting aphakia in infants after removal of congenital cataract. The authors performed a retrospective study of 75 infants who received RGPs after undergoing this surgery between 1987 and 2011. Subjects were divided into four groups: bilateral aphakia; monolateral aphakia with early surgery; monolateral aphakia with late surgery; and aphakia with additional ocular pathologies.

The data showed that the infants tolerated the RPG lenses well. Those treated bilaterally achieved visual acuities up to 1.0; in contrast, monolateral cases frequently developed amblyopia. Also, functional results were better after early surgery than late surgery.

The authors note that as long as the parents are compliant and collaborative, RGPs may be preferable to IOL implantation following congenital cataract surgery in infants. [5474]

Quelling Light Sensitivity

A study conducted in Syracuse, N.Y. found that artificial pupil contact lenses (APCLs) provided significant relief to veterans suffering from light sensitivity, photophobia and light-induced headache (triggered even by levels as low as normal room lighting). Eighteen otherwise normal patients exhibiting these symptoms were seen at the Veterans Administration hospital in Syracuse. (Most of these individuals had been treating their symptoms, both indoors and outdoors, with dark wrap-around sunglasses that eliminated up to 90 percent of light entering the eye.) The patients were fitted binocularly with 4.5-mm APCLs that cut the visual field beyond 70 degrees, reducing light entering the eye by about 30 percent *(See sample, left)*. The subjects were examined and given questionnaires when fitted with the lenses and one month later.

All patients reported substantial benefit from wearing the lenses regularly. Light sensitivity scores dropped 50 percent, with major reductions in headaches. Not needing to wear sunglasses (except in outdoor bright light conditions) allowed subjects to re-engage in normal activities and improved interactions with family and co-workers. The lenses also eliminated the chronic dark-adaptation problems associated with wearing dark sunglasses.

The authors note that the use of APCLs improves upon currently available treatment options, and that these results suggest that peripheral light may be a key cause of these symptoms.[5307]

Working with Multifocals

Researchers in Sydney, Australia, working with financial support from Allergan, conducted a study designed to compare the effect of different commercial contact lens designs on accommodation, facility and phoria in myopic wearers. Forty non-presbyopic subjects wore three different types of contact lenses daily, bilaterally, for a minimum of eight days each with a one-week washout period between lens types. Each subject was randomly assigned a single-vision control lens and two of four possible multifocal lenses (Proclear Distance, Proclear Near, Air Optix Aqua and PureVision).

Participants were seen at baseline and once after each lens-wearing period. Researchers assessed static accom-

modative response and the spherical equivalent using the Eyemapper. Subjects were tested in a fogged state and at four vergences (-2 D, -3 D, -4 D and -5 D) with five repeats in each condition. Accommodative facility was measured using ±2 D flippers, and phoria was measured using a Howell card. Data was averaged for the four exams, to minimize inter-visit variability.

The data showed:

• All lenses produced a myopic shift at +1 D fogging.

• Accommodative response function was relatively linear with the single-vision (control) lenses.

• All center-near multifocals (Air Optix, PureVision and Proclear Near) produced accommodative lead at -2 D, with optimal responses at -3 D and a lag at -4 D and -5 D. In contrast, the center-distance lens (Proclear Distance) produced lag at every test vergence.

• In terms of accommodative facility, all multifocals did worse than the single-vision lenses. The former measured between 14.4 and 16.5 cycles/min; the latter measured 19.2 cycles/min ($p<0.05$).

• No difference in distance phoria was found between lens types.

• Near phoria was significantly different with the Proclear Near multifocal (5.6 exo, $p<0.05$).[4251]

In another study, researchers in Barcelona, Spain compared subjective over-refraction to autorefraction of individuals wearing multifocal contact lenses. (The study was supported by a grant from the Spanish Ministry of Economics; one researcher has a patent interest in the autorefractor used in the testing.) The group evaluated non-cycloplegic distance refractive error in 30 eyes of 15 healthy adult subjects wearing the Air Optix, Proclear and Acuvue Oasys multifocal contact lenses; they compared subjective measurements to those made by the Grand Seiko Auto Refractor/Keratometer WAM-5500.

Mean Difference Between Auto-Refractometer and Subjective Over-Refraction with Multifocal Contact Lenses [5481]

	Spherical Over-refraction	Astigmatic Over-refraction (J0)	Astigmatic Over-refraction (J45)
Air Optix	0.52 ±0.37 D (r: +1.08 to +0.02 D)	-0.04 ±0.03 D (r: +0.32 to -0.55 D)	-0.05 ±0.04 D (r: +0.15 to -0.31 D)
Proclear	0.62 ±0.43 D (r: +0.94 to +0.32 D)	0.17 ±0.07 D (r: +0.22 to +0.12 D)	0.05 ±0.04 D (r: +0.42 to -0.33 D)
Acuvue Oasys	-0.15 ±0.11 D (r: +0.07 to -0.46 D)	-0.23 ±0.17 D (r: +0.03 to -0.50 D)	-0.05 ±0.03 D (r: +0.17 to -0.29 D)

Subjects ranged in age from 25 to 30 years; subjective spherical refraction was -2.43 ±3.56 D (r: +2.50 to -9.50); subjective astigmatic refraction was -0.48 ±0.44 D (r: 0 to -1.25). BCVA (logMAR) was -0.21 ±0.07 (r: -0.1 to -0.34). Results of the comparison are shown in the chart above.

The authors note that there was good agreement between subjective and objective measurements, except in patients with high refractive errors. They conclude that the autorefractor may be acceptable for over-refracting individuals wearing multifocal contact lenses, except if a patient is highly myopic or hyperopic.[5481]

Epidemiology

A second large prospective study conducted by the Japanese research group noted earlier was a five-year study involving 204,975 eyes of 103,001 men and women age 9 to 96 who were prescribed contact lenses at the Okada Eye Clinic in Yokohama between January 2007 and December 2011. The study was conducted to find out how the number of lenses prescribed, and the nature of the prescriptions, changed in different groups. (Anyone who had undergone cataract surgery or orthokeratology, or who had a change in refraction greater than 5 D within a one-year period during the course of the study, was excluded.)

After five years, the data showed:

• The most contact lenses were prescribed to those between the ages of 20 and 24 (19.22 percent of men and 17.58 percent of women), followed by ages 25 to 29 (17.53 percent of men and 15.6 percent of women) and ages 15 to 19 (16.46 percent of men and 15.29 percent of women). All told, about half of the contact lenses were prescribed to individuals in these groups (i.e., between the ages of 15 and 29).

• In terms of which levels of refractive error were associated with the highest rates of contact lens wear, those with refractions from -2.75 to -4.5 D had the most contact lens wearers (40.76 percent of men and 40.97 percent of women with this refraction wore contact lenses), followed by those with refractions between -4.75 and -6.5 D (25.87 percent of men and 24.51 percent of women with this refraction wore contact lenses) and -0.75 to -2.5 D (20.89 percent of men and 23.19 percent of women with this refraction wore contact lenses).

• About 10 percent of those studied had myopia ≤-6.75 D (11.71 percent of men and 9.79 percent of women); about 2.5 percent had myopia ≤-8.75 D (2.85 percent of men and 2.24 percent of women). Less than 1 percent of those in the study had hyperopia ≥+0.75 D (0.27 percent of men and 0.84 percent of women).[5477] REVIEW

Dr. Asbell is a professor of ophthalmology and the director of cornea and refractive surgery at the Mount Sinai School of Medicine.

Preparing for the Health-Care Revolution

Chandak Ghosh, MD, MPH, New York City

Eight ways the new Affordable Care Act may impact your practice, and how to be ready for them.

Having survived a congressional vote, a Supreme Court challenge and a presidential election, the Affordable Care Act continues to roll out, with most provisions enacted by the end of 2014. Focused on reducing health-care costs while increasing quality, ACA aims to revolutionize the way America's health-care system functions. Understanding what the future holds will allow ophthalmologists to shape their practices and adapt quickly to the new environment.

Health policy experts believe that physicians will feel the most impact in the following areas.

30 Million New Patients

With the individual mandate to purchase insurance and the Medicaid expansion, most project 30 million newly-insured patients, all seeking primary-care providers. Insurance will not have lifetime reimbursement caps and must provide, at minimum, basic "essential" benefits in 10 categories. Insurance companies cannot deny patients with pre-existing conditions, cannot cancel policies at whim, must use at least 80 percent of premiums towards patient care and end co-pays for numerous preventive services. For 2013 and 2014, Medicaid reimbursement rates will rise to match Medicare reimbursements so that primary-care providers welcome all. Ophthalmologists should continuously educate primary-care doctors, hospital systems and insurance plans that patients at risk for such conditions as macular degeneration, glaucoma and diabetic retinopathy should be referred for full eye exams.

Practice Efficiency

By analyzing and improving practice efficiency, ophthalmologists will be able to accommodate many of the newly insured. A 3:1 exam room to physician ratio, with a 2:1 ophthalmic technician to physician ratio, optimizes patient flow. Focusing on ways to improve the patient visit, ophthalmologists should investigate their patient no-show rates, length of time until the next available appointment and cycle time from when patients enter the office to when they leave. Maximize patient satisfaction by updating the look of the waiting room and restrooms, training front desk staff to be exceedingly polite and helpful, and taking time to listen to and acknowledge each patient's medical complaints. All of these have a stronger correlation with high satisfaction rates than health outcomes.

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Medicare Fraud

ACA places enormous emphasis on exposing Medicare fraud and reimbursement recovery. Medicare is training more than 2 million senior citizen beneficiaries to report fraudulent billing, and partnering with private auditing firms, which are allowed to keep a percentage of what is recovered. All Medicare providers will be revalidated through licensure checks, site visits and audits. Penalties for fraud are severe, particularly if the crime garners over $1 million. Physicians must reassess all billing practices to be sure they conform to Medicare rules exactly. Medicare's allowing questionable practices in the past is not an acceptable excuse for providers to continue. Code strictly based upon the documented complexity of the patient. If billing for a specific process (i.e., interpreting test results), that process must be written out clearly in the medical record if the ophthalmologist expects remuneration for it.

Rise of Mid-levels

Because America faces a shortage of doctors to treat the newly insured and a rapidly aging population, mid-level professionals like optometrists, physician assistants and nurse practitioners will gain more prominence and responsibility as primary-care providers. A traditional of rivalry and competition between doctors and mid-levels must change to a partnering relationship. For maximum efficiency and better use of limited specialists, primary-care physicians and mid-levels should be trained to use non-mydriatic ophthalmic cameras to triage mainly patients who may require procedures or eye care specialized to ophthalmologists. Every image can be read by an ophthalmologist via telemedicine to determine if a referral is warranted. Your practice can replace the yearly normal diabetic visits, for example, with patients who need interventions. Refractions and contact lens care can be left to optometrists.

Practice Mergers

ACA promotes the Patient-Centered Medical Home model where patients can find a one-stop shop for complete care. An example is the establishment of accountable care organizations, health systems in which physicians focus on care coordination while reducing unnecessary costs. Successful ACOs will share the savings. With ACA favoring large interdisciplinary provider structures, the

inevitability of lower per-patient reimbursements, the high costs of buying and maintaining medical technology, and the cost of malpractice insurance, solo and small group practitioners will stand at a disadvantage. Payment schedules will favor large medical ophthalmology practices that channel procedures to the super cataract surgeon and the super retina injectionist. Within three years, 75 percent of practicing physicians will be employed by health-care systems. Every solo practitioner should consider whether selling or merging his practice may ultimately bring more rewards.

Electronic Health Records

While most physicians are early in the steep learning curve with electronic health records, 75 percent of practices have already computerized. The potential for this technology seems vast: improved coordination among treating providers; reduced testing and treatment duplication; fewer medical mistakes because of misread prescriptions and adverse drug reactions; more accurate and timely billing; improved quality measurements; ability to track patient flow; less paperwork and chart storage; and protection in malpractice lawsuits.

Often, ophthalmologists connected to a PPO or hospital system are tied to EHRs that document eye exams poorly. The next step in the EHR progression is to improve interoperability among different computer systems. Once that occurs, ophthalmologists should move to hardware and programs more suitable to the field. For example, a handheld tablet with a prepopulated eye exam may make documentation faster and easier.

Reimbursement/income

The future holds lower reimbursements, particularly for specialists. The payment system will move away from fee-for-service, which incentivizes increased testing, to bundled payments per episode for both hospitalizations and outpatient visits. For example, currently, for each glaucoma patient, ophthalmologists are paid for each exam, gonioscopy, visual field test and OCT. After a number of pilot studies to ascertain the advantages and risks to this payment approach, in the future Medicare will likely move to a model of reimbursing a fixed amount for each patient to cover as many visits and tests as the doctor feels are necessary for each diagnosis.

New Research and Guidelines

Much of a physician's knowledge comes from experiences and opinions of mentors, teaching attendings, colleagues and pharmaceutical representatives. Thus, many health-care practices proliferate without unbiased scientific evidence of effectiveness. ACA creates the Patient-Centered Outcomes Research Institute to oversee research comparing drugs and procedures to determine which lead to the best outcomes.

The recent National Eye Institute-sponsored bevacizumab vs. ranibizumab comparison for age-related macular degeneration is an example of such "comparative effectiveness" investigations. This research should not only help physicians make more informed practice choices but it will protect in malpractice cases if recommended processes are followed. The influence of pharmaceutical companies will be minimized as medical companies must report publicly any payments of over $10 made to physicians or hospitals. These payments include every form of payment: gifts; consulting fees; travel; grants; royalties; entertainment; etc.

As part of a new movement to re-evaluate what has become standard of care, 17 medical specialty groups collaborated to release a list of 90 common tests and procedures that have not improved health. Decrying the value of such tests as routine EKGs in low-risk, non-symptomatic patients, imaging for nonspecific low back pain or uncomplicated headaches and standard admission or preoperative chest X-rays, this "Choosing Wisely" Campaign also includes five recommendations from the American Academy of Ophthalmology:

- Don't perform preoperative tests for eye surgery unless there are specific medical indications;
- Don't routinely order imaging tests for patients without symptoms or signs of significant eye disease;
- Don't order antibiotics for adenoviral conjunctivitis;
- Don't routinely provide antibiotics before or after intravitreal injections; and
- Don't place punctal plugs for mild dry eye before trying other medical treatments.

The future of health care will revolve around extending care to those who have little or no access currently, improving quality and bringing down costs dramatically so they stop overtaking personal and governmental budgets. Medicare and private insurance companies will be scrutinizing physician practices for better health outcomes and proper billing procedures while offering less in reimbursements. Ophthalmologists can prepare to capture this enlarged patient market by retooling their office efficiency and esthetics, evaluating payment coding, firming relationships with other providers, implementing new technology and employing new practice guidelines. REVIEW

Dr. Ghosh is an ophthalmologist and serves as a senior medical advisor for federal policy with the Department of Health and Human Services. Contact him at chandak.ghosh@gmail.com.

Are You Setting Yourself Up for Burnout?

Michelle Stephenson, Contributing Editor

Physician burnout appears to be on the rise. Here's why, along with some ideas on how to get better control.

While physician burnout has always been a problem, today's doctors have more on their plates than doctors of previous generations, and they seem to be more affected by burnout than professionals in other fields.

A recent survey compared burnout and satisfaction with work/home life balance among physicians and those employed in other professions.[1] The study included 7,288 physicians who completed surveys. When assessed using the Maslach Burnout Inventory, researchers found that 45.8 percent of physicians reported at least one symptom of burnout. Compared with a probability-based sample of 3,442 adults working in other professions, physicians were more likely to have symptoms of burnout (37.9 percent compared with 27.8 percent) and to be dissatisfied with their work/life balance (40.2 percent compared with 23.2 percent).

Why Do Physicians Burn Out?

"There are concerns that the ever-increasing pace of practice might be contributing to burnout because physicians are being asked to see more and more patients in less and less time," says Colin P. West, MD, PhD, FACP, from the Divisions of General Internal Medicine and Biomedical Statistics and Informatics, Departments of Internal Medicine and Health Sciences Research, at the Mayo Clinic, in Rochester, Minn. "That sort of treadmill effect may play a role. There is also concern about what will happen if the practice of medicine continues to go in those directions while social structures are changing. For example, it is much more common to have dual-career households. Fifty years ago, ste-

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reotypically, the physician might work 60 hours a week while his wife was the homemaker. There was often a more starkly defined division of responsibilities. These days, spouses and partners don't want that, and physicians themselves don't want that. Today, there is the shared family model that I think is a societal change as well. That makes work/life balance that much more challenging."

Additionally, there is much less division between work life and home life. With computers and smartphones, physicians may feel like they are always on call. It can be difficult to prevent work issues from invading home time. "One of my colleagues says that physicians can never disconnect from the grid," Dr. West says. "We are connected with our smartphones, and we can remotely access into our patients' data. There has always been some of that—physicians being on their pagers, etc.—but I think the volume may have increased."

The Internet may also play a role. While there are benefits to seeing better-educated patients, some patients may present to the office with specific expectations based on their Internet research. "Some patients may view their relationship with the physician not as a partnership but more as the patient hiring the physician as a consultant and wanting to tell the physician what should be done instead of coming to a mutually agreed-upon decision that involves both of them working together," Dr. West notes.

Helen Meldrum, EdD, an associate professor of psychology in the Program of Health Sciences and Industry at Bentley University in Waltham, Mass., agrees. "It's only in recent times when a physician gives the patient a treatment option, and the patient says, 'that's not what I Googled.' Physicians used to be able to count on a certain amount of authority, but their authority is at an all-time low because patients feel like they are well-educated by the Internet," she says.

The business side of medicine may also be partly to blame. "When doctors go to medical school, they are looking forward to the chance to have relationships with patients," Dr. West says. "Anything that gets in the way of those relationships can contribute to dissatisfaction and burnout. We have focused our work in the past decade on trying to document the problem, and it has been a really interesting transition in recent years. When we first started our group's work, we would receive comments that people didn't believe it was a significant issue. Now, we are getting a lot more acceptance that this is a per-

vasive problem."

A recent study found that surgeons in private practice were more likely to experience burnout than their colleagues in academic practice.[2] The study compared distress parameters and career satisfaction from survey results of surgeons in 14 specialties. It found that academic surgeons were less likely to screen positive for depression or to have suicide ideation. They were also more likely to experience career satisfaction and to recommend a medical career to their children.

For academic surgeons, the most significant positive associations with burnout were being a trauma surgeon, number of nights on call and hours worked. For private practice surgeons, the most significant associations with burnout were being a urologic surgeon, having 31 percent to 50 percent time for nonclinical activities, incentive-based pay, nights on call and hours worked.

Additionally, physicians may be putting unnecessary pressure on themselves because of their personality types. "There have been a couple of articles written over the years on the compulsive personality type and the contribution of perfectionism and excessive sense of responsibility of physicians," Dr. West says. "The people who are selected to go to medical school and self-select to go into medical school are people who tend to have perfectionist tendencies. One definition of burnout that I heard is the distance between what a person is able to do and what he feels he should be doing. Because the bar is very high for doctors, in terms of their own bar and society's bar, it makes it difficult for doctors to live up to their own high expectations as well as the external expectations. As the number of patients increases and the amount of things the doctor feels like she needs to be doing increases, the possibility of living up to her own high expectations becomes smaller, and that creates conditions for burnout as well."

Dr. Meldrum adds that debt may be a contributing factor because many physicians are taking on consulting jobs to pay off their medical school debt. "Many physicians are taking on extra consulting jobs just because they are so saddled with debt," she says. "If you work inhuman hours, where are your friends and family in the picture? They are unhappier with you than ever. When doctors are home, they are often cranky and overstressed and tired."

Dr. West and his colleagues conducted a study to evaluate the relationship between well-being and demographics, educational debt and medical knowledge.[3] The study included 16,187 residents. In this study, suboptimal quality-of-life and symptoms of burnout were common, and higher debt (more than $200,000) was associated with symptoms of burnout.

"Then, there are the physicians who are older in a supervising role and their direct reports have staff to manage," Dr. Meldrum says. "The stress of not having a support staff that has good interpersonal skills means that more and more things get bumped upstairs. Additionally, patients are more demanding, so physicians are hearing more complaints than they did in the past."

Prevention Strategies

Fortunately, there are many things physicians can do to prevent burnout or to turn things around once they start feeling burned out.

Dr. Meldrum conducted a study on physicians' strategies for avoiding burnout and found that some helpful techniques for avoiding burnout included setting limits, sharing issues with friends and family, physical exercise, cultivating relaxation and humor.[4]

Matthew J. Goodman, MD, an internist and co-director of the University of Virginia's Mindfulness-Based Stress Reduction Program in Charlottesville, Va., recommends the following:

- Foster healthy family relationships and friendships.
- Keep hobbies alive.
- Have a religious or spiritual affiliation.
- Look to find meaning in your work.
- Find a mentor.

Dr. Goodman notes that, because there is growing awareness about physician burnout, there are groups of physicians who are looking at ways to get together. "Physicians rarely talk to each other except about medicine and patients, but it can be helpful to become part of a group of like-minded physicians who can serve as a support group or share experiences."

Dr. Goodman and his colleagues have done some work with teaching mindfulness to physicians, and data is becoming available on mindfulness classes to help with physician self-awareness and developing the ability to maintain a sense of calm or to be in difficult circumstances and not get carried away by them.[5]

Dr. Goodman's study included 93 health-care providers, including physicians from multiple specialties, nurses, psychologists and social workers who practice in both university and community settings. The health-care providers attended a continuing-education course based on mindfulness-based stress reduction. The course met 2.5 hours a week for eight weeks plus a seven-hour retreat. The classes included training in four types of formal mindfulness practices, including the body scan, mindful movement, walking meditation and sitting meditation. Providers' Maslach Burnout Inventory scores improved significantly from before to after the course for both physicians and other health-care providers for the Emotional Exhaustion, Depersonalization and Personal Accomplishment scales. Mental well-being also improved significantly.

He notes that, while mid-career physicians are at risk, burnout can

(Continued on page 95)


When Glaucomatous Damage Isn't Glaucoma

Many conditions besides glaucoma can produce the appearance of the disease.

Flora Levin, MD, New Haven, Conn.

When diagnosing glaucoma or monitoring its progression, doctors rely on the appearance of the disc, measures of retinal nerve fiber layer thickness and visual fields. However, other disorders of the optic nerve can also produce visual field findings, nerve fiber layer loss and disc appearance that can mimic glaucoma.

Unfortunately, a misdiagnosis can have serious consequences, not just for the patient's vision but for the patient's overall health and well-being. Here, I'll review some alternative pathologies that can be misleading and share some illustrative case histories. Then, I'll suggest a few strategies that can help ensure your diagnosis is accurate.

Optic Red Herrings

Conditions that can be mistaken for glaucoma include compressive or infiltrative lesions of the optic nerve, previous ischemic optic neuropathy (both arteritic and non-arteritic), congenital and hereditary optic neuropathies, post-traumatic optic neuropathy and inflammatory and demyelinating optic neuritis. Most cases in the compressive category—intracranial mass lesions that cause optic nerve or chiasmal compression—will be pituitary adenomas, craniopharyngiomas, suprasellar aneurysms or meningiomas. Many such tumors will present in patients who are younger than the average glaucoma patient.

Patients with compressive injury may exhibit visual fields that resemble those of a glaucoma patient, with arcuate or nerve fiber bundle loss and shallow optic disc cupping. However, it is optic nerve pallor in excess of cupping, particularly of the temporal rim, that should prompt the physician to seek etiologies other than glaucoma. A vertical step in the visual field, from involvement of the junction of the optic nerve and chiasm or the chiasm itself, should also alert the clinician of possible compression or infiltration, as should a cecocentral scotoma or decreased acuity.

Previous ischemic optic neuropathy may present with nerve fiber bundle field loss if seen after the disc swelling resolves. Arteritic ischemic optic neuropathy may result in cupping resembling glaucoma, from a loss of disc substance produced by profound ischemia. However, this is usually accompanied by marked focal arterial narrowing near the disc, and the patient may give a history of acute loss of vision with headache, jaw claudication, weight loss, anorexia and fever. In non-arteritic ischemic optic neuropathy the contralateral disc may have a small cup; the involved eye may have altitudinal pallor without cupping, but with retinal arterial narrowing.

The third category, congenital and hereditary optic neuropathies, consists of conditions that can result in optic nerve appearance and visual field loss that also resemble glaucoma. Examples of such diseases include autosomal dominant optic atrophy, papillorenal syndrome, optic nerve head pits and colobomas, superior segmental optic nerve hypoplasia and Leber's hereditary optic neuropathy. A careful history and the duration and/or progression of the clinical findings are helpful clues in establishing the correct diagnosis.

Other rare causes of pseudoglaucomatous optic nerve changes include late changes after methanol-

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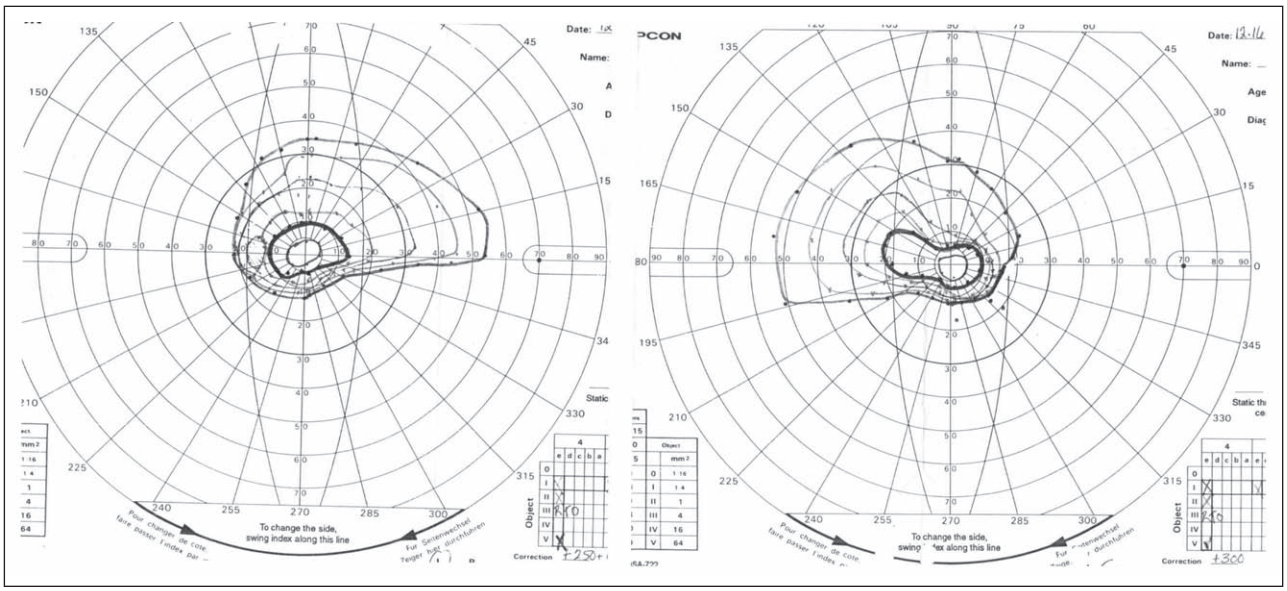

Figure 1A. In case history #1, a Goldmann visual field of a 55-year-old woman with diabetes and hypertension shows bilateral inferior defects.

toxicity and late changes in tertiary syphilis. The history is usually helpful in toxic optic neuropathy, but identification of syphilis may require laboratory testing.

Case Histories

Here are a few real-life examples of patients whose symptoms could have led to a misdiagnosis.

Case 1: A 55-year-old woman with diabetes and hypertension was found to have asymptomatic inferior visual field loss during a routine exam. Her visual acuity, color vision and pupils were all normal; her IOPs were at the upper limit of normal. Her Goldmann visual fields showed inferior arcuate defects, often seen in glaucoma *(See Figure 1A)*. The optic discs appeared to have abbreviated superior rims, which corresponded with the visual field defect and superior displacement of the central vessels and a superior peri-papillary halo *(See Figure 1B)*.

This patient had superior segmental optic nerve hypoplasia, typically a consequence of maternal diabetes mellitus. This is a type of congenital optic nerve anomaly that produces a nerve fiber layer defect that can look

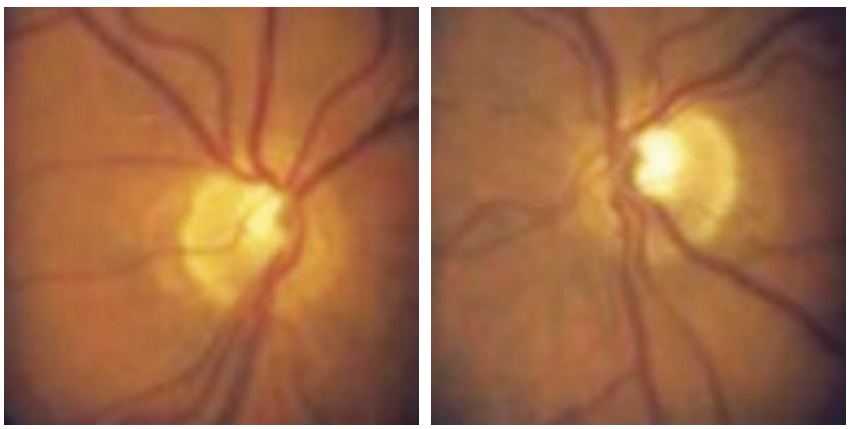

Figure 1B. Optic nerve photographs showing abbreviated superior rims that correspond with the visual field defects (Figure 1A) and superior displacement of the central vessels.

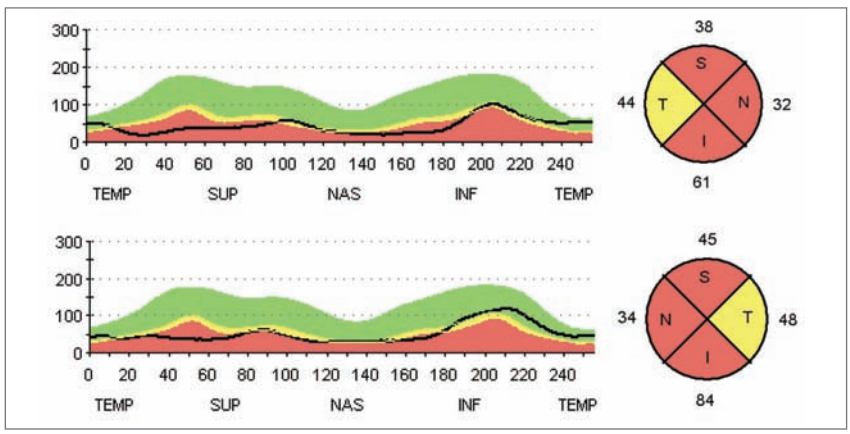

Figure 1C. An OCT shows bilateral generalized RNFL thinning, most pronounced in the superior and nasal segments, creating a "single peak" pattern. The papillomacular bundle is spared, resulting in intact central visual field and acuity.

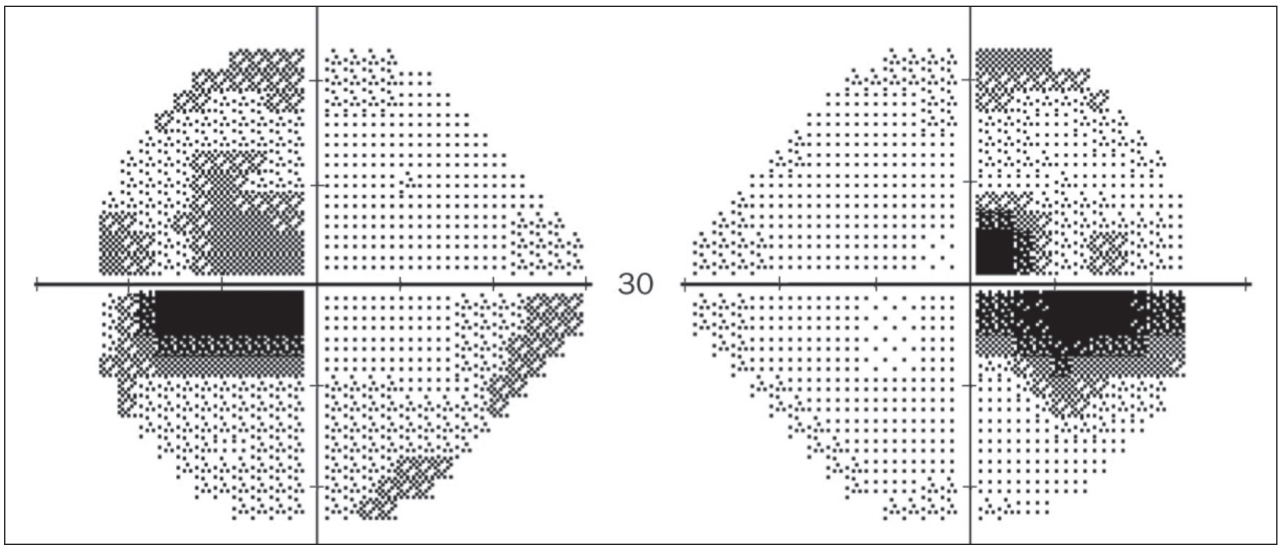

Figure 2A. In case #2, automated perimetry shows bilateral cecocentral scotomas. Intraocoluar pressures were 17 mmHg.

like glaucoma. A tip-off that this is not the case is the apparent inferior visual field loss and the topless disc appearance.

Despite the dense visual field defect, the patient was unaware of it. Patients with congenital visual field loss may be described by others as "clumsy"; the defects explaining their clumsiness are often not picked up until later in life.

The OCT scan was also helpful in the evaluation of this patient *(See Figure 1C, p. 87)*. It showed diffuse RNFL thinning (as opposed to thinning in just the superior area). If this patient had glaucoma, you'd expect more localized thinning corresponding to the visual field loss. In this case, the thinning was also generalized, despite being more pronounced in the superior nasal segment. Characteristically, the temporal quadrant was relatively spared, resulting in a "single peak" appearance and allowing the patient to retain good visual acuity.

In this case, the most important clues that glaucoma was not the source of the problem came from the history (i.e., the fact that the mother had diabetes and the patient was asymptomatic despite long-standing visual field loss); the appearance of the optic disc; and the OCT, which revealed widespread thinning.

Case 2. This patient was a healthy 43-year-old man, 20/60 OD, 20/80 OS, pressures 17 mmHg OU with normal central corneal thickness. Visual field testing showed bilateral cecocentral scotomas *(See Figure 2A)*. He had slightly diminished color vision and no relative afferent pupillary defect. His vision had not changed in the recent past. He had no history of tobacco or alcohol use, and he ate well.

His optic nerves could easily have been confused with glaucomatous

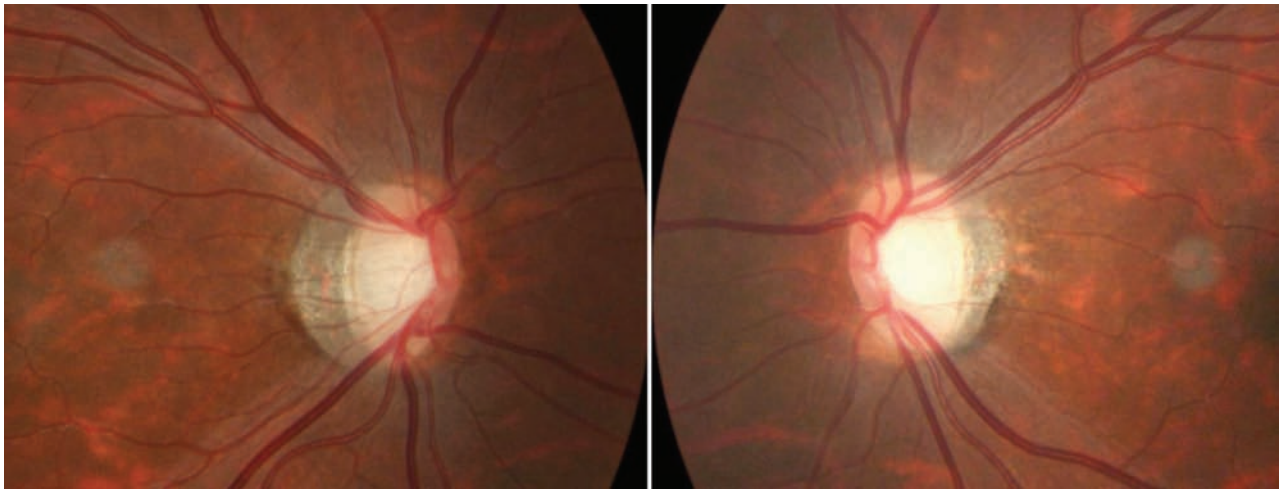

Figure 2B. Optic nerve photographs reveal tilted discs with increased cup-to-disc ratio, temporal crescent and temporal pallor.

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1. LASTACAFT® Prescribing Information. **2.** Torkildsen G, Shedden A. The safety and efficacy of alcaftadine 0.25% ophthalmic solution for the prevention of itching associated with allergic conjunctivitis. *Curr Med Res Opin.* 2011;27(3):623-631. **3.** Data on file, Allergan, Inc., 2005.

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optic nerves because they had a large cup-to-disc ratio *(See Figure 2B, p.89)*. Some might have been tempted to diagnose the problem as normal-tension glaucoma. However, it's important to consider a non-glaucomatous explanation. For example, individuals with a poor diet and/or alcohol and tobacco use may exhibit "tobacco/alcohol or nutritional amblyopia," indicated by bilateral decreased vision and similar cecocentral defects. (Optic nerve pallor might not be present early in this disease.)

This patient had autosomal dominant optic atrophy. Similar to Leber's hereditary optic neuropathy, end-stage dominant optic atrophy can cause disc excavation. However, unlike glaucoma, a careful observer should appreciate some optic atrophy, or temporal pallor; the rim is not going to be as pink as it would be in glaucoma. In these patients, the severity of vision loss usually peaks

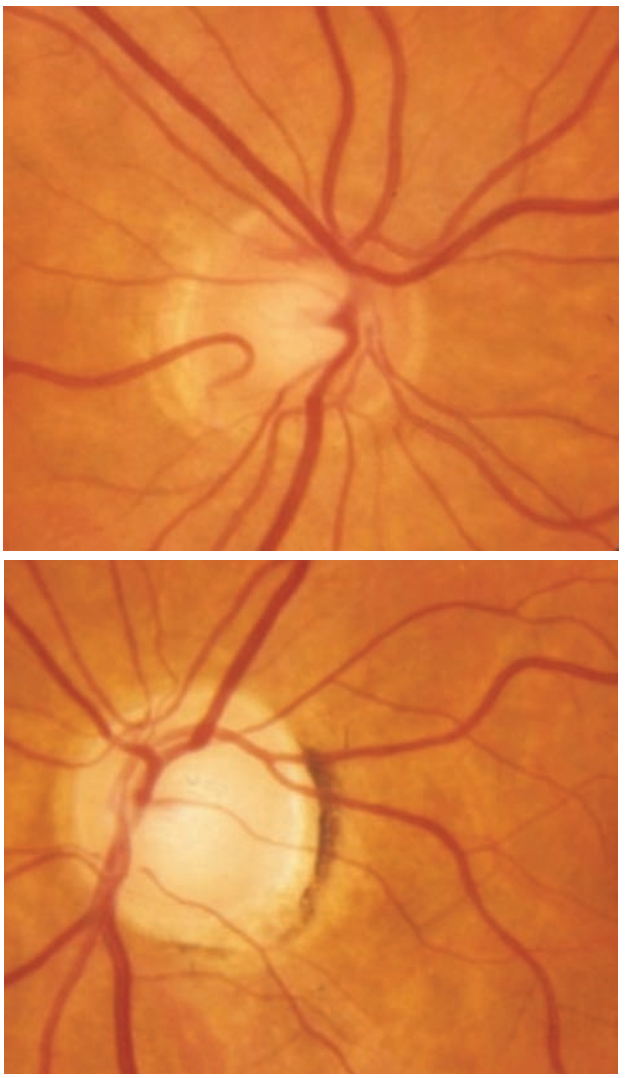


Figure 3A. In case #3, the left optic nerve (bottom) has an increased central cup accompanied by optic atrophy (pallor).

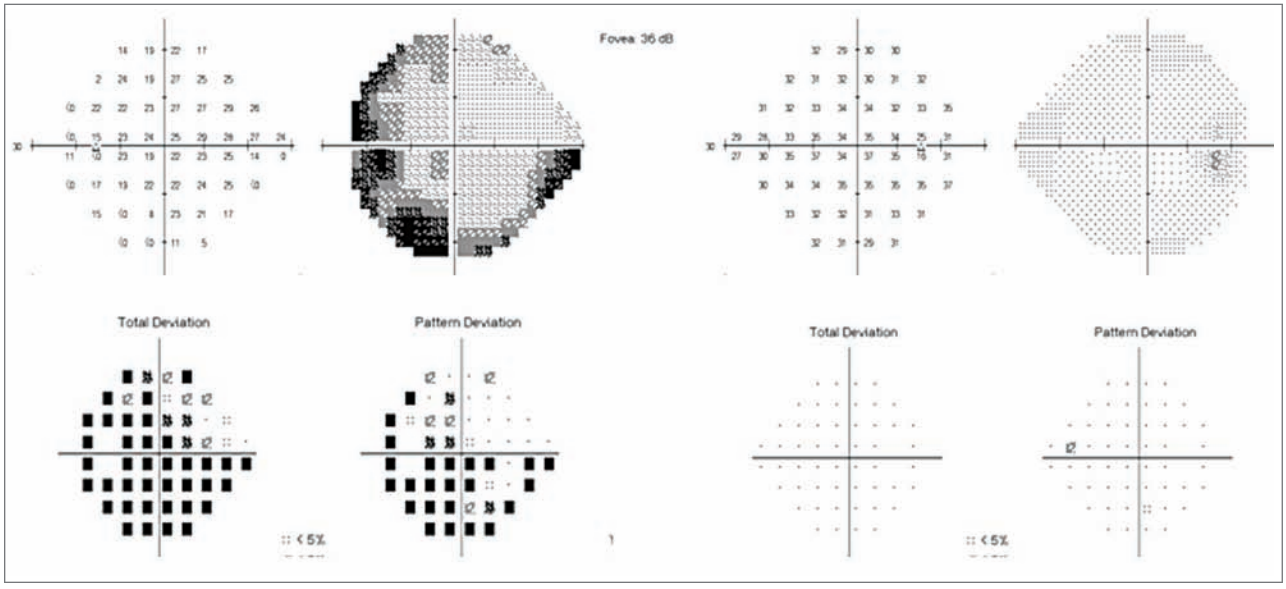


Figure 3B. Visual field testing shows left inferior and superior nerve fiber bundle defects, with diminished foveal sensitivity.

by adolescence and they tend to be stable for many years. The way the eye appears at adolescence is the way it will look for the remainder of the individual's adult life. In addition, examining first-degree family members, or a history of relatives with early-onset vision loss, may aid in the diagnosis.

Case 3. This 42-year-old woman presented with decreased visual acuity OS. Her IOPs were normal, but she displayed a relative afferent pupillary defect and decreased color vision in the affected eye. Her visual fields indicated a left inferior altitudinal defect with a little bit of superior arcuate defect, also involving the central vision *(See Figure 3B)*. The central foveal threshold measurement was diminished, to 36 on the right and 24 on the left. Both of her optic nerves had an increased cup-to-disc ratio. However, the left disc also had atrophy, demonstrated by relative whitening of the rim *(See Figure 3A)*.

The combination of unilateral decreased visual acuity, color vision loss and optic nerve appearance required further investigation with imaging. An MRI of the orbits in this patient revealed an optic nerve sheath meningioma *(See*

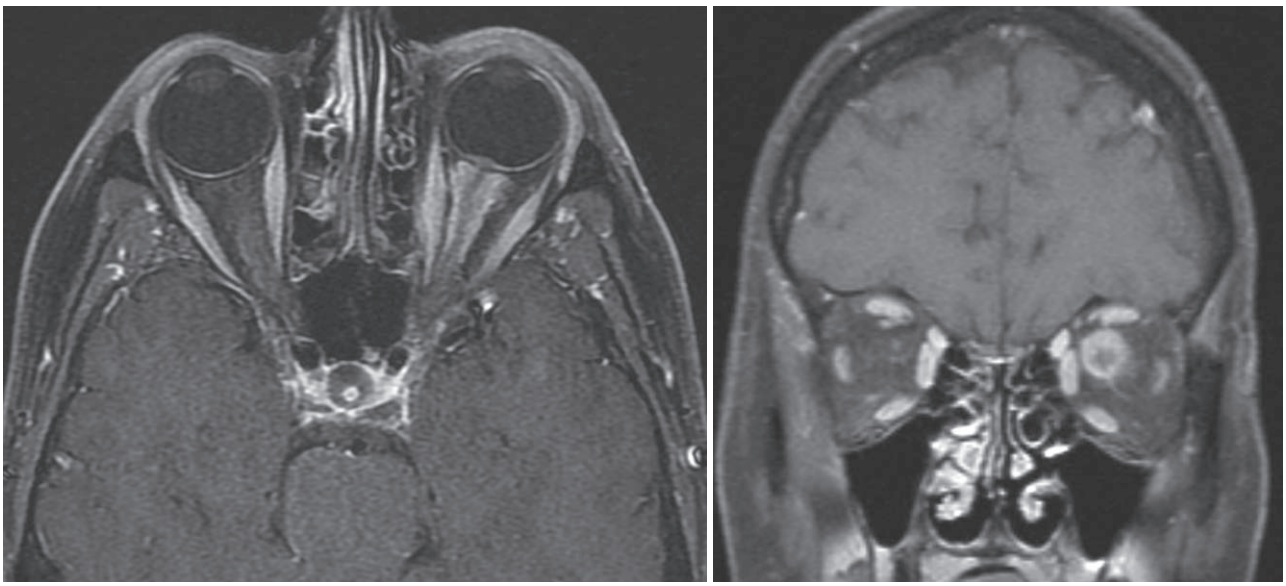


Figure 3C. In this patient, an axial (left) and coronal (right), T1-weighted, contrast-enhanced MRI shows diffuse enlargement and enhancement along the length of the left intraorbital optic nerve sheath.

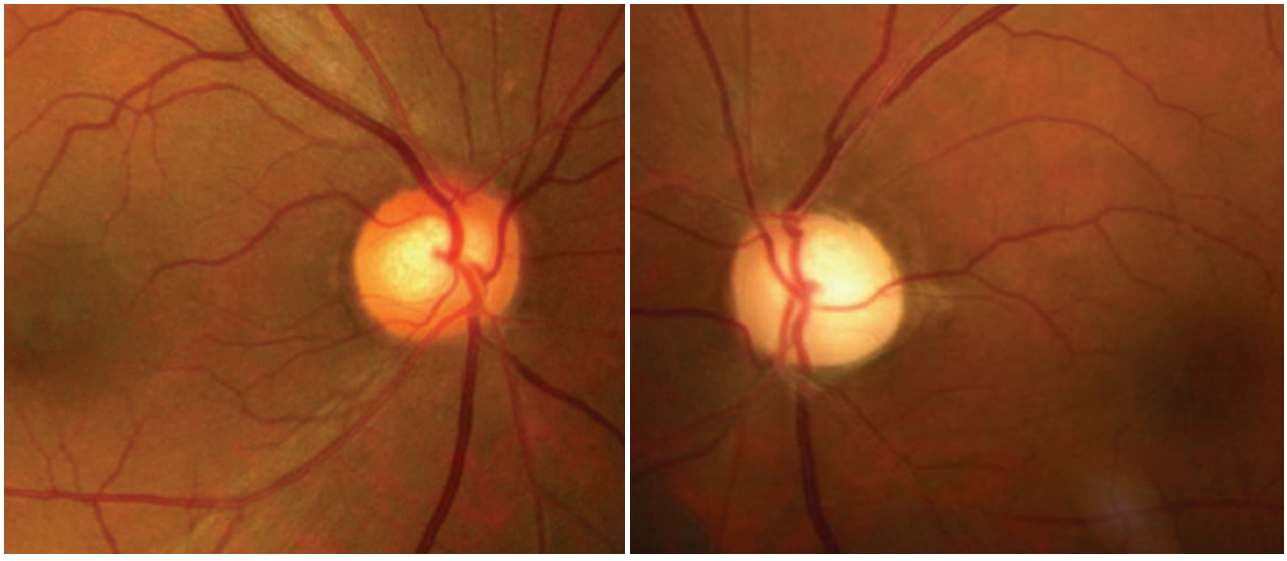


Figure 4A. In case #4, optic disc photographs show a normal right optic nerve; the left optic nerve has an increased shallow cup and pallor of the rim.

Figure 3C). (Differential diagnosis of the MRI appearance would include other conditions such as sarcoid disease or lymphoma.) This compressive optic neuropathy may cause cupping resembling glaucoma, as well as glaucoma-like visual field defects. The difference, again, is the optic nerve appearance, pallor out of proportion to cupping, as well as color vision loss and unilateral visual acuity loss.

Other compressive lesions, such as pituitary adenomas and craniopharyngiomas, can lead to similar unilateral or bilateral clinical presentations. A careful clinical history and examination of the optic discs should alert the examiner to the possibility of non-glaucomatous etiologies and prompt further work-up.

Case 4. The next case was a 48-year-old man with vision loss in the left eye (hand motion only), but 20/20 acuity in the right. He had a left relative afferent pupillary defect. The fundus examination revealed an increased cup-to-disc ratio with pallor on the left disc and a normal optic nerve on the right *(See Figure 4A).* The visual field showed a superior temporal defect on the right with diffuse loss on the left, also known as a junctional scotoma *(See Figure 4B).*

A compressive lesion in the area of the chiasm will produce such a

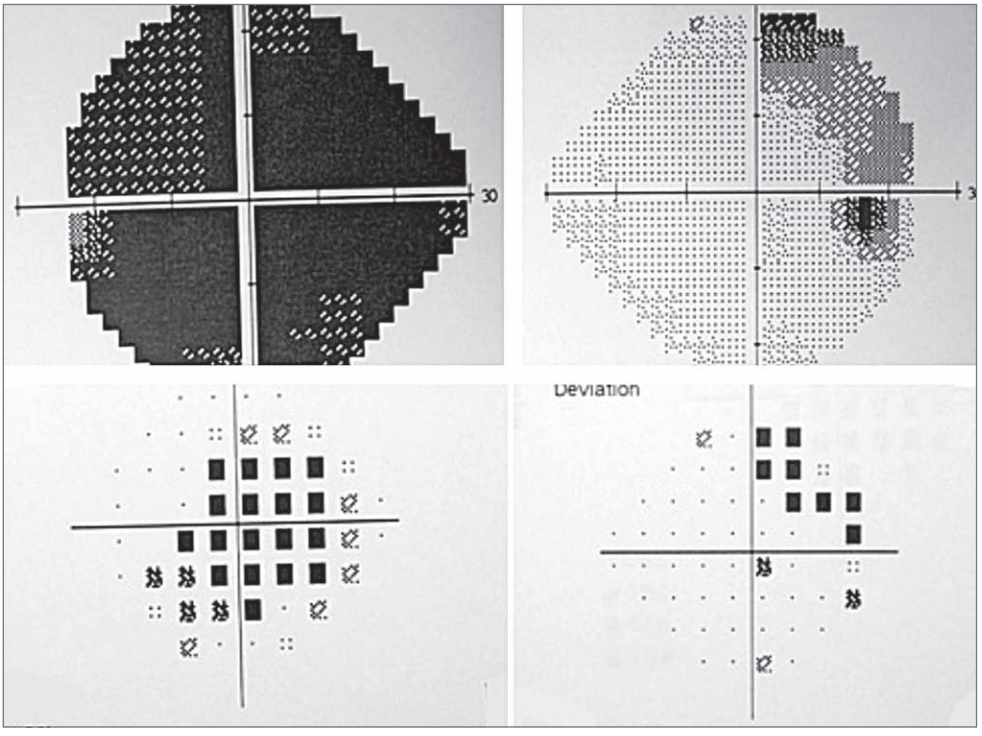
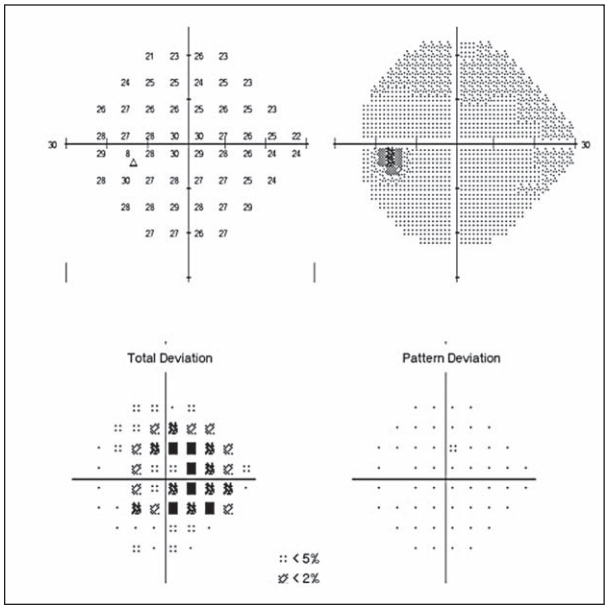


Figure 4B. Humphrey visual field testing shows a junctional scotoma with diffuse loss on the left eye and a temporal defect on the right.



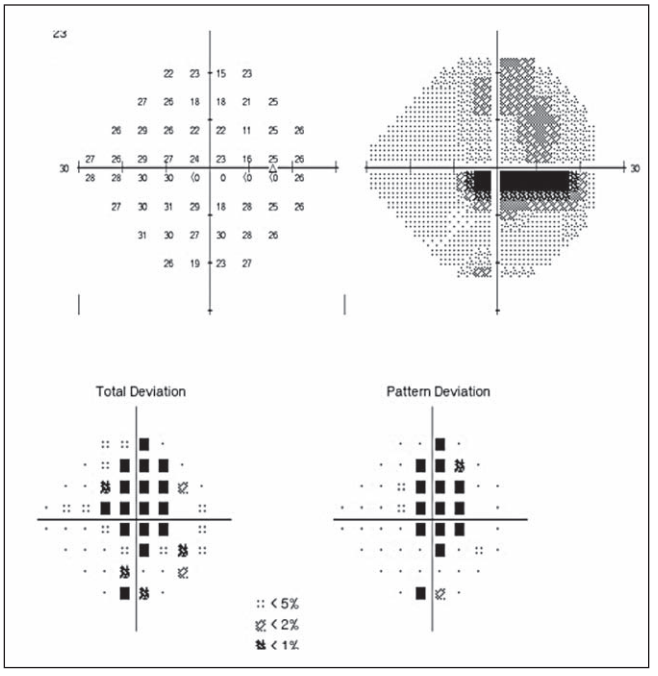


Figure 5A. In case #5 (above and right), automated perimetry shows a left cecocentral visual field defect.

visual field defect; compression of one optic nerve results in central vision loss and contralateral temporal fibers. Depending on the exact location of the compression, various visual field patterns can be seen. In this patient, the relatively young age, the asymmetric involvement, the visual field pattern and the optic nerve appearance prompted imaging and diagnosis of an intracranial mass lesion.

Case 5. The next patient was a 49-year-old man with elevated cholesterol. His visual acuities were 20/20 and 20/30; there was a left relative afferent pupillary defect and cecocentral visual field defect *(See Figure 5A)*, but color vision was normal. Careful examination of the optic nerve revealed inferior swelling of the

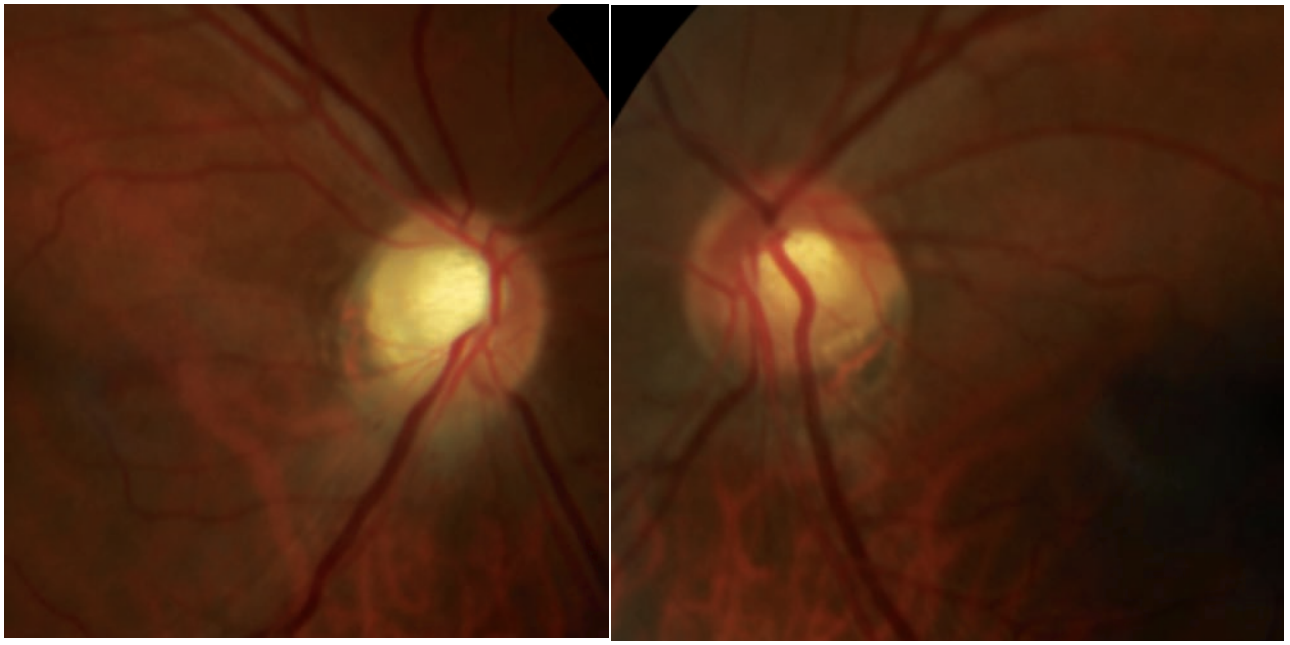


Figure 5B. Optic disc photographs showing right nerve fiber layer swelling, arteriolar narrowing and the development of right optic atrophy. The left optic nerve is tilted with a healthy rim.

nerve fiber layer *(See Figure 5B)*.

The patient was diagnosed with an ischemic optic neuropathy. Over time, the nerve may develop cupping, but the distinguishing feature in this situation is the development of atrophy/pallor. Increased cupping can be seen as sequelae of both arteritic and non-arteritic forms of ischemic optic neuropathy—more often the arteritic form, resulting from temporal arteritis.

Avoiding Being Fooled

A number of general strategies will help ensure that you're not misled by pathologies that can mimic glaucoma.

• ***Get a thorough, detailed history.*** This can be difficult today because we're often limited by time constraints, but many ailments that mimic glaucoma primarily leave clues in the history. Be on the lookout for associated neurologic and endocrine symptoms, e.g., headache; hypopituitarism; the chronicity and pattern of visual loss; past medical history, including trauma; excessively high or low blood pressure; and the patient's diet. Prior blood loss and major surgery may have caused post-surgical ischemic optic neuropathy. A careful review of systems may reveal important information.

Factors such as the family's history of glaucoma and the patient's age are also helpful in determining whether glaucoma is the cause. Patients with non-glaucomatous optic disc cupping tend to be younger than those with glaucoma, in part because some of them have congenital or hereditary problems.[2]

• ***Do a careful exam, and keep an open mind.*** Keep a high level of suspicion when the findings are not typical or what you expect—it's possible that something else is at work. Sometimes ancillary testing, such as optical coherence tomography, may help, but mainly you have to do a thorough examination. Check color vision, scrutinize the optic disc. See whether the pattern of the visual field change that you're seeing correlates with the appearance of the optic disc.

• ***Talk to the patient.*** You really need to do this when you first see the patient, and especially when something doesn't make sense or isn't adding up. What the patient has experienced may contain important clues that you can't detect with an exam.

• ***Note the speed of progression.*** Some lesions will progress more quickly than you would expect glaucoma to progress—or won't change at all.

• ***Don't rely on a single piece of information.*** Visual fields, in particular, can produce results that look like glaucoma when other pathologies are at fault.

• ***When doing a visual field, leave the foveal threshold measurement turned on.*** This may provide useful information about central vision that isn't obvious from simply looking at the overall field.

• ***Check for pallor of the optic nerve.*** This is probably the most important evidence that something other than glaucoma is affecting (or has affected) the optic nerve. Large tumors in the perisellar area, pituitary adenomas or craniopharyngiomas can produce glaucoma-like optic neuropathy. Optic atrophy with pallor of the residual rim is very helpful in distinguishing these from glaucoma. One study that looked at patients with lesions that were compressing on the optic nerve in the chiasm found that pallor of the neuroretinal rim was 94-percent specific for non-glaucomatous cupping.[1]

• ***Remember that a patient may have more than one disease.*** That includes having a tumor in addition to glaucoma. In such cases, it can be very challenging to try to determine what's what and whether there's been progression or not. A multidisciplinary approach to the patient becomes im-portant.

• ***Consider the patient's age.*** Studies have found that cupping in patients under the age of 50 is often due to nonglaucomatous causes.[2] So if the patient is younger, don't just assume that what you're seeing is normal-tension glaucoma. Look for other possibilities.

• ***Note unexpectedly low visual acuity.*** Patients who have non-glaucomatous cupping of the optic nerve tend to have lower visual acuity; studies have found that vision less than 20/40 may indicate non-glaucomatous cupping associated with intracranial masses.[2]

Staying on the Right Track

Of course, not all non-glaucomatous pathologies are equally threatening to the patient's health and/or vision. In conditions such as a hereditary optic neuropathy, a correct diagnosis is important primarily so the patient doesn't have to go through unnecessary testing or procedures, and to help the patient understand what's going on. On the other hand, misdiagnosing an intracranial mass lesion or tumor can have grave consequences. Optic nerve infarction may also have implications for the patient's well-being and general health, especially when vasculitis is involved.

The bottom line is that it's important to keep in mind that not everything that looks like glaucoma is glaucoma. Your patient is depending on you to know the difference. REVIEW

Dr. Levin is an assistant professor of ophthalmology and visual science at Yale University and director of the ophthalmic plastic and orbital section.

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(Continued from page 85)

happen at any age or career stage. "Mid-career physicians have been practicing medicine long enough that some of the novelty has worn off," Dr. Goodman says. "Some of their idealism is being challenged by what they are expected to do. This is a group that is really is need of self-renewal. In our classes, we have had physicians from all stages. There is a certain amount of burnout even among residents."

Dr. Meldrum recommends keeping close tabs on your office environment and quickly addressing any conflicts that arise. "A lot of times, I get called in because the collegial relationships have gotten so petty that it's causing burnout in the office," she says. "People are negatively complaining behind other people's backs about certain staff being treated better than other staff members. If you notice that you are getting up later and later and are not looking forward to going to work, you know that there is growing resistance. When people 'clock watch' in pairs and packs in the practice setting, that's another sign of toxicity. If the office has become a toxic environment, physicians really need to invest in some additional training for everyone at all levels."

Other important ways to avoid burnout are to maintain a healthy work/home life balance and to spend as much work time as possible treating patients, rather than performing administrative tasks. "We know that if you take away autonomy and control from physicians, they do worse," Dr. West says. "So, the idea that physicians should be told when to see patients and how much time they get with each patient doesn't work well. We know that physicians who work themselves into the ground don't have anything left for their patients, so workload is part of this. We know that things that distract physicians from the interpersonal relationships, such as excessive paperwork and excessive administrative burdens, are not good for physician well-being. We know that physicians who work to the point that it detracts from their home lives develop problems. I don't know that anyone has the magic solution to work/personal life balance, but physicians need to be aware of where they are on their own stress curves."

Additionally, physicians need to remember that by taking care of themselves, they are actually caring for their patients. REVIEW

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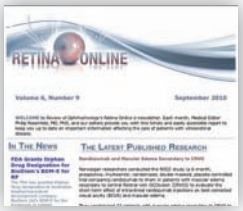

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Current and Potential Uses of Ocriplasmin

A viable pharmacologic option to treat symptomatic vitreomacular adhesion, this drug may offer additional uses.

By Jeffrey S. Heier, MD, Boston

Many attempts have been made to develop a pharmacologic agent that could promote enzymatic vitreolysis. Until now, none had been successful in at inducing both synchesis and syneresis without adversely affecting the retina. Phase III data for ocriplasmin has been published and its Food and Drug Administration approval has confirmed that there is finally a viable pharmacologic option for symptomatic vitreomacular adhesion.

The transparent, gel-like vitreous was once considered innocuous, probably due to being nearly invisible and difficult to examine. However, advances in imaging capabilities have revealed that, in fact, the vitreous is an important ocular structure that plays an integral role in a variety of retinal diseases.[1,2] As humans age, the gel-like vitreous slowly liquefies, the vitreoretinal interface weakens and the vitreous detaches.[3,4] As this process takes place over time, many people will have stages of incomplete dehiscence, producing VMA. If this adhesion does not resolve itself or causes traction that results in visual distortions, it becomes symptomatic VMA. If the disruption to visual acuity is severe enough, it requires treatment.

Ocriplasmin Phase III Data

The Enzymatic Vitreolysis with Ocriplasmin for Vitreomacular Traction and Macular Holes study comprised two separate multicenter, randomized, double-blind clinical trials that treated 464 eyes with VMA with a single, 125 µg intravitreal injection of ocriplasmin *(See Figure 1)* and compared the results to 188 eyes that received a placebo injection. Vitreomacular adhesion resolved in 26.5 percent of ocriplasmin-injected eyes and in 10.1 percent of placebo-injected eyes ($p<0.001$, *See Figure 2*). Nonsurgical closure of macular holes was achieved in 40.6 percent of eyes in the ocriplasmin group, compared with 10.6 percent of placebo-injected eyes ($p<0.001$, *See Figure 3*).

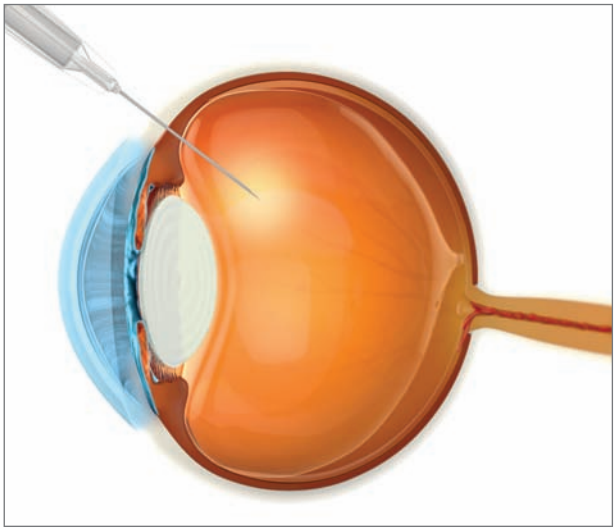

Figure 1. Schematic of an intravitreous injection of ocriplasmin (125 µg) as performed in the Enzymatic Vitreolysis with Ocriplasmin for Vitreomacular Traction and Macular Holes study.[5]

Overall, the safety profile of ocriplasmin was very good. Ocular adverse events occurred in 68.4 percent of eyes in the ocriplasmin group and 53.3 percent of the placebo group. Most of the adverse events were mild in severity and transient, and the difference between groups was driven by temporary adverse

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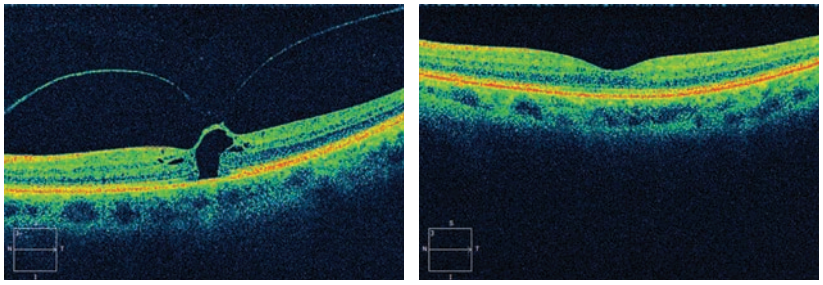

Figure 2. Ocular coherence tomography images prior to (left) and six months following (right) an intravitreous injection of ocriplasmin (125 µg), showing pharmacologic induction of a total posterior vitreous detachment and sustained closure of the full thickness macular hole.

events known to be associated with vitreous detachment. In fact, the incidence of serious ocular adverse events was 7.7 percent in the ocriplasmin group, as compared with 10.7 percent in the placebo group.

There were some instances of acute vision loss associated with an injection, but in all cases vision returned to baseline or an improvement over time. One hypothesis is that acute induction of posterior vitreous detachment caused these changes and that stabilization over time allowed for visual recovery.

Analysis of the subgroups also provides interesting information. In patients with VMA diameter of 1,500 µm or less, 34.7 percent in the ocriplasmin-treated group achieved resolution compared to 14.6 percent in the placebo group *(Ray S. Independent baseline features predictive of pharmacologic VMA resolution in the phase 3 ocriplasmin clinical program. Presented at the American Academy of Ophthalmology Retina subspecialty day. November 2012, Chicago)* In patients with VMA diameter greater than 1,500 µm, resolution rates were 5.9 percent and 0.0 percent, respectively. In patients without epiretinal membrane, 37.4 percent in the ocriplasmin-group achieved resolution compared to 14.3 percent in the placebo group. In patients with epiretinal membrane, the numbers were 8.7 percent and 1.5 percent, respectively. Lens type also seemed to be an influence. Among phakic eyes, 34.2 percent of ocriplasmin-injected eyes achieved resolution of VMA compared with 12.6 percent in the placebo group, while pseudophakic eyes achieved resolution in 13.4 percent and 3.8 percent of the groups, respectively.

Which Patients Can Benefit

There are two primary indications for ocriplasmin. The first is for patients who have mild to moderate symptomatic VMA, and also have good visual acuity. Patients may be experiencing metamorphopsia, but test 20/40 or better on a Snellen visual acuity chart. Metamorphopsia can be tremendously disabling to functional capabilities, especially for those whose work requires them to read frequently or perform detailed visual tasks. However, vitrectomy surgery would not be a viable option for this group, because their vision is too good to risk the complications associated with surgery, including cataract formation, retinal tear, retinal detachment, bleeding and endophthalmitis.[6] Historically, disease management for these patients has been careful observation, hoping the VMA would spontaneously resolve. However, the literature shows that many do progress and lose vision.[7] The FDA approval of ocriplasmin provided surgeons with a minimally invasive means of treating these patients who previously had no viable option.

The second set of patients are those with more moderate VMA whose visual acuity has deteriorated to 20/80 or worse, sufficient to justify surgery. Ocriplasmin is the ideal first choice in these patients. I have found that it does not require drops before or after, nor any eye patch, and the patient need not be in the prone position. Administering the injection is very straightforward and patients go home shortly thereafter. It is important to note that the large majority of responders demonstrated resolution of VMA by day seven, and all did so by day 28 of the study.

An example of the significance of this is with macular hole. Two main factors in the success of surgery for macular hole are baseline vision and size; thus delaying surgery could have a negative impact on the final prognosis. Patients and physicians will know quickly if the injection has worked, allowing them to proceed to surgery with minimal to no delay if necessary. In addition, a lack of response to the injection has no influence on the success rate of surgery.

During the preparation for similar clinical trials, I began to evaluate how many patients would fall into these two groups. I was surprised to realize that a small but steady number of candidates came into my clinic each week who might benefit from this treatment modality. These were patients who were either symptomatic from the VMA or vitreomacular traction, or suboptimally responsive to treatments for underlying disease (such as anti-VEGF treatment for neovascular AMD or diabetic macular edema). We do not know if the patients with underlying disease and VMA will respond better following this treatment, but it is a reasonable approach to relieve the VMA in an

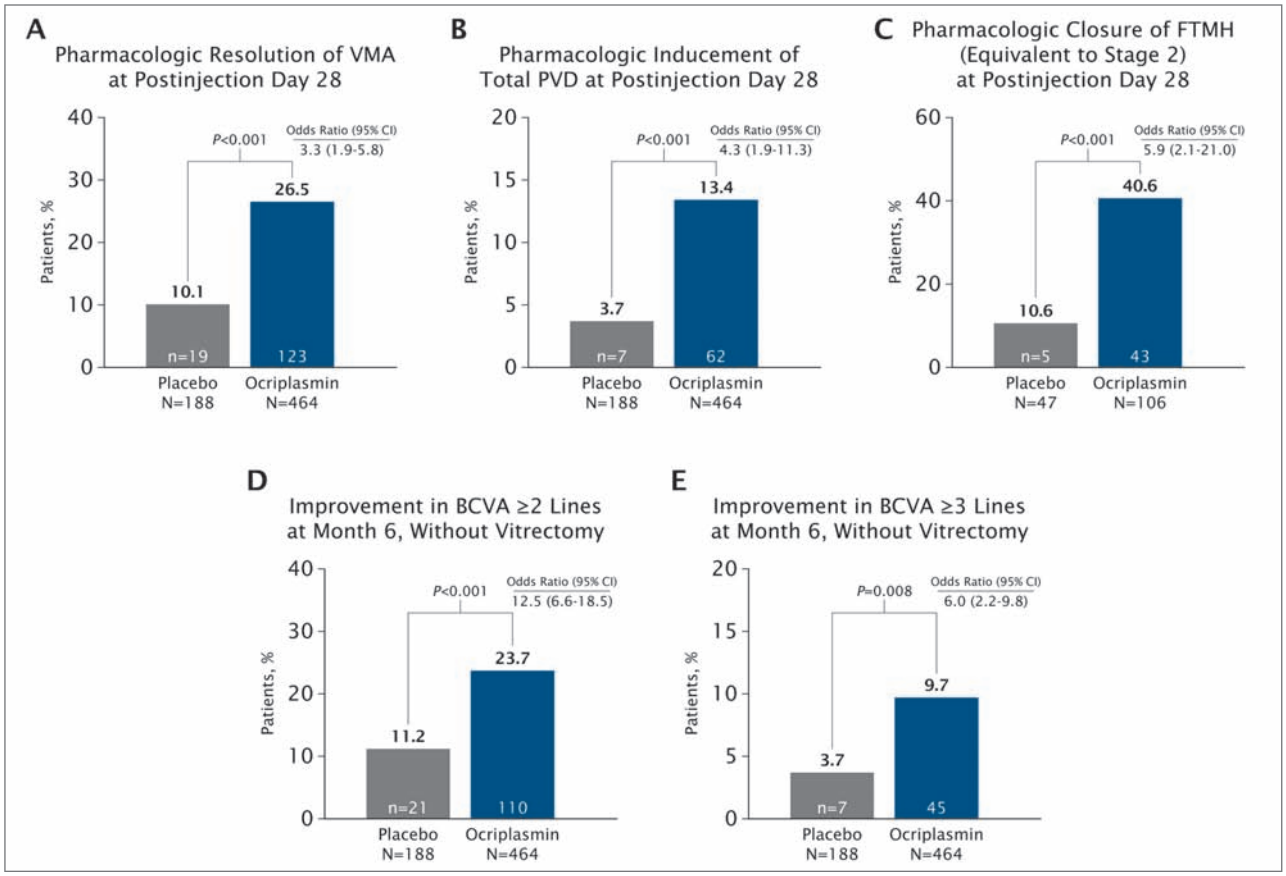

Figure 3. Primary and secondary endpoints from the Enzymatic Vitreolysis with Ocriplasmin for Vitreomacular Traction and Macular Holes study.[5]

attempt to improve treatment response. Surgery is only a last-ditch option, as the durability of intravitreal injections decreases following vitrectomy.[8-11] We do know that it is less effective in patients with epiretinal membranes. When patients were stratified, 37.4 percent of ocriplasmin-injected eyes and 14.3 percent of placebo-injected eyes achieved resolution of VMA when no ERM was present. This is in stark contrast to the 8.7 percent and 1.5 percent of eyes with ERM, respectively, that achieved resolution of VMA.

Future Indications

The potential for enzymatic vitreolysis presents an enormous shift in the current treatment paradigm, and I believe that our early use will be in the groups described above. We are still learning to identify VMA and recognize how many disease states it impacts. Going forward, we will formally investigate the anecdotal claims of the positive influence of resolution of VMA on response to anti-VEGF treatments. As we expand our use of ocriplasmin, we may modify the delivery method to achieve even greater efficacy at inducing resolution of VMA or full posterior detachment. REVIEW

Dr. Heier is the director of the Vitreoretinal Service at Ophthalmic Consultants of Boston; and the director of retinal research and co-director of the vitreoretinal fellowship at OCB/Tufts Medical School. He is a scientific consultant to Thrombogenics, Genentech and Regeneron. He also receives research income (through Ophthalmic Consultants of Boston) from Genentech and Regeneron. Contact him at jsheier@eyeboston.com.

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New Therapies: Of Kinases and Cascades

How various kinases act within the eye and the potential for targeting them to produce therapeutic results.

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

In last month's column we discussed the role of the four Janus kinases, or Jaks, in cytokine signaling, and described how inhibition of this kinase activity has become a major goal of drug discovery efforts in ophthalmology and other specialties. From the Human Genome Project we know there are about 580 kinases in the human body, and many of these function at critical signaling junctions in development, homeostasis and reaction to trauma or other bodily insults.[1] In the response to allergen exposure, for example, a series of kinases participates in the initial orchestration of an immunological response to the foreign invasion.[2] One of these, spleen tyrosine kinase, is a key target of current drug development efforts aimed at improving therapies, including treatments for ocular allergy and inflammation. The ever-growing number of biologics and small-molecule drugs designed to interfere with kinase signaling underscores the importance of this cadre of therapeutic agents.

This month, we'll examine the challenges to development of kinase-targeted drugs such as Syk inhibitors, and describe a handful of other kinase targets of particular relevance to ophthalmologists.

Why Target Kinases?

Kinases are enzymes that transfer phosphate groups from an ATP donor to a target protein, sugar or fat molecule.[1-3] In some cases, these transfers are part of a metabolic pathway such as the breakdown of glucose, but in many others the addition of the phosphate molecule acts to change the function of the kinase substrate. Often this change dramatically alters the activity of the substrate target, switching it from an inactive to an active state. Phosphorylation ignites the breakdown of glucose in glycolysis, facilitates muscular cross-bridge formation during contraction and mediates hundreds of hormone and neurotransmitter responses, from epinephrine and insulin to VEGF. All these phosphorylation-based events require the enzymatic participation of one or more kinases.

In terms of intracellular signaling pathways, there are many examples of kinase cascades, which are a succession of enzymes activating each other in turn. This stepwise process in signaling provides opportunities for integration of cell inputs, as well as a degree of signaling redundancy. From our point of view, it presents potential targets for therapeutic intervention and physiologic modulation. As a group, kinases represent the single most important class of enzymes, in terms of their role in cell signal transduction.[3]

One aspect of kinase function that is central to their role is their reversibility: There is a corresponding phosphatase poised to turn off the phosphorylation signal for almost all kinases. There are many examples of physiological processes activated by phosphorylation, and inactivated by dephosphorylation. In some cases, the phosphatases may even be a more attractive alternative to the kinases with regard to therapeutic modulation.[4]

The shared characteristics of different kinases are important because the single biggest hurdle in development of kinase-targeted therapeutics is specificity. This is particularly true for drugs that compete with ATP bind-

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ing, since this is a shared function of all kinases. The largest class of kinase inhibitors, termed type I inhibitors, all act by interfering with binding of ATP. Not surprisingly, many kinases share similar binding site characteristics and so the drugs targeted at them often display a lack of kinase specificity. Future inhibitor development may focus on allosteric sites, or on recognition of sequences surrounding the sites where phosphates are added, to improve drug selectivity.[3,4]

The Flow of Allergic Signaling

One of the best examples of a kinase signaling cascade underlies the acute allergic reaction. In the mast cell, cross-linking of the $F_c\varepsilon$ receptor with antibody-antigen complexes trips a switch eventually leading to calcium entry and degranulation. This path involves at least five kinases acting in concert to convert detection of a foreign antigen into histamine release *(See Table, right)*.[5] By mapping the path of the degranulation signal through the mast cell it's possible to compare and contrast the benefits and limitations of targeting each step for potential therapeutic intervention.

Following the initial encounter with antigen on the mast cell surface, one of the earliest measurable responses is the activation of Lyn kinase, an enzyme that is physically associated with the antibody-receptor complex on the intracellular side of the cell membrane. Genetic deletions of Lyn kinase eliminate the ability of antigen to trigger histamine release or mast cell degranulation but, paradoxically, drugs that inhibit Lyn kinase activity actually increase mast cell degranulation responses. This is because in addition to being an early step in mast cell activation, Lyn is also part of the "off switch" for degranulation: It starts a separate signal cascade involving the phosphatases that ultimately reverse the kinase-mediated secretion.

Mast Cell Degranulation Pathway: A Multi-kinase Cascade

Kinase/ other signal	Activated by:	Tissue expression	Inhibition blocks degranulation?**
Lyn	$F_c\varepsilon$ receptor/IgE	hematopoietic cells; neurons; liver	no
Syk	Lyn phosphorylation	hematopoietic cells	yes
PI3K	Syk phosphorylation	ubiquitous	yes
Btk	PI3K* phosphorylation	hematopoietic cells	yes
phospholipase	inositol phosphates	ubiquitous	yes
PK C	lipids	ubiquitous	yes
Ca2+ release	inositol phosphates, lipids	ubiquitous	yes

Note: Kinases typically target multiple substrates in addition to those listed. * PI3K does not directly phosphorylate Btk. ** Blocking defined as a >75-percent reduction in degranulation.

Other players in this kinase cascade process are unsuitable therapeutic targets for other reasons. Phosophoinotiside 3-kinase and protein kinase C are each members of kinase families expressed in many cell types, so specificity is likely to be an issue with any inhibitors of these drugs (inhibitors of these two kinase families are used for advanced stages of some cancers). In contrast, two hematopoietic-cell specific kinases, Syk and Bruton's kinase, are the best targets based upon tissue specificity and importance to the degranulation pathway.[5] Btk is found primarily in B cells and in T cells, and is an important regulator of B cell maturation. While there is less data on this enzyme, preliminary studies suggest inhibitors may be effective therapeutically against inflammatory diseases such as rheumatoid arthritis.[6,7]

Inhibitors of Syk kinase are in development for a number of diseases, including heparin-induced thrombocytopenia and lymphocytic leukemia.[8,9] These conditions involve antigen or B cell signaling, pathways similar to those seen for mast cell degranulation. The demonstrated efficacy of Syk inhibitors in these studies suggests that these same compounds (or other Syk inhibitors) can be effective when used to disrupt Syk signaling in other settings, including ocular allergy.

An Inhibitor for All Conditions?

In surveying recent drug discovery work on protein kinases, there is a recurring theme in which initial development of inhibitors addresses a specific type of cancer, especially cancers of the blood-forming tissues and those that are relatively intractable to current treatments. Researchers then take candidate therapeutics from these efforts and repurpose them to treat other disorders. Interest in these compounds for ocular diseases is just beginning to gain traction, and it may not be possible to identify the

best candidates from existing studies alone. Preclinical models of various ophthalmic disorders will provide key guidance as this process moves forward.

Last month we described the key role of the Jak kinases in cellular inflammatory signaling. Another pro-inflammatory target for kinase inhibitors is the nuclear factor κB pathway used by cytokines, including tumor necrosis factor-alpha, interleukin-2 and interleukin-6. An inflammatory gene expression profile is activated when kinases such as IκK activate the κB factor, and blockade of this kinase has demonstrated anti-inflammatory effects in preclinical models of endotoxin-induced uveitis.[10]

One area of interest for kinase inhibitors is as alternative anti-angiogenic therapies for ocular diseases. Drugs such as Imatinib, Sorafenib or Sunitinib all inhibit a range of growth-promoting tyrosine kinases including vascular endothelial growth factor-receptor kinases, and were originally developed to treat late-stage renal, liver and lung cancers. Preclinical studies suggest such drugs may be useful, either in combination or as monotherapy, for reducing corneal or retinal neovascularization.[11] One or more of these multikinase inhibitors may also be useful in treatment of ocular melanomas.[12]

Many ophthalmic diseases involve a premature, pathologic degeneration of retinal neurons, and there has been great interest in the role of kinase-mediated signaling in apoptotic, or programmed, neuronal cell death. A recent study used genomic profiling to implicate leucine zipper kinases in retinal cell apoptosis.[13] Another kinase, first identified as the mammalian target of rapamycin, or mTor, has since been shown to play a key role in cell development and survival.[14] A handful of mTOR inhibitors, such as Everolimus, have been approved as anti-cancer therapies and several of these are currently in clinical trials as therapies for advanced AMD.

Another aspect of mTOR signaling relates to our previous description of kinase cascades, those signaling pathways in which one kinase activates a second, which then activates a third, and so on until the ultimate target is reached. Interestingly, in some cells mTOR functions in a cascade that leads from PI3K to protein kinase B to mTOR. Thus, depending on tissue expression, there is overlap between the cell survival pathway of mTOR and the degranulation pathway described for mast cells, that includes Syk kinase. This type of overlap is the rule, not the exception, in most cell regulatory paradigms.

Many ophthalmic diseases involve a premature, pathologic degeneration of retinal neurons, and there has been great interest in the role of kinase-mediated signaling in apoptotic, or programmed, neuronal cell death.

As with other new therapeutics, exploring ophthalmic indications for these kinase inhibitors involves new formulation development and optimization of topical or intravitreal delivery methods. Even with established safety profiles, there is still work to be done before any kinase inhibitors will be FDA-approved for ophthalmic use. However, it's important to realize that Syk inhibition of the degranulation signal cascade represents more than just another new anti-histamine or anti-inflammatory; these drugs would prevent the initial release of histamine and other mast cell allergic mediators, effectively stopping ocular allergic disease before it has a chance to start.

For patients suffering from conjunctivitis, keratoconjunctivitis, vernal keratoconjunctivitis and other chronic, inflammatory ocular surface conditions, halting the flow of the allergic kinase cascade may be a game-changing therapeutic advance. REVIEW

Dr. Abelson is a clinical professor of ophthalmology at Harvard Medical School and senior clinical scientist at the Schepens Eye Research Institute. Dr. McLaughlin is a medical writer at Ora Inc.

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Reversing LASIK and Premium IOL Woes

Taking a logical, stepwise approach and fighting for every line of visual acuity will pay dividends for you and your patients.

Arun Gulani, MD, Jacksonville, Fla.

In surgery, as in life, the mind truly controls the body, and I teach my fellows all the time: "Your hands cannot do what your mind has not decided. Performing surgery should be a breeze—it's the preoperative planning that should exhaust you." If a patient is referred to you with a post-refractive surgery complication and you view his case as a difficult problem for which there is only one solution, such as corneal transplant, then you'll never see the potential for better vision by way of a custom-designed procedure. If, however, you can change your mindset and see a complication as an opportunity to improve vision, then myriad options will open themselves up to you. Here, I'll explain how to approach complications with a different point of view.

Formulating a Plan

The basis of my approach to managing complications is the attitude that every complication can be corrected to 20/20 vision, what I call Best Visual Potential. It's not good enough to just make an attempt to correct a complication and leave the patient with somewhat better vision. You have to aim to correct the patient to the point where he's truly seeing 20/20 or better. In that way, not only are you taking him from a bad situation to a satisfactory one, you're taking him to an elevated level of vision. Along these lines, you have to constantly battle the urge to just do a default procedure such as penetrating keratoplasty—the procedure of least resistance—and be done with it. Though PK may be easy for you, it's suboptimal for the patient, leaving him with less than 20/20 vision and a full-thickness wound that could potentially open up at any point during his lifetime. PK is the last resort.

Also, let the patient know your plan. By bringing a patient in on your surgical plan, he becomes your partner. He'll also be impressed that even though you have access to textbook techniques such as PKP or lens exchange, you'd rather fight for his best vision using a plan that's custom designed for his situation.

To help systematically approach complications, I created an algorithm, I refer to as the Five-S system:

- ***Sight.*** Is the patient correctable to 20/20 with glasses and/or hard contact lenses?
- ***Scar.*** Is there a scar involved?
- ***Strength.*** This point asks whether there is a thickness problem. Do you need to add tissue as in a lamellar keratoplasty (for ectasia), or remove it as in epikeratophakia?
- ***Shape.*** Is the corneal shape affected? This is central to everything we do in refractive surgery.
- ***Site.*** Is the problem central or peripheral?

There is no case that can't fit into this 5S system, and the evaluation of these 5S attributes will unfold the blueprint for a unique approach to each case, either single or staged, which will move towards the patient's BVP.

Putting the Plan into Action

Once you see a complication as a situation that needs to be dealt with rather than as an error or a headache, and approach it in a logical fashion, you'll find things will become more manageable. Here are some examples of approaching common complications with this mindset.

- ***Postop corneal scar.*** When a patient presents with a scar, it's important to look at it from her perspective. She

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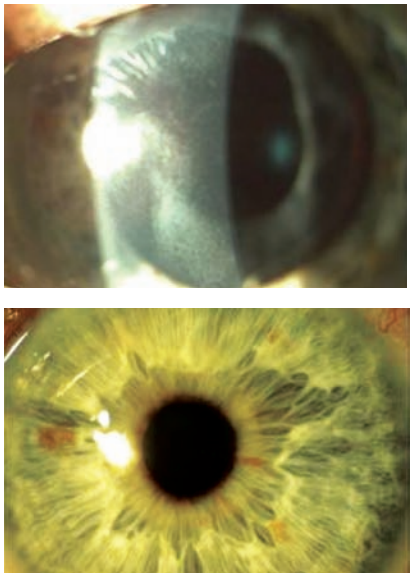
doesn't come in and say, "Hey, doc, I've got a corneal scar to deal with." Instead she simply says, "I can't see." The patient is asking for vision. This is why I emphasize the use of PRK, not PTK, for scars. PTK is the wrong concept because with it, you dig at the scar but damage the cornea's shape. Since vision is determined by corneal shape, it's better to shape the cornea with a PRK. The intended, fortunate side effect of this shaping is that the "shavings" that result from it are the scar tissue. I have numerous patients in whom you may still see the residual corneal scar but who see 20/20.

For the sake of simplicity, I divide corneal scars into "on-cornea" and "in-cornea." An on-cornea scar is above Bowman's and causes a camouflaged shape resulting in false topography and refraction, such as high, irregular astigmatism on the order of 6 or 7 D. The in-cornea scar has become part of the cornea, such as in cases of herpetic keratitis, so it contributes to the actual topography and refraction. For on-cornea scars, you can peel away the scar under the laser and proceed with refractive PRK. For a scar that's in the cornea, you can do refractive laser through-and-through using that refraction as your guide.

A 68-year-old patient came to me with a post-RK cornea scar. Every doctor he had been to told him he needed a penetrating transplant. However, using my 5S system to approach the scar and shape, I made a staged plan. Following my plan, I was able to easily peel the scar under the laser. Following that, I performed a myopic ablation and the patient immediately began crying beneath the laser, since he could finally see out of that eye. Since he was 68, after a period of stabilization, I performed cataract surgery and implanted a toric lens, and the patient now sees 20/20. Both surgeries were topical and brief and the eye looks as if no one has ever touched it.

• ***Post-LASIK ectasia.*** Though corneal ectasia isn't trivial, it shouldn't be viewed as a railroad that runs straight to a PK. In many cases, ectasia can be viewed as a case of a thin cornea with astigmatism in the 5S system. In ectasia cases in which the astigmatism is the main component but corneal thickness isn't too bad, you can place Intacs in a directional pattern using an asymmetric combination, with a thick and a thin segment, including superficial and deep channels associated with a steep-axis technique. After about three months, you can perform PRK to bring the patient to his BVP.



A multifocal IOL patient with a corneal scar post-laser refractive surgery and 20/200 vision (top) was brought to 20/20 vision with laser and a piggyback lens (bottom).

However, if the patient has a very thin cornea, such as less than 200 µm, and maybe also has a scar, you can instead perform lamellar keratoplasty (in 5S terms, you'd add "Strength" and remove "Scar"). With this approach, you remove the LASIK flap and discard it and place the lamellae of a donor cornea that's thicker than that being replaced. A thicker donor is preferable because it will deturgesce with time and also provide tissue for future laser PRK ablation. Six months later, return to the eye and do a PRK to get the patient to his BVP of 20/20.

• ***Multifocal intraocular lens nightmare.*** You can also take a stepwise approach to managing postop issues with premium IOLs. You may perform what I call "Optical Manipulation" with all types of IOLs, ICL, etc., and then use the cornea as a final vision rehabilitative platform. Alternately, you can clear the cornea to lead to more accurate biometry and then perform lens-based surgery.

For example, in one case I dealt with, a surgeon implanted a multifocal ReSTOR lens, but the patient ended up with a hyperopic surprise. The surgeon attempted to correct the refraction with LASIK but a corneal scar resulted, which the surgeon then tried to remedy with more laser, making the refraction worse. The surgeon also performed a YAG capsulotomy. When the patient presented to me, she was very depressed, could see only 20/200 best-corrected out of the eye, and wanted to sue the original surgeon.

Approaching the case, I saw that the scar was on-cornea, with false irregular, hyperopic astigmatism. I performed a laser ablation first to take care of the scar to achieve a clear and "measurable" cornea, and then waited three months to observe refractive stability at +6 D with 20/25 best-corrected vision. It's at this point that you have to not settle for satisfactory, but push yourself to give the patient the vision that she was used to or better. Given this high hyperopia, I wanted a lens-based surgery, but since a YAG had been done the ReSTOR lens removal wouldn't make sense. Therefore, I decided to leave the lens in place and add a piggyback lens on top of it, which brought the patient back to 20/20 vision, and lifted her spirits in the process.

In the end, treating complications is all about inflicting the least trauma (surgically and psychologically) and getting the BVP. REVIEW

Dr. Gulani is in private practice.

IOP Asymmetry in Diagnosing Glaucoma

Inter-eye asymmetry of intraocular pressure is a common finding in patients with glaucoma; there is a direct relationship between the amount of IOP asymmetry between fellow eyes and the likelihood of having glaucoma.

In a collaborative, retrospective study, former Wills Eye Institute fellows collected single pretreatment measurements of IOP on patients diagnosed as having definite glaucoma (n=326) based on characteristic optic nerve damage and confirmatory visual field damage. Controls were patients with a normal eye examination (n=326) who had normal-appearing optic discs and no apparent glaucoma, or a normal eye examination in association with refractive error or cataract.

Intraocular pressure asymmetry is a risk factor for having glaucoma (risk: 2.14; 95 percent CI, 1.86-2.47; $p<0.001$). Absence of IOP asymmetry between the fellow eyes is associated with a 1 percent probability of having glaucoma. A difference of 3 mmHg is associated with a 6 percent probability and a difference of >6 mmHg with a 57 percent probability of having glaucoma. The association between IOP asymmetry and glaucoma status is significant for subjects with both elevated IOP ($p=0.014$) and statistically normal IOP (maximum IOP ≤21 mmHg; $p<0.001$).

J Glaucoma 2013;22:216-218.
Williams A, Gatla S, Leiby B, Fahmy I, et al.

IOP During Femtosecond Pretreatment of Cataract

An interventional prospective study from the Launceston Eye Institute in Tasmania concludes that femtosecond laser pretreatment is associated with a mean peak increase in intraocular pressure of 18.5 mmHg from baseline and appears to be safe and well-tolerated.

Femtosecond laser pretreatment was performed using the Catalys Precision Laser System with Liquid Optics Interface. The IOP was measured using an iCare PRO rebound tonometer during different stages of surgery and analyzed by number of docking attempts, vacuum time, treatment time and central corneal thickness.

The mean baseline IOP in the 25 study eyes was 17.5 ±2.5 mmHg. During vacuum application, the mean IOP rise was 11.4 ±3.3 mmHg. Peak IOPs were recorded immediately after laser capsulotomy and lens fragmentation (mean: 36.0 ±4.4 mmHg; mean increase from baseline 18.5 mmHg) and remained above baseline two minutes after the procedure (26.6 ±4.0 mmHg; $p<0.001$). Multiple regression analysis found no association between IOP rise and number of docking attempts, vacuum time, treatment time or CCT.

J Cataract Refract Surg 2013;39:339-342.
Kerr N, Abell R, Vote B, Toh T.

Changes in PEDs a Predictor for Anti-VEGF Retreatment

Research from the Bascom Palmer Eye Institute suggests that quantitation of the change in retinal pigment epithelial detachment volume and area may be useful in determining when to retreat eyes undergoing spectral domain optical coherence tomography-guided, as-needed, anti-vascular endothelial growth factor therapy.

Fourteen eyes from 14 patients with vascularized PEDs undergoing SD-OCT treatment with anti-VEGF drugs were retrospectively identified. The decision to retreat these cases was based on qualitative assessments of fluid in the macula. SD-OCT images from visits in which treatment was withheld were retrospectively analyzed, and a novel algorithm was used to measure the area and volume of PEDs at these visits.

Retreatment was withheld at 57 visits. When the SD-OCT algorithm was used to evaluate the scans from these visits, the PED volume increased at eight visits. At all of these eight visits, a treatment was needed at the next follow-up visit. For the remaining 49 visits in which treatment was withheld, the PED volume did not increase and no treatment was needed at the next follow-up visit.

Retina 2013;33:459-466.
Penha F, Gregori G, Filho C, Yehoshua Z, et al.

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SAVE THE DATE

2013 CALENDAR

CONTINUING PROFESSIONAL EDUCATION

Dear Residency Directors,

We would like to invite you to review this Save the Date Calendar for third-year residency programs we are planning for 2013. Each program offers a unique educational opportunity for third-year residents by providing the chance to meet and exchange ideas with some of the most respected thought leaders in ophthalmology. The programs are designed to provide residents with a state-of-the-art didactic and wet lab experience. The programs also serve as an opportunity to network with residents from other programs. After reviewing the material, it is our hope that you will select and encourage your residents to attend these educational programs.

Best regards,
Review of Ophthalmology

August 2-3, 2013
Fort Worth, TX

Course Director:
Tommy Korn, MD
Attending Ophthalmologist, Sharp Rees-Stealy Medical Group, Sharp Memorial Hospital, San Diego, CA

August 9-10, 2013
Fort Worth, TX

Course Director:
James Katz, MD
Midwest Center for Sight Des Plaines, IL

September 27-28, 2013
Fort Worth, TX

Course Director:
Mitchell A. Jackson, MD
Founder/Medical Director, Jacksoneye Chicago, IL

SAVE THE DATE
VITREORETINAL FELLOWS
August 16-18, 2013
Chicago, IL

Course Director:
William F. Mieler, MD
Professor of Ophthalmology, Vice Chairman and Director of the Ocular Oncology Service, University of Illinois Eye and Ear Infirmary

SAVE THE DATE
CORNEA FELLOWS
October 11-12, 2013
Fort Worth, TX

Course Director:
Natalie Afshari, MD
Chief of Cornea and Refractive Surgery and Professor of Ophthalmology at Shiley Eye Center, University of California, San Diego.

SAVE THE DATE
GLAUCOMA FELLOWS
October 18-19, 2013
Fort Worth, TX

Course Director:
Kuldev Singh, MD
Professor of Ophthalmology and Director of Glaucoma Service at the Stanford University School of Medicine, California

For more information and to register:

Visit: www.revophth.com/ResFellowEdu2013

Email: ReviewLogistics@Jobson.com Call: Denette Holmes 866–627–0714

There is no registration fee for these activities. Air, ground transportation in Fort Worth, hotel accommodations and modest meals will be provided through an educational scholarship for qualified participants.

These activities have been approved for *AMA PRA Category 1 Credit(s)™*.

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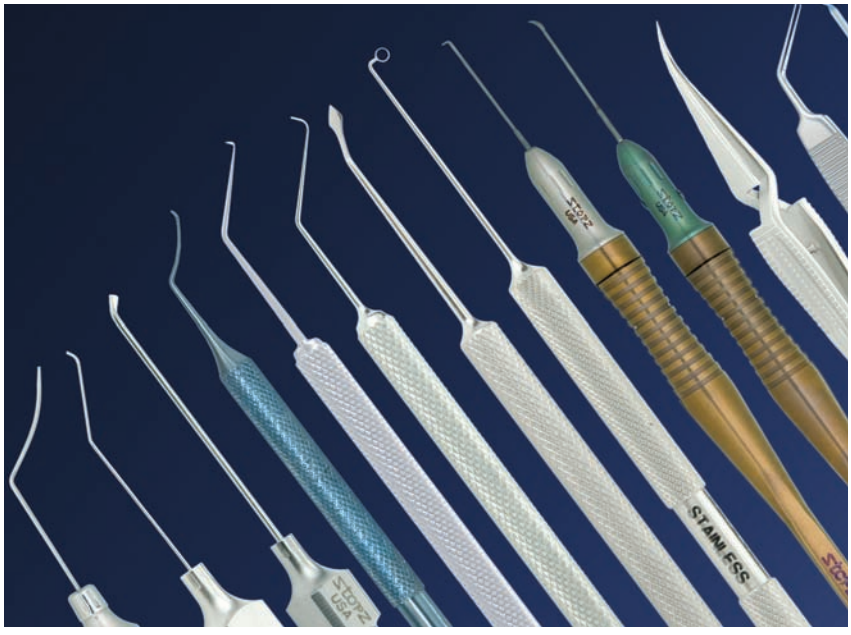
B+L Offers Femto Cataract Surgical Set

Bausch + Lomb Storz says it is the first company to offer a Femtosecond Cataract Instrument Set designed specifically to be used with femtosecond laser platforms. Developed in collaboration with some of the world's leading femtosecond laser surgeons, the unique 13-product set includes: a CapsuleGuard I/A Handpiece; a Slade Laser LRI Dissector; a Hu Capsule Polisher; a Nichamin 27-Gauge Hydrodissection Cannula; a Slade Vertical Nucleus Cracker; a Slade Coaxial Horizontal Chopper; an Utrata Capsule Cap Removal Forceps; a Weinstock Wound Dissector; a Hu Femto Incision Spreader; a Hu Femto Hydrodissection Cannula; a Daya Femto TransLens Hydrodissection Cannula; an Osher Double-Ended Femto Wound Dissector; and a Hu Femto Side-Port Chopper.

The development of the instruments in the suite was inspired by observations made by the surgeons during their femtocataract procedures and pursued through close interaction with the instrument design team at Bausch + Lomb Storz.

The 13 new femtosecond cataract instruments are available in the United States and will soon be introduced in markets outside the US. All instruments with the exception of the CapsuleGuard I/A Handpiece are reusable. They can be ordered individually or as a set. Information on the complete range of Bausch + Lomb Storz instruments is available at StorzEye.com, or by calling customer service at 1 (800) 338-2020. If you have an idea for a new surgical instrument, contact the company to learn more about its New Product Development Program.



Job Recruiter Local Eye Site Acquires EyeBuzz

Ophthalmic recruiting service Local Eye Site has acquired EyeBuzz (eyebuzz.net). Headquartered in Boston, EyeBuzz provides online job search and recruitment services primarily for ophthalmic technicians/assistants, ophthalmic nurses, ophthalmologists and opticians.

Since 2007, Local Eye Site has been dedicated to connecting the eye-care industry in order to create one central and powerful online recruiting portal for all eye-care professionals. Connecting more than 25 industry-specific partners through its Power Network, LES partners with the leading publishers and professional organizations in eye care to reach all segments of the eye-care industry. (*Review of Ophthalmology* parent company, Jobson Healthcare Information, owns a minority interest in Local Eye Site.) For more information, visit localeyesite.com. REVIEW

This article has no commercial sponsorship.

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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ALLERGAN®

(Continued from page 64)

entire graft detachment or limitation in visual restoration, say researchers at the University of Cologne, Germany.

Ten patients (eight female) at the university were examined three to four hours, five to seven hours and seven to nine hours after DMEK surgery using both a time-domain OCT and a spectral-domain OCT. Parameters included presence, localization and potential reduction of graft detachment.

In all patients and at all time points, localized graft detachment and subtle, clinically undetectable interface fluid were observed. Graft detachments of differing degrees were localized at different positions of the cornea in between the examinations. Detachments were better visualized by SD OCT than by TD OCT.

Inconsistent localization of detachments is thought to be caused by interface fluid shift due to air bubble movement within the eye. These findings suggest considerable tissue rearrangements early after DMEK despite nearly complete anterior chamber air filling.[3096]

Researchers from the University of California, Irvine, have devised a "mini-bubble" technique that may be useful in both deep anterior lamellar keratoplasty and in donor tissue preparation for DSAEK. It features wide pulse spacing and very low pulse energy delivered in multiple passes, resulting in a smoother stromal plane in the deep cornea, compared to tight spot spacing and higher pulse energy levels.

Ten fresh human corneal scleral donors were mounted on artificial anterior chambers and exposed to femtosecond laser dissections 30 to 50 µm anterior to Descemet's membrane using an iFS 150 kHz laser. Variables studied were spot separation, pattern of laser scanning and pulse energy. Key outcomes were ease of tissue separation, gross inspection of the tissue bed, SDOCT and Trypan blue/alizarin red staining of the endothelium.

Separation of the tissue plane was easiest with a combination of close spot separation (4x4 µm) and high pulse energy (3.5 microjoules). The smoothest bed was obtained with wide pulse spacing (10x10 µm); low pulse energy just higher than threshold (0.4 5 to 0.6 µJ) and eight alternating raster and spiral passes, rotated 45 degrees between each pair of passes. OCT revealed stromal separation either at or slightly anterior to Descemet's membrane. Staining showed no evidence of endothelial injury.[3100]

Recognizing that DSAEK causes a transient increase in recipient corneal hydration, surgeons in Aarhus, Denmark wanted to learn whether structural changes in the recipient cornea also occur.

For at least one year after DSAEK, they followed 76 patients treated for endothelial dystrophy. At all visits, they measured central corneal thickness and calculated the difference in CCT from three days to one year postop (ΔCCT=CCT3days–CCT-1year) as a crude measure of postoperative corneal edema. At their latest visit, patients were examined with SD-OCT to determine recipient corneal thickness (RCT). SD-OCT was also used to determine CCT in a group of normal corneas.

From one to six years after DSAEK, RCT averaged 490 ±29 µm, which was significantly less than the CCT of 531 ±18 µm that was observed with SD-OCT in normal corneas ($p<0.001$). RCT measured 487 ±28 µm after one year (n=43); 491 ±29 µm after two years (n=24); and 505 ±26 µm after three to six years (n=9), with a slight but significant increase over time. Correlating RCT with ΔCCT also showed a significant correlation between postop corneal edema and RCT, with more edema causing the recipient cornea to become thinner over time ($p=0.006$).

The correlation between postop edema and RCT may suggest that wash-out of stromal ground substances induce the thinning, with the subsequent gradual increase in thickness being caused by resynthesis of extracellular material, the authors hypothesize. However, the long-lasting nature of the observed changes could also suggest underlying structural abnormalities in endothelial dystrophy, they conclude.[3101]

Miscellaneous

In evaluating the product besifloxacin ophthalmic suspension, 0.6%, researchers have identified a number of new bacterial conjunctivitis pathogens. The study compared the prevalence and distribution of ocular pathogens encountered across five multicenter, randomized, double-masked, clinical studies evaluating besifloxacin in 2009 to 2011 versus 2004 to 2007.

A total of 2,348 baseline isolates from 3,379 patients were collected; 1,324 recovered in 2004 to 2007 and 1,024 in 2009 to 2011. Recovered isolates across all treatment groups were evaluated for baseline frequency, microbial eradication and antimicrobial susceptibility profiles.

Fifteen new bacterial conjunctivitis pathogens not recovered from study eyes between 2004 and 2007 were isolated in the later studies, including the potentially emerging pathogens *Dolosigranulum pigrum* (n=26) and *Corynebacterium accolens* (n=5). The five most frequently isolated species or taxonomic groups remained the predominant bacterial conjunctivitis pathogens across all five besifloxacin studies. Microbial eradication rates of pathogens isolated in besifloxacin-treated subjects in the more recent studies included 100-percent eradication of *D. pigrum*

(14/14), *Acinetobacter calcoaceticus/baumannii* complex (3/3), and *Elizabethkingia meningoseptica* (2/2).

The most prevalent bacterial conjunctivitis pathogens remained consistent over the seven-year period; however, additional pathogens have emerged as causative agents of bacterial conjunctivitis. This emergence of additional pathogens may be due to improved methods for the identification of bacterial isolates, or changes in human or bacterial ecology that promote the spreading of these species to the ocular surface, the authors say.[5450]

Corneal decompensation is a known risk of anterior chamber implantation of older glaucoma shunts, but far less is known of this risk with Ex-Press shunts. In what they call the first case series to document corneal decompensation after Ex-Press placement, surgeons from New Orleans and Italy report that DSAEK surgery can be successful in treatment of corneal decompensation after Ex-Press valve placement.

The study reviewed all cases of DSAEK performed since 2005 that had prior Ex-Press shunt surgery from one corneal surgeon. Ocular history including number of surgical procedures, intraocular pressure and BCVA before and after Ex-Press surgery and before and after DSAEK, as well as surgical complications were reviewed.

The average age and average IOP prior to Ex-Press shunt placement was 63.8 years ±3.4 standard deviation and 24.6 mmHg ±0.4 SD respectively. BCVA prior to Ex-Press shunt placement was logMAR 0.64 ±0.16 SD. The average postoperative IOP after Ex-Press shunt was 16.8 mmHg ±1 SD. The mean number of surgeries prior to DSAEK was 2.8 ±1.64. Four of the five patients with corneal decompensation after Ex-Press placement had one or more prior filtering procedures with a mean of 1.75 ±0.83. One of these patients also had two prior failed Ex-Press shunts. Vision decreased to count fingers in all patients before DSAEK. The average age at which significant corneal decompensation was identified and DSAEK was performed was 66 years ±3.2 SD with average time of onset of corneal edema after Ex-Press shunt of 2.2 years ±0.44. The average BCVA after DSAEK was 0.78 ±0.18 with decreased vision resulting from optic nerve damage in all cases. All corneas remained clear. IOP was controlled in four patients; one required cyclocryotherapy for IOP control.

Long-term follow-up of patients who have had Ex-Press shunt surgery is needed to determine if the shunt device itself increases the risk of corneal decompensation, the authors say.[3089] REVIEW

Dr. Afshari is a professor of ophthalmology and Chief of Cornea and Refractive Surgery at the Shiley Eye Center, University of California San Diego.

REVIEW Advertising Index

(Continued from page 53)

associated with visual acuity in the better seeing eye.

The mean discounted cost (all figures in Canadian dollars) of ISBCS was $1,335 and of DSBCS was $1,783. The difference between the two cataract surgeries, ISBCS and DSBCS, equaled a 0.08 net utility gain. The cost-effectiveness of ISBCS was calculated to be $1,391 per QALY gained per patient treated. A 3 percent annual discount rate was used, resulting in 0.96 discounted QALYs gained over a 12-year life expectancy.[4397]

A study in Portland, Ore., assessed the impact of electronic health record systems versus paper on operating room workflow and documentation time during cataract surgery at an ophthalmic ambulatory surgery center.

For one month prior to and 10 months following EHR implementation at the Oregon Health & Science University ASC, a trained observer recorded cataract surgery duration, intraoperative documentation time, operating room turnover time and number of nursing staff.

Mean cataract surgery duration was 16.7 minutes (SD=11.4). Mean paper-based intraoperative documentation time was 6.8 (SD=1.2) minutes per surgery. During the initial two weeks after EHR implementation, intraoperative documentation time increased to 17.1 (SD=4.3) minutes ($p<.0001$), then decreased to 7.9 (SD=2.3) minutes by six to 10 months after EHR implementation, although this remained greater than paper documentation time ($p<.05$). There was no statistically significant difference between mean operating room turnover time with paper records (14.4 minutes) and mean turnover time two weeks or six to 10 months after EHR implementation (12.9 and 12.8 minutes, respectively). Only one nurse was needed per cataract surgery to complete both clinical care and documentation while using paper records, compared to a mean of 1.8 nurses while using EHRs.

EHR implementation for cataract surgery operative care was associated with increased intraoperative documentation time, but no significant change in operating room turnover time. Initially after EHR implementation, mean intraoperative documentation time more than doubled and was greater than mean surgery duration. Although EHR documentation time decreased over subsequent months, this was in the setting of increased nursing staff requirements.[4414]

Primary IOL implantation in children under 2 does not appear to confer any visual benefit in the first postoperative year, say British researchers. Nor does it alter the high risk of aphakic/pseudophakic glaucoma, but often commits children to early re-operation requiring repeat general anesthetic during the crucial neurological developmental period.

The IOLunder2 study, a prospective observational cohort study undertaken through the British Isles Congenital Cataract Interest Group, assesses outcomes following surgery with and without primary intraocular lens implantation in children less than 2 years old.

The group has collected one year postoperative outcomes data available on 221 children (131 bilateral cataract, 90 unilateral cataract). Ocular comorbidity was common: persistent fetal vasculature in 47 percent UC, 8 percent BC; axial length <16 mm in 23 percent BC, 8 percent UC; horizontal corneal diameter <9.5 mm in 10 percent BC, 3 percent UC. 56/131 BC and 48/90 UC children had primary IOL implantation. Implantation was more common in more socioeconomically deprived children (49 percent vs. 31 percent, $p=0.01$). The outcomes at one year after surgery included:

- Vision in normal range for age in 31 percent of all children with BC and 22 percent in all operated UC eyes, and also in normal range in 49 percent of BC children and 31 percent UC eyes without ocular comorbidity or cerebral visual impairment.
- Additional surgery for visual axis opacity (VAO) in 24 percent of all BC & 50 percent of all UC eyes.
- Postoperative glaucoma in 10 percent of all BC, and 9 percent of all UC eyes; additionally, ocular hypertension in 6 percent BC, 16 percent UC; 47 percent of pseudophakic BC eyes and 47 percent of UC eyes achieved early refraction within 1 D of planned outcome. Primary IOL was not independently associated with either visual outcome or postoperative glaucoma, but was associated with VAO (OR: 6.7 $p=0.006$ in BC, OR: 6.2 $p<0.05$ in UC), where VAO was more likely with single-piece IOLs (OR 43.7 $p<0.01$).

The group plans further follow-up of the IOLunder2 cohort to provide currently unavailable data on predictors of favorable and adverse long-term outcomes.[5672] REVIEW

Dr. Blecher is the co-director of Cataract and Primary Eye Care at the Wills Eye Institute, and the founding chief medical editor of the Review.

IOLunder2 Study: Ocular Comorbidities[5672]

Ocular Comorbidity	Bilateral Cataract	Unilateral Cataract
Persistent fetal vasculature	8%	47%
Axial length <16 mm	23	8
Horizontal corneal diameter<9.5 mm	10	3


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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® causes changes to pigmented tissues, mostly increased pigmentation of the iris, eyelid, and eyelashes as long as LUMIGAN® 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® 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®. LUMIGAN® 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.

Adverse Reactions: The most common (25%-45%) adverse event with LUMIGAN® 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.

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LUMIGAN® 0.01%
(bimatoprost ophthalmic solution) 0.01%