REVIEW® of Ophthalmology

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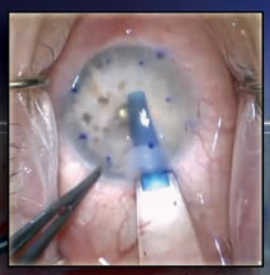
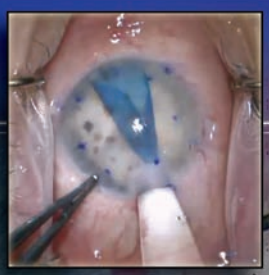
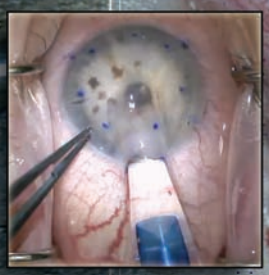
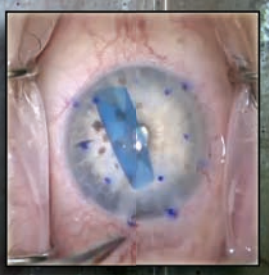
CORNEA ISSUE

Is DMEK Ready for Prime Time?

P. 28

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The world's fastest refractive platform features:

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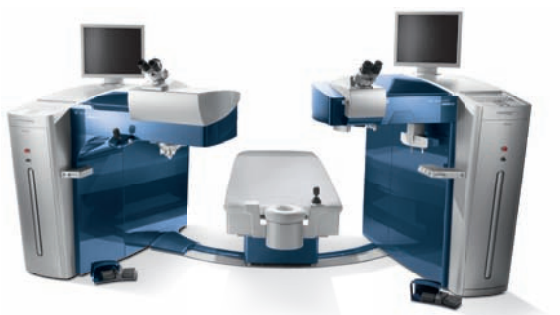
*Based on typical treatment parameters for myopia.
For important safety information about this product, please refer to the adjacent page.



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Important Safety Information about the WaveLight® Excimer Laser Systems

This information pertains to all WaveLight® Excimer Laser Systems, including the WaveLight® ALLEGRETTO WAVE®, the ALLEGRETTO WAVE® Eye-Q , and the WaveLight® EX500.

Caution: Federal (U.S.) law restricts the WaveLight® Excimer Laser Systems to sale by or on the order of a physician. Only practitioners who are experienced in the medical mangement and surgical treatment of the cornea, who have been trained in laser refractive surgery (including laser calibration and operation) should use a WaveLight® Excimer Laser System.

Indications: FDA has approved the WaveLight® Excimer Laser for use in laser-assisted in situ keratomileusis (LASIK) treatments for:

- the reduction or elimination of myopia of up to - 12.0 DS and up to 6.0 D of astigmatism at the spectacle plane;
- the reduction or elimination of hyperopia up to + 6.0 DS with and without astigmatic refractive errors up to 5.0 D at the spectacle plane, with a maximum manifest refraction spherical equivalent of + 6.0 D;
- the reduction or elimination of naturally occurring mixed astigmatism of up to 6.0 D at the spectacle plane; and
- the wavefront-guided reduction or elimination of myopia of up to -7.0 DS and up to 3.0 D of astigmatism at the spectacle plane.

The WaveLight® Excimer Laser Systems are only indicated for use in patients who are 18 years of age or older (21 years of age or older for mixed astigmatism) with documentation of a stable manifest refraction defined as ≤ 0.50 D of preoperative spherical equivalent shift over one year prior to surgery, exclusive of changes due to unmasking latent hyperopia.

Contraindications: The WaveLight® Excimer Laser Systems are contraindicated for use with patients who:

- are pregnant or nursing;
- have a diagnosed collagen vascular, autoimmune or immunodeficiency disease;
- have been diagnosed keratoconus or if there are any clinical pictures suggestive of keratoconus; or
- are taking isotretinoin (Accutane*) and/or amiodarone hydrochloride (Cordarone*).

Warnings: The WaveLight® Excimer Laser Systems are not recommended for use with patients who have:

- systemic diseases likely to affect wound healing, such as connective tissue disease, insulin dependent diabetes, severe atopic disease or an immunocompromised status;
- a history of Herpes simplex or Herpes zoster keratitis;
- significant dry eye that is unresponsive to treatment;
- severe allergies; or
- an unreliable preoperative wavefront examination that precludes wavefront-guided treatment.

The wavefront-guided LASIK procedure requires accurate and reliable data from the wavefront examination. Every step of every wavefront measurement that may be used as the basis for a wavefront-guided LASIK procedure must be validated by the user. Inaccurate or unreliable data from the wavefront examination will lead to an inaccurate treatment.

Precautions: The safety and effectiveness of the WaveLight® Excimer Laser Systems have not been established for patients with:

- progressive myopia, hyperopia, astigmatism and/or mixed astigmatism, ocular disease, previous corneal or intraocular surgery, or trauma in the ablation zone;
- corneal abnormalities including, but not limited to, scars, irregular astigmatism and corneal warpage;
- residual corneal thickness after ablation of less than 250 microns due to the increased risk for corneal ectasia;
- pupil size below 7.0 mm after mydriatics where applied for wavefront-guided ablation planning;
- history of glaucoma or ocular hypertension of > 23 mmHg;
- taking the medication sumatriptan succinate (Imitrex*);
- corneal, lens and/or vitreous opacities including, but not limited to cataract;
- iris problems including , but not limited to, coloboma and previous iris surgery compromising proper eye tracking; or
- taking medications likely to affect wound healing including (but not limited to) antimetabolites.

In addition, safety and effectiveness of the WaveLight® Excimer Laser Systems have not been established for:

- treatments with an optical zone < 6.0 mm or > 6.5 mm in diameter, or an ablation zone > 9.0 mm in diameter; or
- wavefront-guided treatment targets different from emmetropia (plano) in which the wavefront calculated defocus (spherical term) has been adjusted;

In the WaveLight® Excimer Laser System clinical studies, there were few subjects with cylinder amounts > 4 D and ≤ 6 D. Not all complications, adverse events, and levels of effectiveness may have been determined for this population.

Pupil sizes should be evaluated under mesopic illumination conditions. Effects of treatment on vision under poor illumination cannot be predicted prior to surgery.

Adverse Events and Complications

Myopia: In the myopia clinical study, 0.2% (2/876) of the eyes had a lost, misplaced, or misaligned flap reported at the 1 month examination.

The following complications were reported 6 months after LASIK: 0.9% (7/818) had ghosting or double images in the operative eye; 0.1% (1/818) of the eyes had a corneal epithelial defect.

Hyperopia: In the hyperopia clinical study, 0.4% (1/276) of the eyes had a retinal detachment or retinal vascular accident reported at the 3 month examination.

The following complications were reported 6 months after LASIK: 0.8% (2/262) of the eyes had a corneal epithelial defect and 0.8% (2/262) had any epithelium in the interface.

Mixed Astigmatism: In the mixed astigmatism clinical study, two adverse events were reported. The first event involved a patient who postoperatively was subject to blunt trauma to the treatment eye 6 days after surgery. The patient was found to have an intact globe with no rupture, inflammation or any dislodgement of the flap. UCVA was decreased due to this event. The second event involved the treatment of an incorrect axis of astigmatism. The axis was treated at 60 degrees instead of 160 degrees.

The following complications were reported 6 months after LASIK: 1.8% (2/111) of the eyes had ghosting or double images in the operative eye.

Wavefront-Guided Myopia: No adverse events occurred during the postoperative period of the wavefront-guided LASIK procedures. In the Control Cohort (traditional LASIK treatment) one subject undergoing traditional LASIK had the axis of astigmatism programmed as 115 degrees instead of the actual 155 degree axis. This led to cylinder in the left eye.

The following complications were reported 6 months after wavefront-guided LASIK in the Study Cohort: 1.2% (2/166) of the eyes had a corneal epithelial defect; 1.2% (2/166) had foreign body sensation; and 0.6% (1/166) had pain. No complications were reported in the Control Cohort.

Clinical Data

Myopia: The myopia clinical study included 901 eyes treated, of which 813 of 866 eligible eyes were followed for 12 months. Accountability at 3 months was 93.8%, at 6 months was 91.9%, and at 12 months was 93.9%. Of the 782 eyes eligible for the uncorrected visual acuity (UCVA) analysis of effectiveness at the 6-month stability time point, 98.3% were corrected to 20/40 or better, and 87.7% were corrected to 20/20 or better. Subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: visual fluctuations (28.6% vs. 12.8% at baseline).

Long term risks of LASIK for myopia with and without astigmatism have not been studied beyond 12 months.

Hyperopia: The hyperopia clinical study included 290 eyes treated, of which 100 of 290 eligible eyes were followed for 12 months. Accountability at 3 months was 95.2%, at 6 months was 93.9%, and at 12 months was 69.9%. Of the 212 eyes eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 95.3% were corrected to 20/40 or better, and 69.4% were corrected to 20/20 or better. Subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms as "much worse" at 6 months post-treatment: halos (6.4%); visual fluctuations (6.1%); light sensitivity (4.9%); night driving glare (4.2%); and glare from bright lights (3.0%).

Long term risks of LASIK for hyperopia with and without astigmatism have not been studied beyond 12 months.

Mixed Astigmatism: The mixed astigmatism clinical study included 162 eyes treated, of which 111 were eligible to be followed for 6 months. Accountability at 1 month was 99.4%, at 3 months was 96.0%, and at 6 months was 100.0%. Of the 142 eyes eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 97.3% achieved acuity of 20/40 or better, and 69.4% achieved acuity of 20/20 or better. Subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: sensitivity to light (52.9% vs. 43.3% at baseline); visual fluctuations (43.0% vs. 32.1% at baseline); and halos (42.3% vs. 37.0% at baseline).

Long term risks of LASIK for mixed astigmatism have not been studied beyond 6 months.

Wavefront-Guided Myopia: The wavefront-guided myopia clinical study included 374 eyes treated; 188 with wavefront-guided LASIK (Study Cohort) and 186 with Wavefront Optimized® LASIK (Control Cohort). 166 of the Study Cohort and 166 of the Control Cohort were eligible to be followed at 6 months. In the Study Cohort, accountability at 1 month was 96.8%, at 3 months was 96.8%, and at 6 months was 93.3%. In the Control Cohort, accountability at 1 month was 94.6%, at 3 months was 94.6%, and at 6 months was 92.2%.

Of the 166 eyes in the Study Cohort that were eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 99.4% were corrected to 20/40 or better, and 93.4% were corrected to 20/20 or better. Of the 166 eyes in the Control Cohort eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 99.4% were corrected to 20/40 or better, and 92.8% were corrected to 20/20.

In the Study Cohort, subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: light sensitivity (47.8% vs. 37.2% at baseline) and visual fluctuations (20.0% vs. 13.8% at baseline). In the Control Cohort, the following visual symptoms were reported at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: halos (45.4% vs. 36.6% at baseline) and visual fluctuations (21.9% vs. 18.3% at baseline).

Long term risks of wavefront-guided LASIK for myopia with and without astigmatism have not been studied beyond 6 months.

Information for Patients: Prior to undergoing LASIK surgery with a WaveLight® Excimer Laser System, prospective patients must receive a copy of the relevant Patient Information Booklet, and must be informed of the alternatives for correcting their vision, including (but not limited to) eyeglasses, contact lenses, photorefractive keratectomy, and other refractive surgeries.

Attention: Please refer to a current WaveLight® Excimer Laser System Procedure Manual for a complete listing of the indications, complications, warnings, precautions, and side effects.

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REVIEW NEWS
Volume XXI • No. 9 • September 2014

Patients Blind from LCA Regain Vision with Oral Medication

An international research project led by the Research Institute of the McGill University Health Centre in Montreal reports that a new oral medication is showing significant progress in restoring vision to patients with Leber's congenital amaurosis. Until now, this inherited retinal disease that causes visual impairment ranging from reduced vision to complete blindness, has remained untreatable. The study was published *The Lancet*.

"This is the first time that an oral drug has improved the visual function of blind patients with LCA," says the study's lead author, Robert Koenekoop, MD, PhD, who is director of the McGill Ocular Genetics Laboratory at the Montreal Children's Hospital of the MUHC, and a professor of human genetics, pediatric surgery and ophthalmology at McGill University. "It is giving hope to many patients who suffer from this devastating retinal degeneration."

The study involved 14 participants from around the world with LCA ranging in age from 6 to 38 years old. Their blindness was caused by either mutations in the genes RPE65 or LRAT, leading to a serious defect in the retinoid cycle. The retinoid cycle is one of the most important cycles in the human retina because it produces a molecule called 11-cis retinal which has the special capacity to capture light and initiate vision. Patients with RPE65 or LRAT mutations cannot produce this crucial molecule thus the retinal cells cannot create vision, and slowly die.

"By giving patients with RPE65 or LRAT mutations an oral retinoid intermediate (QLT091001) most patients' vision improved rapidly. We discovered that a certain portion of the retinal cells that were not working because of the lack of 11-cis retinal could be woken up," explains Dr. Koenekoop. "Contrary to what was previously thought, children with LCA and defects in RPE65 or LRAT are not born with dead retinal cells; the cells can simply go dormant, and they can remain dormant for years before they eventually die. The oral drug we tested awakened these cells and allowed patients to see."

Ten out of the 14 patients expanded their visual fields; others improved their visual acuity. The research team performed special brain scans of the visual cortex, which showed marked improvements in brain activities in patients who also improved in field size and acuity. More research will now be conducted to learn more about the ret-

U Iowa Researchers Map Proteins that Trigger Vision Loss

University of Iowa researchers have created the most detailed map to date of a region of the human eye long associated with blinding diseases, such as age-related macular degeneration. The high-resolution molecular map catalogs thousands of proteins in the choroid. By seeing differences in the abundance of proteins in different areas of the choroid, the researchers can begin to figure out which proteins may be the critical actors in vision loss and eye disease.

"This molecular map now gives us clues why certain areas of the choroid are more sensitive to certain diseases, as well as where to target therapies and why," says Vinit Mahajan, MD, PhD, assistant professor in ophthalmology at the UI and corresponding author on the paper, published in *JAMA Ophthalmology*. "Before this, we just didn't know what was where."

The researchers set out to determine why some areas of the choroid-RPE are more susceptible to disease than others, and what is happening at the molecular level. Dr. Mahajan and Jessica Skeie, PhD, a post-doctoral researcher in ophthalmology at the UI, created a map that catalogs more than 4,000 unique proteins in each of the three areas of the choroid-RPE: the fovea, macula and the periphery.

They found that a CFH, a protein that helps prevent a molecular cascade that can lead to AMD, is most abundant in the fovea. That helps, because now they know to monitor CFH abundance there."Now you can see all those differences that you couldn't see before," explains Dr. Mahajan.

Previous studies have compared the abundance of single proteins in the fovea, macula and periphery. The UI choroid-RPE map corroborates findings from these studies, while also opening a whole new avenue of research into thousands of proteins that may be involved in vision loss.

"We were able to identify thousands of proteins simultaneously and develop a map that shows what are the patterns of proteins that make these regions unique. This has helped explain why certain genes are associated with macular degeneration, and helps point us to new treatment targets," says Dr. Skeie, the study's first author.

inal function in blind people in relation to dosage and methodology.

Targeting AMD-related Depression

Depression is a common risk for people who have lost their vision from age-related macular degeneration, but a new study shows that a type of rehabilitation therapy can cut this risk in half.

"Our results emphasize the high risk of depression from AMD, and the benefits of multi-disciplinary treatment that bridges primary eye care, psychiatry, psychology and rehabilitation," said Barry Rovner, MD, a professor of psychiatry and neurology at Thomas Jefferson University in Philadelphia. Dr. Rovner and his colleagues published their findings in *Ophthalmology*.

"The depression is a response to disability, so we reasoned an effective treatment would be to reduce the disability through rehabilitation," Dr. Rovner said. In the Low Vision Depression Prevention Trial (VITAL), he led a team of psychologists, ophthalmologists, optometrists and occupational therapists to test an approach called behavior activation.

"Behavior activation involves helping people to focus on activities they enjoy, to recognize that loss of those activities can lead to depression and to re-engage in those activities," said Robin Casten, PhD, a co-author and an associate professor of psychiatry and human behavior at Jefferson. Helping people maintain an active social life is an important part of the approach, she said.

The trial recruited 188 participants with bilateral AMD from an ophthalmology practice affiliated with Wills Eye Hospital in Philadelphia. "We felt that this trial addressed an important

Ophthalmic Product Development Insights

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

Repurposing With Purpose

In this column I will highlight a few aspects of a newly announced deal in which Nicox agreed to aquire Aciex Therapeutics. Aciex was founded with technology licensed from Afferent, a spin-out company from my company, Ora, based on concepts for repurposing of products approved for uses outside the eye.

This program ties together several of our prior columns on business models, development and funding. For early-stage physician-entrepreneurs and for pharmaceutical companies looking to efficiently enter the space or spin-out certain assets, it serves as a good example of an efficient virtual model for product development, strategic investment and partnership with a contract research organization, or CRO, and how to approach repurposing known compounds into unmet needs.

Background on Repurposing

Re-purposing is the phrase used to describe drugs that have been used for other indications, and formulating or reformulating them for another use (in this case ophthalmology), a strategy that is seen frequently across the pharmaceutical industry to elevate the likelihood of success.

There are several advantages to this approach. An active pharmaceutical ingredient (API) has known pharmacology; has been shown to be efficacious in relevant models or diseases outside the eye, validating the mode of activity; has existing toxicology information and known physiochemical parameters; and usually has an active drug master file (DMF) for the API, which can be referenced in the file to the Food and Drug Administration, greatly supporting the Chemistry, Manufacturing and Controls, or CMC program. Generally speaking, available systemic toxicology information does not have to be repeated as long as: a) there is an appropriate bridge of potential systemic bioavailability of the drug from the topical ocular dose to doses used in prior systemic toxicology data; and b) an appropriate "no observed adverse effect level," or NOAEL, was identified in the systemic studies.

For example, if you calculate the theoretical systemic exposure, assuming 100 percent of the entire topical dose is absorbed and becomes systemically bioavailable, and that amount is still significantly (e.g., 10 times) less than the systemic NOAEL level (adjusted for weight), then generally speaking the existing systemic information would cover that for ocular use. The preclinical safety program can then focus on ocular toxicology (with ocular dosing). The FDA's typical requirement for ocular toxicology, two species, may also many times be reduced to a single species, if the API has already been approved in the United States for other uses at a relevant and supportive dose. Of course, this should always be confirmed via an early pre-IND communication with FDA.

The re-purposing approach generally leverages a type of new drug application (NDA) called 505(b)(2), in which one or more investigations that the applicant relies on was not conducted by the applicant, and there is not a right obtained from the original applicant (21 U.S.C. 355(b)(2)). Types of information that can be leveraged in a 505(b)(2) include published literature and the FDA's prior findings of safety and efficacy.

In cases of the re-purposing of active ingredients, it is important to point out the approach to protecting the products with patents. One can approach patent protection with: a) method of use if use in the eye is non-obvious; b) formulation patents created by inventive steps around specific formulations for optimizing efficacy with concentration range, dwell time/duration of action, penetration, comfort and safety; c) manufacturing process (e.g., novel crystalline forms); and d) delivery technology leveraging novel platforms for sustained release.

Repurposing in Action

Aciex was funded by three top healthcare venture capital firms (Bay City Capital, New Enterprise Associates and Healthcare Ventures), Ora Investment Group and a subsequent strategic investment by Akorn. Ora provided turnkey CRO development services at reduced fees and also made further investment through its financing arm, a creative mechanism some CROs are using. But in our case at Ora, this effort is differentiated by being focused in the area of expertise and broad operational capability within ophthalmology.

Aciex remained a virtual organization, which is commonplace now among start-ups looking to be capital-efficient and leverage outside expertise, with no more than two employees at a given time. Engaging a CRO at this level of partnership aligns the parties and enables the rapid allocation of resources internally within the organization as needed to meet the ever-changing plans typically seen in a pharma start-up. This enables the partnership at the strategic level to focus on the common objective rather than a fee-for-service, vendor-type relationship, and in this case resulted in a high amount of work performed, and additional work as needed, within budget.

The deal demonstrates also the still unmet needs in some key front-of-eye areas. Ophthalmology has seen a dramatic increase in the number of products in development, for example, in the high-profile and large dry-eye market. Yet opportunities remain for differentiated products in indications such as allergy and postoperative inflammation, where there are established and efficient development pathways.

The lead product announced in this deal is an ocular formulation of the well-known allergy drug cetirizine, the main ingredient in the systemic allergy medication Zyrtec, now an over-the-counter product. While systemic cetirizine is approved for relief of nasal and ocular symptoms, controlled studies have shown that topical treatment has a greater therapeutic effect than systemic administration. Cetirizine has potent efficacy for rhinitis, and has a very safe systemic profile, well-known to both ophthalmologists and non-eye-care professionals, including primary-care physicians, allergists and pediatricians, who drive more than half of the prescriptions of ocular allergy drugs. This product will provide ophthalmologists another option for treating patients with allergies in an area where a percentage of patients remain non-responsive to the leading antihistamine products. The cetirizine data also demonstrated higher level of efficacy in patients with more severe and widespread level of allergic signs and symptoms, including those

with lid swelling.

The second re-purposed product is a formulation of fluticasone for post-surgical inflammation. Steroids and NSAIDs have been the mainstay treatment for treating inflammation after surgery, and while there has been work across the field on development of soft-steroids, the opportunity for a more potent steroid, with more complete anti-inflammatory effects, and possible once-daily dosing, is still available. Fluticasone has been known under the names Flonase and Flovent for many years, and is a more potent steroid at the glucocorticoid receptor compared with dexamethasone, prednisolone and difluprednate.

The Aciex portfolio also included an exciting program investigating a new chemical entity. Syk-kinase has a key role in the degranulation of mast cells, and inhibition has potent effects in reducing the release of pro-inflammatory mediators from the mast cell, with proven efficacy in systemic disease, in addition to broad anti-inflammatory effects. Syk-kinase inhibition has potential to thus impact both acute phase reaction via mast cell stabilization, and have ongoing anti-inflammatory activity in allergy and other inflammatory indications. Recent advancements in the design of the conjunctival allergen challenge (CAC) model enables more sensitive assessment of specific anti-inflammatory effects (late phase), versus antihistaminic effects (early phase). An estimated 30 to 40 percent of ocular allergy patients report not being sufficiently treated with current antihistamines with complete relief of symptoms, and still have redness and persistent late-phase allergy or allergic inflammation.

The signing of the agreement for Nicox to aquire Aciex is an example of a strategic exit for a company that was spun-out as re-purposed concepts, funded early on by investment from the CRO and VCs, entry of another strategic pharma investor, and ultimate acquisition by a strategic partner looking to advance its future commercial presence in the space.

Mr. Chapin is senior vice president of the Corporate Development Group at Ora Inc. Ora provides a comprehensive range of product development, clinical-regulatory and product consulting for developers, due diligence support for investors and buyers, clinical trial services, and asset and business partnering and commercialization support in ophthalmology. We welcome comments or questions related to this or other development topics. Please send correspondence to mchapin@oraclinical.com.

need. Ophthalmologists have many tools at the ready for treating AMD, and we are continuing to forge links with other health-care providers to effectively treat the whole patient," said Allen C. Ho, MD, director of the Clinical Retina Research Unit at Wills Eye Hospital and professor of ophthalmology at Jefferson.

The participants averaged 84 years of age, 70 percent were women and 50 percent lived alone. All had a best-corrected vision of less than 20/70. Each participant had mild depressive symptoms and was at risk for developing clinical depression, based on a subtest of the Patient Health Questionnaire.

During the trial, the participants had two visits with an optometrist, during which they were prescribed low-vision devices such as handheld magnifiers. After those initial visits, the participants were randomized to two groups.

One group received behavior activation from an occupational therapist specially trained in the approach. The occupational therapist worked with participants to guide them on using the low-vision devices, to make changes around the home (using brighter lights and high-contrast tape), to increase their social activities and to help them set personal goals and break these down into manageable steps.

"Blending the behavior activation with low-vision rehabilitation was straightforward and natural," said Mark Hegel, PhD, a co-author and professor of psychiatry at Dartmouth's School of Medicine in Hanover, N.H. "Occupational therapy helps people regain valued activities in their daily lives, and behavior activation capitalizes on this through formal goal setting and reinforcement of progress."

The second group of participants served as controls. They talked about their difficulties to a therapist, but did not receive behavior activation or low-vision occupational therapy. Both groups had six one-hour therapy sessions in their homes over a two-month period. All participants were allowed to take antidepressants, but less than 10 percent did so. All received medical management of AMD as prescribed by their primary eye care providers.

By four months, 12 participants in the control group and seven participants in the behavior activation group had withdrawn from the trial or passed away. Of the remaining 169 participants, 18 in the control group and 11 in the behavior activation group developed clinical depression, based on retesting with the PHQ-9. Behavior activation had the most benefit for participants with the worst vision (less than 20/100), reducing the risk of depression by about 60 percent compared to controls. When the data were adjusted for vision status, physical health and baseline PHQ-9 score, behavior activation reduced the risk of depression by 50 percent compared to the control treatment.

"AMD is typically diagnosed and treated in primary eye-care settings, where there is no defined standard of care for depression. This study was a unique and compelling effort to address that issue by strengthening teamwork between eye-care professionals and mental health professionals," said Eleanor Schron, PhD, of the National Eye Institute.

Dr. Rovner hopes the study will serve as a model for similar approaches to preventing and treating depression in AMD. "Stronger links between primary eye-care and mental health care workers would be needed to make behavior activation more widely available for AMD patients," Dr. Rovner said. Specialized instruction would also be needed for occupational therapists, who are not typically trained in behavior activation.

The study is continuing to follow participants to see if the benefits of treatment are maintained out to one year. REVIEW

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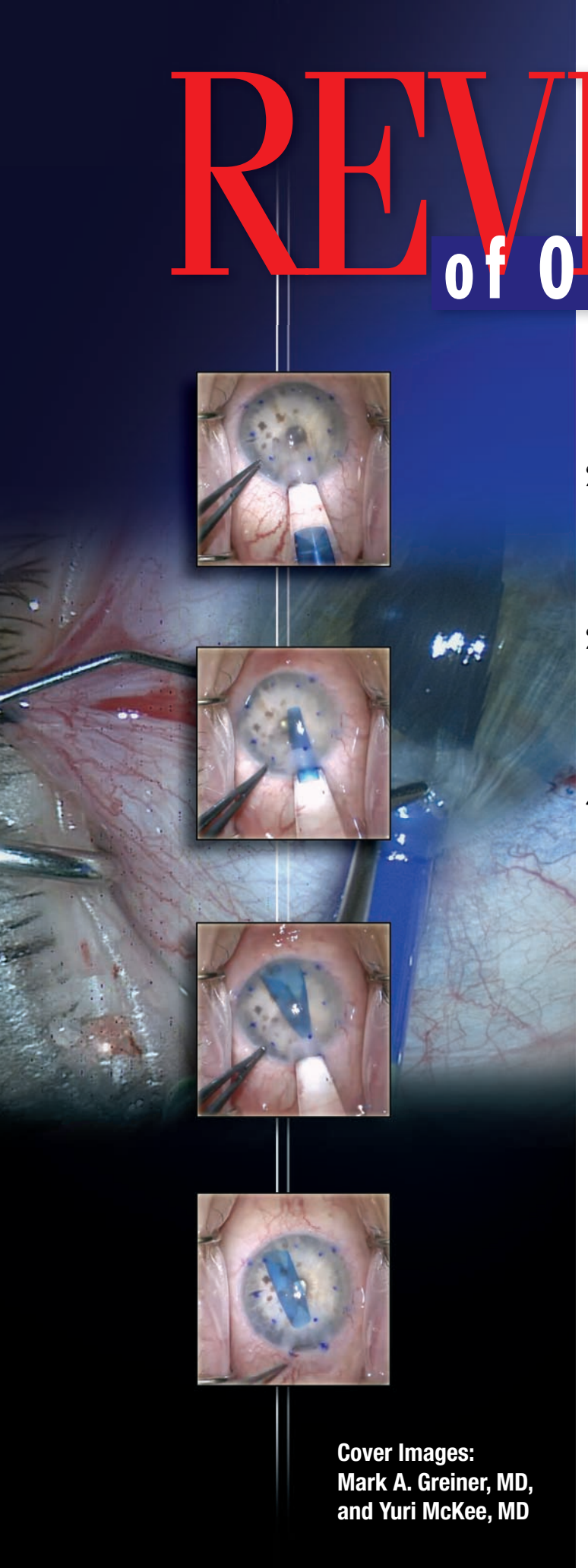

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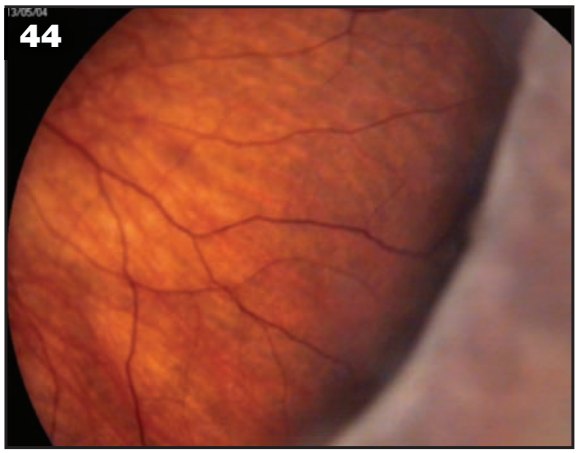

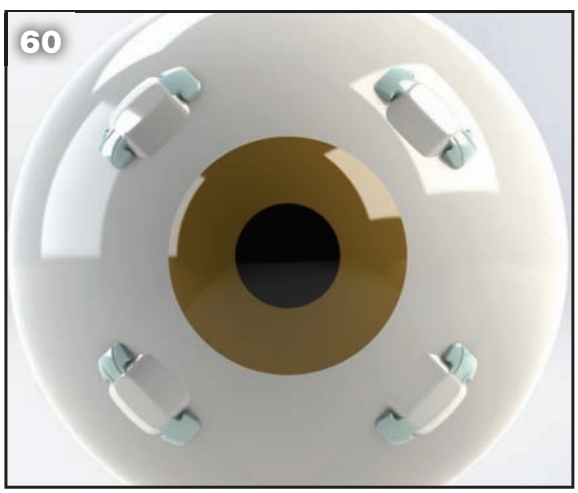

Restasis®
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THE DRY EYE TREATMENT SHE NEEDS TODAY. BECAUSE TOMORROW MATTERS.

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Indication and Usage

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

Important Safety Information

Contraindications

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

Warnings and Precautions

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

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

Adverse Reactions

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

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

Reference: 1. RESTASIS® Prescribing Information.

ALLERGAN

APC20AF14 141005

RESTASIS® (Cyclosporine Ophthalmic Emulsion) 0.05%

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

INDICATION AND USAGE

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Potential for Eye Injury and Contamination

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

Use with Contact Lenses

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

ADVERSE REACTIONS

Clinical Trials Experience

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

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

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

Post-marketing Experience

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C

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

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

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

PATIENT COUNSELING INFORMATION

Handling the Container

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

Use with Contact Lenses

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

Administration

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

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REVIEW® of Ophthalmology

REVIEW Editor's Page

Christopher Glenn, Editor in Chief

How Many Doctors Does It Take to …

… care for a nation?

Among the things our health-care system does well, you would not list a nimble and efficient ability to respond to changing demand for new physicians. The oft-cited geographic maldistribution and preference for subspecialty practice at the expense of primary care were just two of the institutional shortcomings targeted by a recent task force of the National Academy of Science's Institute of Medicine.

A controversial report from the IOM expert panel released last month describes a graduate medical education system that continues to operate on decades-old assumptions and predictions, to the detriment of both the nation's health and to medical interns' and residents' preparedness to practice medicine in the 21st century. The report acknowledges that "Health care reimbursement and the organization of health care services, for example, are far more important than GME in determining the makeup and productivity of the physician supply." Nonetheless, the panel suggests that the system by which the nation contributes $15 billion annually to GME through Medicare funding needs major changes.

In a press conference following the release of the report, the panel chairs listed five recommendations, whose net effect would move funding away from traditional, teaching-hospital-based residency funding and toward more community-based training that more closely reflects what new physicians will face in practice. The panel calls for spending the same overall funding from Medicare over the decade, adjusted for inflation. But it would be distributed much differently, with a declining share providing direct subsidies to teaching programs. An increasing share would go instead to a "GME transformation fund" that would finance new ways to provide and pay for training and fund training positions "in priority disciplines and geographic areas."

The panel suggested that the changes would also address a long-standing absence of accountability in GME funding and an emphasis on outcomes, concepts that are becoming standard in every other area of health care.

Any of the proposed changes are subject to Congressional approval, and politically well-connected hospital groups and others representing medical colleges have already reacted harshly to the proposals.

Despite the best efforts of the best minds in the field, changing models of care and the rise of new technologies mean we don't know and can't predict with any assurance of accuracy, how many physicians we'll need 10 years from now. Relying on market forces has not worked. Cranking out more graduates, by itself, is not a solution.

1. IOM (Institute of Medicine). 2014. Graduate medical education that meets the nation's health needs. Washington, DC: The National Academies Press.


Surgical Supervision For the 21st Century

High-speed, high-definition technology is making it possible to help guide surgery taking place in remote locations.

Christopher Kent, Senior Editor

As the world gets smaller and communication technology advances, telemedicine has become a more feasible prospect. Nevertheless, surgeon training and supervision has seemed too difficult to manage remotely. That may be changing, however, as surgeons investigate using the latest communication technology to supervise other less-experienced surgeons.

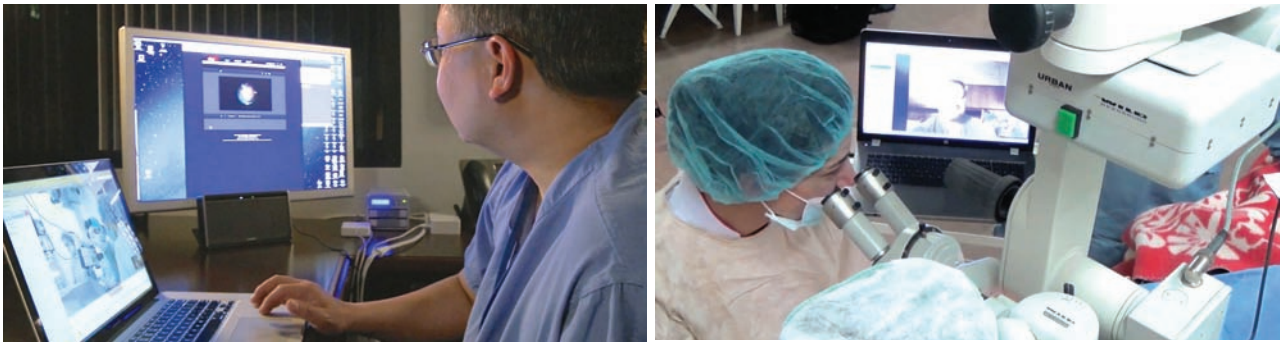
One surgeon who is helping to pioneer this effort is Thomas C. Lee, MD, associate professor of ophthalmology and director of both the Vision Center at Children's Hospital Los Angeles and the Surgical Retina Fellowship at the Keck School of Medicine, University of Southern California. For several years he has worked with Roger Ohanesian, MD, president of the Armenian Eye Care Project, helping to train doctors. "We've been deploying online education programs since 2009, primarily to teach doctors in Armenia to diagnose and manage retinopathy of prematurity," Dr. Lee explains. "At first, they'd use the Retcam platform to image kids' retinas and then email the images to us, a form of telemedicine called 'store and forward.' I'd check my email, upload the image and get back to them.

"However, this didn't help the patients who failed treatment and needed surgery," he continues. "They were managing this by sending the children to St. Petersburg, Russia, for the surgery. Without the surgery a child would go blind—but getting a premature child to Russia in an ICU ventilator is not an ideal scenario. So, their government approached us again and asked us to train their doctors to do the surgery.

"At first, they flew their doctors here," he says. "They'd stay here for six months, watch us manage ROP and then go back to their country. Unfortunately, that system really didn't work. The doctors weren't observing their own patients, and they weren't doing the procedures themselves and developing a level of competency and comfort. So, at their request, we decided to do the reverse, so the doctors could stay in their own country and treat their own patients. Ultimately, we realized they also needed a video support system.

"There's been a historical problem in the way we've been trying to get skills and expertise to developing countries," explains Dr. Lee. "The existing model has historically required the doctor to come here for a year, at a huge cost. The doctors would incur significant debt because they had to shut down their practices at home and had to move their families. Then, when they went back, the only way for them to service that debt and pay off the interest was to see patients who could pay money. That was often not the population for which they were hoping to provide care. If, however, they didn't have to spend a year here—instead they could maybe spend a month with me and then go back because I could continue the supervision remotely—that was a totally different prospect. They could stay in their own country. They wouldn't have to shut down their practice, run up a crushing debt and disrupt their family life.

"I knew this arrangement would be challenging, because the most experienced surgeons over here can't spend an extended time in Armenia," he notes. "But after some thought I realized that we have the ability to be there virtually. The problem was, we could communicate face-to-face



The interactive video setup designed by Thomas C. Lee, MD, uses Skype on one computer screen for communicating with the remote surgeons while the endoscopic surgical image appears on a separate screen, transmitted via the Slingbox, designed for use with cable television.

using Skype, but that wasn't enough. The surgeon at our end needs to be able to see what the surgeon in Armenia is seeing during the surgery in order to make useful comments and suggestions. That was not feasible using Skype, both because of the low-resolution of the signal and the lack of an easy way to get the surgical images into the camera view."

Making the Connection

Dr. Lee favors the use of endoscopy for performing ROP surgery, although he acknowledges that some surgeons are skeptical of this approach. "Our group has extensive experience with this method and we've found it to be safe and effective," he says. "In any case, the fact that the endoscopic image is two-dimensional and already in the form of a high-definition video signal turned out to be an advantage in this situation; it would be very difficult to share the 3-D view you have through the surgical microscope, but it's easy to share a 2-D image. What we needed was a way to stream a high-definition copy of the video signal from the endoscopic camera in Armenia to our surgeons in the United States in a way that was affordable. One existing system that could manage this type of video and audio exchange is the Polycom video conferencing system; however, their units cost about $15,000, and we'd need two of them, one at each end. It occurred to me that some other existing technology might be able to meet our needs, perhaps less elegantly, but at a much lower cost."

The technology Dr. Lee thought of using was the Slingbox, made by Sling Media. "The Slingbox is designed to work between your cable box and TV," he explains. "The video and audio coming out of the cable box go into the Slingbox, which passes the signal along to your TV but also diverts the signal into its computer. The computer does real-time compression and streams the result out to the Internet at 1080p, 30 frames per second. Once that's operating, you can log onto the Slingbox signal remotely from anywhere around the world. My guess is that the company has a server that accepts the signal from the Slingbox, so that when you log in you're logging into their server.

"The reason the Slingbox was a good option in our situation is that it accepts any HDMI input—including the signal output from the S-video composite jack on the endoscope," he continues. "So, the surgeon in Armenia takes an S-video cable, hooks it up to the back of the endoscopic unit and plugs it into the back of the Slingbox. The Slingbox is then connected to the Internet in the OR, allowing me to log onto Slingbox and see the same image the surgeon in Armenia is seeing. When surgery is being performed, we have a video Skype call going both ways. That allows me to see what's going on in their OR and have real-time communication. At the same time, on a separate computer screen, the Slingbox signal shows me the surgery itself, so I can comment on it and offer advice. *(See pictures, above.)*

"The beauty of this setup is that we only need one Slingbox, which costs about $150—far less expensive than the Polycom alternative," he says. "The downside is that there's a delay of about 10 seconds, so what I'm seeing is the endoscopic view from 10 seconds earlier. This limits my ability to respond in real time. If we could get the latency down, I could be more reactive and bring more value to the case, so we're investigating other platforms to reduce the latency. Nevertheless, I can still provide overall guidance, helping the surgeons strategize their way through the surgery."

Dr. Lee says that when the surgeons in Armenia have a case they believe would benefit from supervision, they contact Dr. Lee to arrange a date and time. "At the appointed hour I log onto Slingbox and we initiate the Skype video call," he says. (You can see a video of this in action at https://vimeo.com/89036200.) "To date, we've done several cases this way. We do get a decent image using the Slingbox system, despite the fact that is was not designed for this purpose. We're finding that this system is good

enough for me to get an overall sense of the severity of the case, allowing me to offer useful advice regarding the best way to proceed."

Dr. Lee says that in the near future they will try using a streaming device at both ends. "With that setup, not only will I see them in real time, they'll see me in real time watching the surgery," he says. "This will allow me to point out details in the image produced by their endoscope, such as where in the pathology I think they should cut. This will make it easier for me to offer more specific advice, as opposed to just offering overall strategy. In theory, we could do this with Skype, but we haven't figured out how to get an external webcam to link into the call. If we could tie in an external webcam, we could point the webcam at the computer screen and then I could show them the image they're streaming me and where I think they should be cutting."

Dr. Lee notes that, by itself, this arrangement would not constitute sufficient supervision to protect patients from inexperienced surgeon error. "What we're currently doing is sending a younger doctor to Armenia to act as an onsite attending physician," he says. "Right now the doctor filling this role is Chien Wong, MD, who trained with me for a year and a half after doing a retina fellowship at Moorefield's in London. He has less experience than I do, but has a good idea how these cases should be done; he knows the mechanics very well. Thus when I log on and offer advice on a surgery, I'm one of two attending surgeons, supplementing the advice of my younger colleague. This type of arrangement—having a trainee with limited experience at the location while an expert in another location provides overall guidance—could be very useful for training surgeons in remote locations."

The surgical team in Armenia holds a Slingbox, illustrating its small size.

The Future: Coming Fast

Dr. Lee notes that someone might argue that attempting to do this is premature—that the technology is not up to the task yet. "They'd be absolutely right," he says. "I'd be the last person to say that this is a scalable model that will work all the time, because we're still trying to figure out what's safe and what's feasible. However, given the speed at which technology is developing, it will be there very shortly. Moore's Law states that every 18 months the number of transistors able to fit onto a chip doubles, and there's a similar law for bandwidth, called Neilson's Law, which says the availability of residential bandwidth will double every 18 months. Whether you're in the United States or sub-Saharan Africa, that law will probably hold true. Furthermore, improved video compression algorithms are letting us fit far more data into the same bandwidth.

"For example, Netflix will soon be streaming a 4K image—four times the resolution of HD—to your home cable box," he continues. "To me, that's medical-grade bandwidth. We're figuring out the workflow and solving some of the problems, so that when the technology is ready—which I think will be in two or three years—we'll have a platform that will be ready to let us help doctors around the world. Wayne Gretsky, the renowned hockey player, once said that you never skate to where the puck is, you skate to where it's going to be. That's what we're trying to do."

Regarding how this might be used in countries with less infrastructure, Dr. Lee notes that many of these countries are skipping the earlier communication technologies we've lived with for decades, instead moving straight to the latest technology. "In sub-Saharan Africa or Indonesia no one's bothering to put up cables or wires—they're going straight to wireless broadband systems," he says. "I suspect that within a few years, the prevalence of broadband in developing countries will be surprisingly good. A decent 4G signal gives you about as much bandwidth as a cable modem, and the Slingbox can work via Wi-Fi. This change will provide educational opportunities we wouldn't otherwise have."

Dr. Lee believes this type of arrangement will make a big difference in how quickly skills can be transferred to other countries. "Currently it takes one or two professional generations to get enough experience to be able to operate successfully on some of these seriously sick children," he says. "If we can make this system work, we can fast-track the skill set and expertise surgeons can bring to their countries. And once a surgeon is proficient, he can train other surgeons in his country. This has the potential to shorten the learning curve for the entire country. Our work with Armenia is the test case." REVIEW

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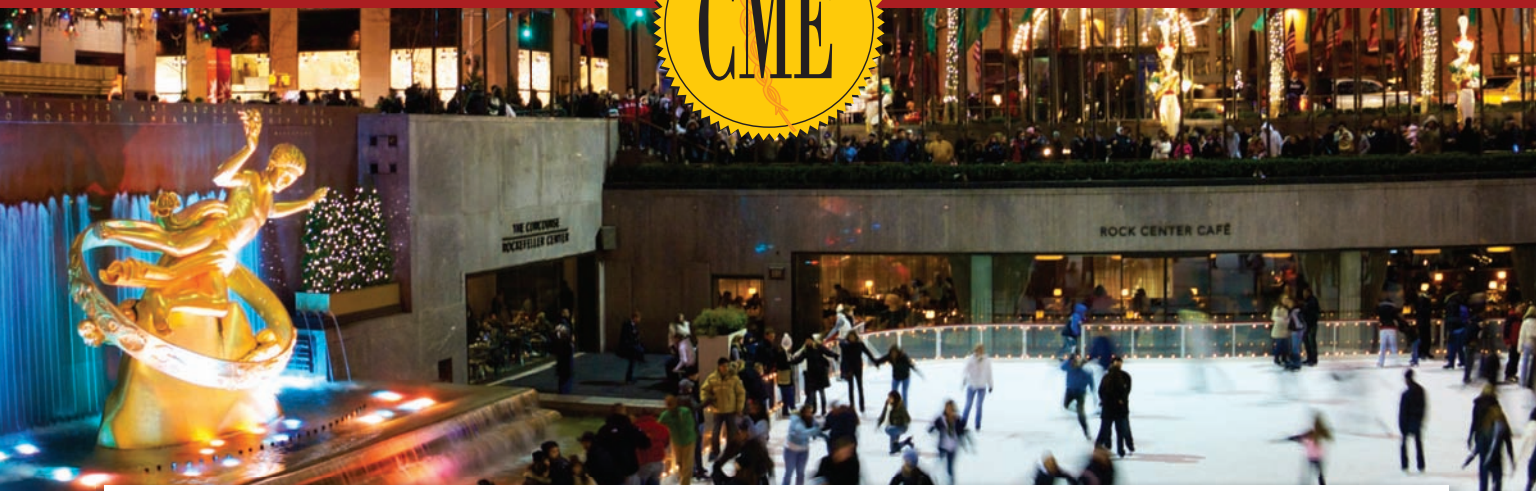

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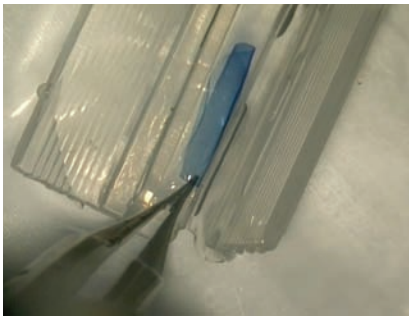
Make a Positive Transfer To DMEK

Walter Bethke, Managing Editor

With DMEK, your DSEK skills can lift you up in some cases and trip you up in others, surgeons say.

When Indianapolis ophthalmologist Yuri McKee was a flight surgeon in the Air Force, one of his duties was putting together various bits and pieces of information to figure out why a plane crashed. In one instance, an experienced officer who was flying a jet he had never flown before reached for what he thought was the flap control—it was always in that position in his previous plane—but instead activated the plane's speed brakes, causing it to crash on landing. When Dr. McKee questioned the officer about it, the pilot swore that he had only raised the flaps. It wasn't until Dr. McKee showed him the photos of the controls' position upon crashing that he realized what he had done.

In his course on transitioning from Descemet's stripping endothelial keratoplasty to Descemet's membrane endothelial keratoplasty, Dr. McKee uses this case as an example of the sinister phenomenon known as negative transfer, where a skill or maneuver that used to be useful in one task is now actually detrimental in a new one. "You have to be careful when you transition from DSEK to DMEK," Dr. McKee says, "and not take some of those skills that worked well for DSEK and try them in DMEK where they won't work so well."



The wispy DMEK graft is floated into a modified IOL injector cartridge. All images: Yuri McKee, MD, and The Digital Manual of Ophthalmic Surgery and Theory.

With that in mind, in this article DMEK experts offer advice on making the transition from DSEK to DMEK, give their best pointers for succeeding with the tricky parts of DMEK and even point out areas where your DSEK skills will hurt you in DMEK.

Preop Considerations

Surgeons say there are some steps you can take preoperatively to ease the transition and make your first cases manageable.

• ***Patient selection***. Dr. McKee, who works with DMEK guru Francis W. Price Jr., MD, at the Price Vision Group, says that especially for a beginner, DMEK works well in patients who still have their vitreous and have

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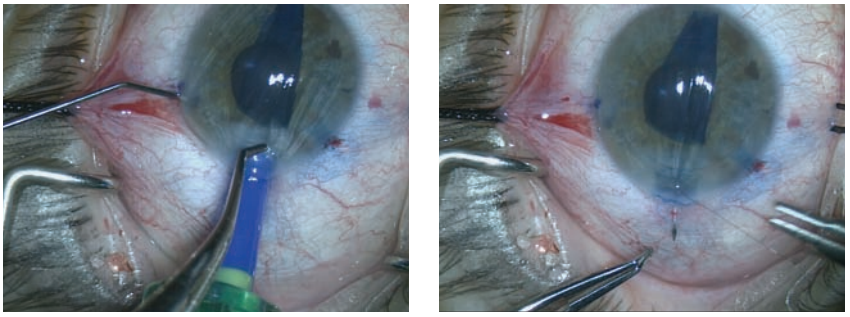
References: 1. Liew M, Zhang M, Kim E, et al. Prevalence and predictors of Sjögren's syndrome in a prospective cohort of patients with aqueous-deficient dry eye. *Br J Ophthalmol.* 2012;96:1498-1503. **2.** Kassan SS, Moutsopoulos HM. Clinical manifestations and early diagnosis of Sjögren syndrome. *Arch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

an intact hyaloid face. "It also works best in pseudophakic patients because a beginning DMEK surgeon will likely induce a cataract," he says. "So, a pseudophakic Fuchs' patient or a Fuchs' patient with a cataract, who hasn't had a vitrectomy or a retinal detachment, would be ideal to start on."

• ***The donor tissue.*** Because of the nature of the donor tissue that's placed in the eye, DSEK and DMEK start to diverge at this point. "For myself, I don't pay too much attention to the age of the donor tissue for DSEK," says Albert Jun, MD, associate professor of ophthalmology at Johns Hopkins' Wilmer Eye Institute. "Even though I acknowledge that the corneal donor study indicated that donor age wasn't a huge factor, in endothelial cell survival, at least, for DMEK I do pay attention to the donor age. In terms of how the donor handles during surgery, it turns out that tissue from older donors is both easier to prepare and to handle. For DMEK, I know that if I get a donor who is under 50—which is something of an arbitrary cutoff—then I may have more difficulty in surgery. The younger donor tissue will be just more difficult to unfold in the recipient's eye."

In terms of preparing the donor tissue, Dr. Jun says it might be best for the beginning DMEK surgeon to take a page from the DSEK surgeon and let the eye bank prepare it. "DSEK really took off after eye banks became involved with tissue preparation," Dr. Jun says. "And if someone's really serious about doing DMEK, at least in the United States, he should have the tissue prepared at an eye bank. This is one of the things I tell people in lectures on making the transition from DSEK to DMEK: You could prepare the DMEK endothelial graft yourself, but why would you? By having the eye bank do it, you take the donor preparation part of the procedure—which involves extra time and stress—completely out of the equation. It's just another variable, and a substantial one, that you won't have to be concerned with."



Experts say that, before removing the injector cartridge, shallow the anterior chamber via a paracentesis and place gentle pressure across the keratome wound to avoid ejecting the graft from the eye (left). Then, use a 10-0 nylon suture to secure the wound (right).

Dr. McKee, however, thinks it's a good idea for the beginner to prepare the donor tissue. "It teaches you to work with Descemet's membrane while you learn to prepare the tissue," he avers. "To prepare the tissue, one of the things you'll need is a microdissector. Mastel makes the one I prefer to use, called the Microfinger. Moria also makes one.

"Though there are different ways to approach preparing a graft, the one we use is called the 'submerged cornea using backgrounds away' technique that Art Giebel, MD, developed," Dr. McKee continues. "In the SCUBA technique, we keep the donor cornea submerged in a viewing chamber and score the peripheral edge of Descemet's near the trabecular meshwork. Then, we use the Microfinger to elevate an edge and make sure there are no radial tears. Once the edge is elevated, we use small Tubingen forceps to carefully peel about 90 percent of the graft, leaving just the center of Descemet's attached. Then we do a trephination that's the size of the graft we want, and pull off all the peripheral Descemet's that's been touched. That leaves a central 8- or 9-mm graft that's not been touched and is only attached to the cornea with a 1-mm square area in the middle. At that point, touching just one part of the graft on the very edge, we pull off that 1-mm square bit and the entire graft comes free and curls up like a scroll."

Intraoperative Issues

It's during the surgery itself that the differences between DSEK and DMEK become even greater, especially when it comes to working with the fragile DMEK graft.

• ***Host preparation.*** There are differences in preparing the recipient cornea that the DSEK surgeon will need to take note of. "The technique for stripping the host cornea is the same technique as in DSEK," says Dr. McKee. "However, in DSEK, most surgeons will strip a little bit smaller than the planned size of the graft so they don't get any peripheral edema where there's no coverage of the cornea. But in DMEK, any retained Descemet's will actually repel the DMEK graft. So, for DMEK, we strip the same size or maybe even a little bigger than the donor size."

Chicago surgeon Thomas John says that it can be challenging working on the inner dome of the DMEK host cornea using just a straight instrument, so he developed a curved instrument called the Dexatome as part of a set of DMEK instruments from Storz/Bausch + Lomb. (He has no financial interest in them.) "The Dexatome has a curvature much like the curve of a sickle," Dr. John explains. "Since you've got

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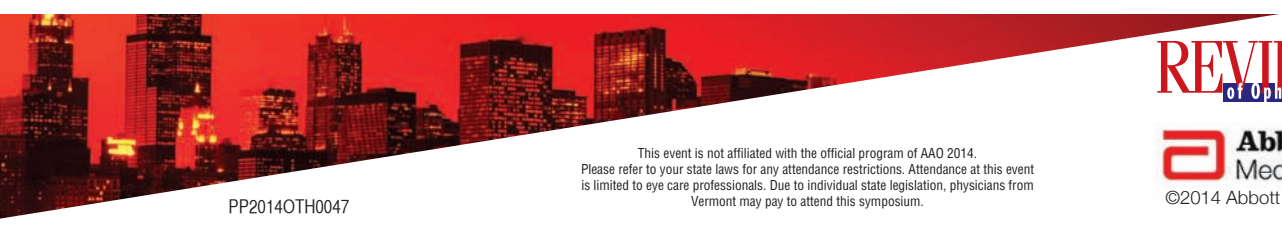

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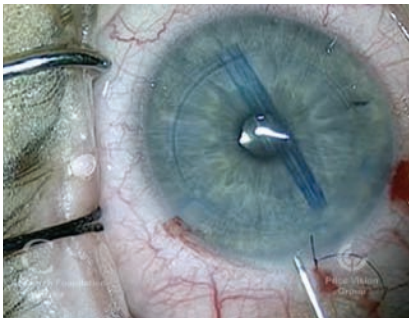
one point of entry into the cornea from which to work on the corneal dome, the curved shape allows you to do it easily. When you remove Descemet's membrane in the host, you want to remove it as a single disk, because you'll be looking through a cloudy cornea and the view won't be the best. It's nice to be done in one shot and then come out of the eye with the disk you want to remove. And, when you remove the Descemet's membrane, only touch the folded part with each stroke. By doing that, you don't touch the exposed inner corneal stroma, and the patient's corneal surface on the inside will remain pristine. This is important because the host inner corneal surface represents half of the donor/recipient interface, and the better the interface the better the quality of vision after the surgery."

Dr. McKee adds that one particular maneuver that may have been useful in DSEK is now the opposite in DMEK, in his opinion. "A couple of years ago, Mark Terry described how roughening the peripheral stroma in the area where you're going to place your DSEK graft might help the graft adhere better," Dr. McKee says. "But that's an absolute no-no with DMEK, because the stromal fibers are soft in the posterior cornea. If they were to get roughened, they'd stick up from the back of the cornea and prevent the DMEK graft from adhering flat."

• ***Injecting the donor tissue.*** If the surgeon didn't prepare his own graft tissue, then this part of the procedure may be the first encounter he'll have with the super thin, 12- to 15-µm thick DMEK graft. The differences between it and the thick DSEK graft will be stark. "The DSEK graft is more like a lenticule or a disk," says Dr. McKee. "The DMEK graft is just a scroll. The DSEK lenticule has mass to it, and wherever you put it is where it will stay. The DMEK scroll, though, is virtually weightless. As a result, the scroll will flow like water. Like a jellyfish, wherever the fluid current goes, the scroll will follow. It can maneuver its way around sutures, out of paracenteses, through peripheral iridotomies, behind lenses and even into the back of the eye in an aphakic patient. You have to be gentle and understand fluid dynamics."



A DMEK graft can be scrolled so tightly it can be difficult to determine whether it's upside down or not.

Before inserting the graft into the eye, Dr. John likes to stain it with trypan blue ophthalmic solution (Vision Blue, DORC) to aid visualization. For this he uses a small block with two wells from his DMEK instrument set. "When you try to stain the membrane and then use a Weck-Cel sponge on the fluid in a conventional concave well, the Descemet's membrane is attracted to the sponge," Dr. John says. "The extra rim in this block prevents the graft from adhering to the Weck-Cel sponge."

To inject the graft into the recipient, surgeons say the most popular instrument is a modified intraocular lens injector, such as the Viscoject 2.2-mm injector (Bausch + Lomb) used by Dr. McKee. Dr. Jun says if you use an IOL injector, it's important that it's a closed-fluid system. "If you use one without a closed-fluid system, there will be cases where you'll just run out of fluid," says Dr. Jun. "It will leak around the graft and it won't produce the size of fluid wave you need to get the graft tissue into the eye. If your system has a piece of tubing that's attached to some sort of pipette that's attached to a syringe, then it's a closed-fluid system. But if you have an IOL injector with a big space where the IOL is supposed to slide in, and you then put viscoelastic in and you have a plunger—and the system isn't closed to fluid—it can lead to difficult situations. For instance, you may encounter an instance where you have positive pressure where you need a little more fluid to get the graft in the eye but you'll basically run out of fluid. Also, a closed-fluid system allows you to aspirate the graft into the injector without the graft physically resting on the injector material. If it's continually surrounded by fluid it will float, and not make contact with the hard surface of the inserter device."

Dr. McKee says it's at this point, the injection, that you have to watch out for another difference between DSEK and DMEK: "You want to keep the eye very soft," he says. "If there's pressure in the eye as you inject the graft, it can eject from the eye. With DMEK, this will happen whenever there's a pressure differential. When we use the closed-system injector, we always burp one of the paracenteses until there's no difference in pressure between inside the anterior chamber and outside the eye so when we remove the injector the graft doesn't come shooting out after it. Again, this is because the graft will follow fluid as if it were fluid.

So, you pull out the injector when the eye's soft and, before injecting any fluid at all, you put a stitch in to keep your main wound closed. Once you have a suture placed, you can gently refill the chamber and you'll see your scroll floating in there. As you do this, though, remember that having a high pressure in the anterior chamber results in more potential flow through the incisions and increases the risk of ejecting the graft out of a paracentesis or even around the suture of the primary incision. In short: Don't ever make the eye firm." For irrigation/aspiration during the procedure, Dr. McKee says standard bimanual I/A tips—he uses tips from Asico—are all the surgeon needs.

• ***Chamber depth***. Surgeons say this aspect of DMEK is often the one that is most difficult for DSEK surgeons to acclimate to, since it runs counter to the protocol of almost all other intraocular surgeries: In DMEK, the chamber has to be fairly shallow.

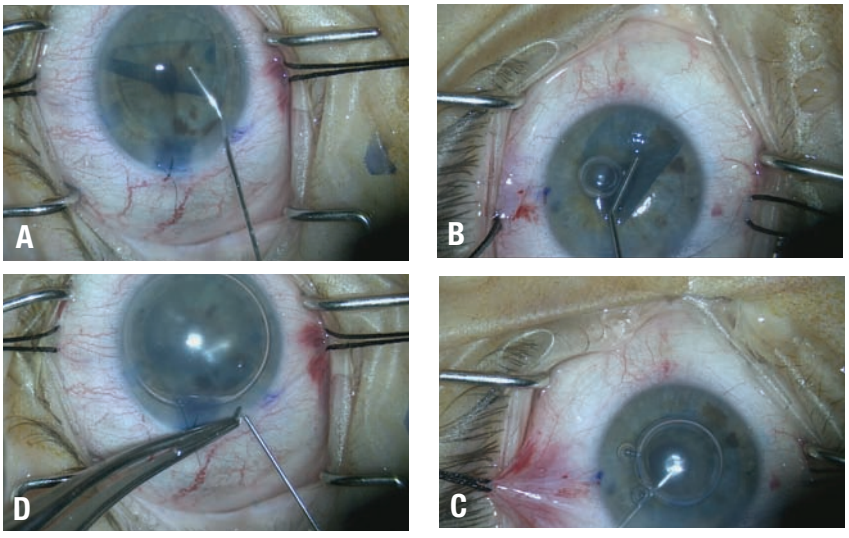
"When you put a DSEK graft into the eye, you typically deepen the chamber and the graft unfolds itself because it wants to unfold and go back to its lenticular shape," says Dr. McKee. "It doesn't like to be folded up as it goes through the EndoSerter or Busin glide. Unfolding the DSEK graft is one of the easiest things to do. The opposite is true for DMEK. If you deepen the chamber with DMEK, the DMEK graft turns into the scroll that it wants to be. However, of course the whole point is to unscroll it into the proper orientation and get it adhered to the back of the cornea. That's one of the biggest differences: The key is to shallow the chamber so when you do unscroll the DMEK graft the iris can act as your third hand and hold the graft open. This is a foreign concept to the DSEK surgeon."

• ***Graft orientation***. Because the graft will be rolled up and is so flimsy compared to a DSEK graft, it can be a challenge to determine whether it's right-side-up. One strategy that Dr. McKee uses is a handheld slit lamp from Eidelon. "It looks like a small Maglite flashlight, with a small cylinder in the front that makes a slit beam," he explains. "We put it in the finger of a glove so it stays sterile during surgery. We can then hold this slit beam and maneuver it at any distance or any angle to the eye. When you do that, you'll first see a slit beam going through the anterior chamber, then the little wedge of cornea and then your graft. The graft always scrolls endothelium side out, so when you put the beam in there and see two little scrolls coming up at you, that means that if you unroll it in that orientation the endothelium will face iris as it should. On the other

hand, if you see one broad scroll and the little scrolls going away from you, that means it's upside down."

• ***Graft manipulation.*** As surgeons alluded to earlier, the DMEK graft is so delicate that once it's in the eye, it can only be manipulated with liquid and air. Surgeons say this is one of the aspects of the surgery where the intuition you've developed in DSEK and other intraocular surgeries can mislead you. "The main difference in mindset between DSEK and DMEK is to realize that DSEK is a hands-on procedure and DMEK is hands-off, so to speak," explains Dr. John. "It's a no-touch technique. The donor tissue in DSEK has a stiffness that allows you to attach it with forceps, move it around, et cetera. Whereas with DMEK, the tissue is so thin that if you directly handle it, you can easily tear it. What that means is that even if you're in the comfort zone with DSEK, when you transition to DMEK, it's back to the drawing board. You have to depend a lot on fluidics to make the tissue do what you want it to do in the recipient's anterior chamber."

Dr. McKee says that to get good at using fluid as an instrument in the eye using a 27-ga. angled cannula, you have to be ready to embrace the counterintuitive. "You have to think about how fluid flows and understand that, whatever you do, the graft will do exactly what you told it to do, even if you don't understand what you did," he says. "Its response is based on fluid dynamics in a closed system. You have to understand eddy flows and how the graft will follow a current of fluid. People will watch me perform DMEK and say, 'What you just did was counterintuitive to what the graft did—but somehow you seemed to know where the graft was going to go.' I tell them that even though you don't see the fluid, it's constantly swirling around inside the chamber. That's why even though I shot the fluid jet in the opposite direction of the graft, the graft responded and went where I wanted it to go. I was literally bouncing the fluid off the back of the cornea to make the graft do what I wanted."



(Clockwise from top left) A: Shallowing the anterior chamber allows the iris to help hold the newly inserted graft in a partially unfolded position. B: Gentle pressure from a 27-ga. cannula on the corneal surface over the scrolled edge of the graft, followed by a quick release of pressure, can help it unfold. C: When the graft is unfolded and well-centered, a 30-ga. needle injects air to create a bubble to hold the graft in place. Venting excess fluid avoids over-pressurization of the chamber. D: Putting gentle pressure on the needle tract as the needle is removed prevents air from escaping and the chamber from collapsing.

The surgeons have several tactics for using fluid to manipulate the graft. "When you inject fluid, you have to keep two factors in mind," says Dr. John. "One is the direction of the injection; in other words whether it's going in a radial fashion toward the center of the chamber or in a tangential fashion toward the periphery. The second factor is how forcefully you inject it.

"When you put the Descemet's membrane graft in the anterior chamber, it's rolled like a carpet that's been rolled up on a floor, with the outer surface being the endothelium," Dr. John continues. "So, when you inject fluid diagonally, you can turn this DM scroll on its long axis and, depending on the force of your injection, cause it to partially unroll. If you want the rolled membrane to move more centrally, then you can direct the fluid tangentially, setting up a circular current in the anterior chamber which will rotate the membrane on its vertical axis and, in doing so, partially unroll it."

When the graft is partially unrolled, you can begin using air and indirect pressure on the surface of the cornea with an instrument to finish the case, surgeons say. "In our technique, when the graft is partially unscrolled, we hold it in place using the iris in a relatively shallow anterior chamber, then slide a small air bubble behind the graft to hold it against the back of the cornea," Dr. McKee says. "We then tap on the corneal surface to get it to unroll completely, then place a large bubble to hold it in place."

The act of tapping to maneuver the graft has an art to it too, says Dr. Jun. "You can tap on the corneal surface with a cannula to create fluid waves that move the graft into position," Dr. Jun explains. "If you tap on the corneal surface within the margin of the graft, you can get it to unfold. Alternately, if you tap beyond the edge of the graft, you can get it to shimmy across the iris in a certain direction. Again, this comes down to the proper chamber depth. If the chamber is the right depth—rela-

tively shallow—as you do these maneuvers you'll see the response you want to see."

Dr. John says the initial small air bubble may not be necessary. "The problem with using the small air bubble to unroll the Descemet's membrane is you sometimes have difficulty getting the right-sized bubble," he says. "And, when you tap on the air bubble, it can go outside the graft and into the wrong position, making the procedure more difficult." As an alternative, Dr. John uses a smoother he designed as part of the DMEK set. "It's a curved instrument with a ball at its distal end," he says. "You can touch the corneal surface with the smoother and unroll the membrane and then move it to any desired position in a fairly consistent manner using gentle pressure on the outer corneal surface."

Since a nearly full air bubble is required at the end of the case, however, surgeons note it's important to perform an inferior peripheral iridotomy either a couple of weeks preop or intraoperatively.

• ***No vent necessary.*** Corneal venting incisions, which many surgeons use in DSEK to evacuate interface fluid, are actually counterproductive in DMEK. "You can't use a venting incision in DMEK," says Dr. McKee, "because when you put your diamond blade through the corneal stroma to vent you'll go right through the DMEK graft."

Build Your Knowledge

For surgeons looking to get serious about DMEK, there are resources from national societies, the Internet and individual corneal surgeons.

"All the traditional places for education are excellent," Dr. Jun avers. "The AAO and ASCRS offer skills transfer courses, and surgeons such as Mark Terry, Francis Price and Gerrit Melles all welcome people to come and learn from them. We also provide learning opportunities here [at Johns Hopkins]. It's best to take an actual course first, then follow that up with online resources such as case videos. Stay in close communication with people who have experience, both before and after you begin your own cases."

Dr. McKee says there's no substitute for experience. "DMEK is tough to do, but you have to stick with it," he says. "I can picture someone coming in, taking our course, then going home and trying to apply what he'd learned and getting frustrated. To avoid that, he has to be in the wet lab practicing a lot. He has to have enough patients to do this on a regular basis, just like phaco. If you don't do enough phaco you won't get good at it. Residents have to do a minimum of 86 phaco cases to graduate, and even if they do 100 they're still just good enough to get by. It takes practice and experience to do DMEK properly, but as your experience level grows, your operative time will decrease, and it will all have been worth it." REVIEW

Is DMEK Ready for Prime Time?

Christopher Kent, Senior Editor

The challenging nature of this procedure has given surgeons pause, but those with experience say it's worth the trouble.

Treating a corneal problem such as Fuchs' dystrophy used to mean performing penetrating keratoplasty. More recently, Descemet's stripping endothelial keratoplasty, which transplants only the posterior layers of the cornea, has been refined to the point at which it's now a common choice for treatment.

In the past few years, this trend toward minimizing tissue replacement has continued with the development of Descemet's membrane endothelial keratoplasty, or DMEK, which replaces only the endothelial layer—the graft includes no stromal tissue. Results have been impressive, but the difficulty of the procedure has caused many surgeons to balk at attempting it. Here, four surgeons with extensive experience in corneal transplants share their thoughts on the current state of DMEK, and whether it's reached the point at which it should be considered the procedure of choice.

How Good Is It?

"DMEK is ready for prime time, with certain caveats," says Francis W. Price Jr., MD, president of the Price Vision Group in Indianapolis and founder and board president of the Cornea Research Foundation of America. (Dr. Price has done more than 1,000 DMEK procedures.) "DMEK is significantly better than any other transplant procedure. Postoperative visual acuity is better with DMEK; the wound sizes are smaller because we're putting in less tissue; and the visual recovery is predictable—not as predictable as phaco, but pretty predictable. For that reason, when patients need to have both eyes done, we're now beginning to do the eyes a week apart. The patients are doing really well. There are a few exceptions, of course; we have a few primary failures and some patients have residual edema. But for about 80 percent of these patients, we can do their eyes one week apart.

"One reason for this is that our research has found that the stroma is important for inducing rejection—something we never thought until we started analyzing our DMEK data," he continues. "We used to think that the endothelial layer was most important for stimulating immune rejection of the graft, but our data suggests that either the amount of donor tissue matters, or the stroma is more important. We're actually seeing more rejections in our DALK [deep anterior lamellar keratoplasty] surgeries than we see with DMEK. That's a huge shift in our understanding of corneal transplants."

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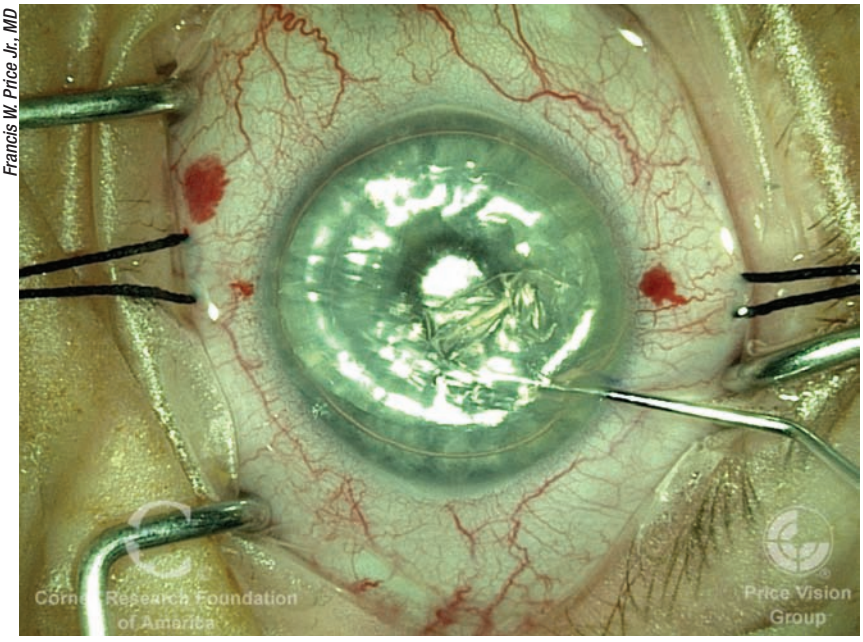

Descemet's membrane is stripped off the back of the recipient's cornea in preparation for implantation of the donor graft.

professor of cornea and external diseases at the University of Iowa hospitals and clinics and the Department of Ophthalmology and Visual Sciences, and assistant medical director at the Iowa Lions Eye Bank, has been doing DMEK, including fellowship training, since the spring of 2012. "I started on faculty at the University of Iowa that September, recommending the increased use of DMEK," he says. "Since then, we've done about 150 cases in two years. I typically perform five to 10 DMEK cases a month.

"We've been impressed with our clinical results," he continues. "I can get most patients into glasses a month after DMEK, where it takes six to eight weeks with DSAEK. And patients who have had DSAEK in one eye and DMEK in the other have remarked on their perceived improved visual benefits from DMEK. Even when the Snellen acuity is the same, patients almost invariably tell me that the DMEK eye has better vision. My interpretation is that without the stroma/stroma interface you have in DSAEK, you get less light scatter and thus have fewer higher-order aberrations."

Mark A. Terry, MD, director of corneal services at the Devers Eye Institute in Portland, Ore., and professor of clinical ophthalmology at Oregon Health & Science University has been doing DMEK for about four years. "We now do about seven per week, 28 each month," he says. "In comparing DMEK to DSAEK, we find that the quality of vision and the rapidity of visual improvement is better with DMEK.

"Previously there were a lot of nonstandardized steps to the DMEK procedure," he adds. "However, in the past year and a half the technique here at Devers has been standardized to the point where, using pre-stripped and pre-marked tissue, we now teach skills-transfer courses in DMEK. The surgeons that leave our courses are getting low rebubble rates and good results with their initial DMEK cases."

The Learning Curve

In terms of the caveats to DMEK's readiness for prime time, Dr. Price says the learning curve is a concern. (Difficulty mastering the procedure has clearly been a factor in many surgeons' reluctance to undertake the procedure.) "DMEK is definitely more difficult to do than DSEK," he notes. "The problem is, DMEK is just like phaco in that it takes a lot of pattern recognition and a lot of experience to do it well. If a surgeon had to start learning phaco from scratch instead of from a residency program, and he was only doing one or two phacos a month, he'd never get there. Maybe a few surgeons could master DMEK under those conditions, but the vast majority of surgeons could never accumulate enough experience to develop the necessary pattern recognition, the ability to intuitively know what's going on in the surgery. Unfortunately, the only way to get that kind of extensive training is to do a fellowship at a center like ours, where multiple DMEKs are done each week."

Dr. Terry notes that despite the complexity of DMEK surgery, it becomes routine once the surgeon has really learned to do it. "The key with DMEK is patience," he says. "It's not like DSAEK, where if you do the same thing over and over, you get the same result over and over again. With DMEK you have to recognize that one technique of unscrolling may be perfect for one piece of tissue and not work as well with the next graft. That's why it's important to have a repertoire of techniques and strategies to fall back on." He adds that the need for patience extends to the tissue unscrolling. "One tissue may unscroll in a few seconds, while another might take nine or 10 minutes," he says.

To help other surgeons learn DMEK, Dr. Price recently completed an electronic book on the topic with coauthor Yuri McKee, MD, titled *The Digital Manual of Ophthalmic Surgery and Theory: DMEK*. The iBook is available at the iTunes book sec-

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The Australian Graft Registry: Is PK Better?

Recently, the Australian Graft Registry surprised most corneal surgeons by reporting that its long-term data suggested that penetrating keratoplasty produced better outcomes than Descemet's stripping endothelial keratoplasty or Descemet's membrane endothelial keratoplasty.[1] Francis W. Price Jr., MD, president of the Price Vision Group in Indianapolis, says that flies in the face of most surgeons' experience. "The Australians reported all these problems with poor graft survival, even though if you look at their data, everybody's switching to DSEK and a few are switching to DMEK. Why are they having all these problems?

"The reality is, even with DSEK, which is less involved than DMEK, you have to do a certain volume to become good at it," he says. "If you have a country that's very spread out the way Australia is—people are far apart—and no one really has a high volume, they don't develop the skill sets to do complex surgeries efficiently and effectively. In order to get good results with DMEK, you have to have centers where people do a lot of these surgeries every month."

Dr. Price notes that there are a number of factors confounding the Australian Registry data that might help explain why the PK results look better than the endothelial keratoplasty results. "For one thing, the PK results include the visual acuity of patients wearing hard contact lenses," he says. "Any surgeon can do that with a PK patient—put a contact lens on the eye and the patient sees 20/20. You might actually have more 20/20 outcomes with PK than with DSEK if you use a hard contact lens. But grandma can't take that contact lens in and out every day, so that's not a realistic way to measure the outcome.

"At the same time," he continues, "PK will leave you with more patients who are count-fingers, hand-motion and blind because of complications or irregular astigmatism. With EK, you don't lose eyes from suprachoroidal hemorrhages; you don't have a neurotrophic cornea with no sensation or a breakdown of the ocular surface because the patient has no feeling on the eye. You don't have all of the wound-healing problems—the sutures getting loose, getting vascularized, and having them reject the graft, and you don't lose the eye from infection. You eliminate all of that with endothelial keratoplasty."

Dr. Price notes another factor that may have skewed the reported results. "The report didn't show the center effect," he says. "In other words, centers that were doing a lot of DMEKs didn't have better results than those that weren't, although they did find that effect with PKs. So I emailed them and asked: How many grafts a year did it take for a center to be designated as an EK center? They said 15. That's one a month! If you're not doing four or five DSEKs a month, you're not likely to develop the skill set to get good outcomes.

"It's true that when a surgeon is learning to do EK, he'll have more primary failures, which is a problem because you don't want to waste tissue," he admits. "But even if you have to do two DSEKs on one eye, the patient will still get her vision back, and she'll get it back a year or two sooner than with a PK. Yes, when surgeons go through the learning curve they lose more grafts—but they lose fewer eyes. And people end up with more functional vision, despite what the Australian data shows.

"Right now, some people argue that it's not that much better to do DMEK than DSEK," he concludes. "But how many people would say that about DSEK vs. PK? The Australians seem to be saying that, but in the United States it would be hard for someone to stand up and say, 'I think it's fine to do a PK on my Fuchs' dystrophy patients.' The data is overwhelming that the risk, the visual recovery, everything is better with DSEK."

—CK

tion for $19.99, although the authors sometimes offer the book at a sale price of 99 cents (which they are doing in conjunction with this article for a three week period in September, 2014). "The reason we used the iBook format is that you can have unlimited photos, figures and video embedded into the text," he explains. "So it's like a textbook, but with all those additions. However, you can only download it onto an iPad or Mac with the Mavericks operating system."

Given the learning curve problem, should a surgeon even attempt to add DMEK to his armamentarium if he has very few patients likely to need the surgery? "That's highly surgeon-dependent," says Dr. Terry. " Some surgeons can do one or two DMEKs a month and be very good at it. Others will have a miserable time reaching and maintaining the necessary skill level with only one or two cases a month. Only the surgeon can make that decision. But if you want to offer DMEK, you have to commit to going through the learning curve. Then see how it goes; if you don't start to feel comfortable with it after 10 cases, you have to decide whether that's likely to change or whether you should stop and refer those patients to another surgeon from now on."

The Argument for Waiting

Although everyone seems to agree that DMEK can produce better outcomes than DSEK, many surgeons feel that the potential benefits do not outweigh the drawbacks of the high learning curve. "DMEK is a wonderful procedure," says William W. Culbertson, MD, director of the Bascom Palmer Eye Institute Laser Vision Center and professor of ophthalmology at the University of Miami Miller School of Medicine. "People get their improved vision earlier, and ultimately, they probably get a little bit better vision than patients with DSEK

do. However, there are a number of practical problems standing in the way of its acceptance. If a surgeon could just do DMEK and have it be successful every time, it would be the procedure of choice. The problem is, right now DSEK has a higher success rate."

Dr. Culbertson notes that there are several reasons for this. "For one thing, the learning curve is steep compared to DSEK," he says. "You have to be able to unfold the tissue inside the eye and maintain its orientation during the unfolding event. It has a fairly high frequency of partial attachment or nonattachment, or developing folds in the graft. Then you have to take the patient back into the OR and do something to correct the problem, such as putting more air in the eye, and you may have to do this more than once. There are a handful of surgeons in this country who do DMEK almost exclusively, and do a lot of it. They can say it's their regular procedure. But it's going to be a less dependable procedure for the other 99 percent of corneal surgeons.

"Another problem is the logistics of having to redo your work if the graft doesn't stick," he says. "This may be easy to manage if DMEK is almost the only thing the surgeon does and he's working in his own center, where he can just walk across the hall and try to reattach a graft with more air or more manipulation. But if you have to schedule this in a surgery center on a day that's not your regular day, or do it after hours, and it can't be easily done in the office or adjacent to the office, it becomes a logistical problem. It can also become a financial problem, because the patient's insurance may not pay for a reoperation.

"Having to bring the patient back to rebubble the graft can have other consequences as well," he notes. "In Florida, if you take a patient back to surgery within 30 days of the original surgery, it's reportable to the state board. What happens next depends on how they interpret that. As surgeons, we all accept that DMEK is a worthwhile reason to take somebody back for reoperation, but it may not appear that way to the state board or insurance company. So you end up having to defend yourself to regulatory agencies and hospitals and boards."

Dr. Culbertson also points out that DSEK has become very dependable, and patients are thrilled with its results. "I have yet to see a successful DSEK patient who wasn't ecstatic," he says. "Patients that have these surgeries go from 20/200 to 20/30 with DSEK, or from 20/200 to 20/20 with DMEK; they're happy either way. So in terms of patient satisfaction, DSEK is every bit as good as DMEK."

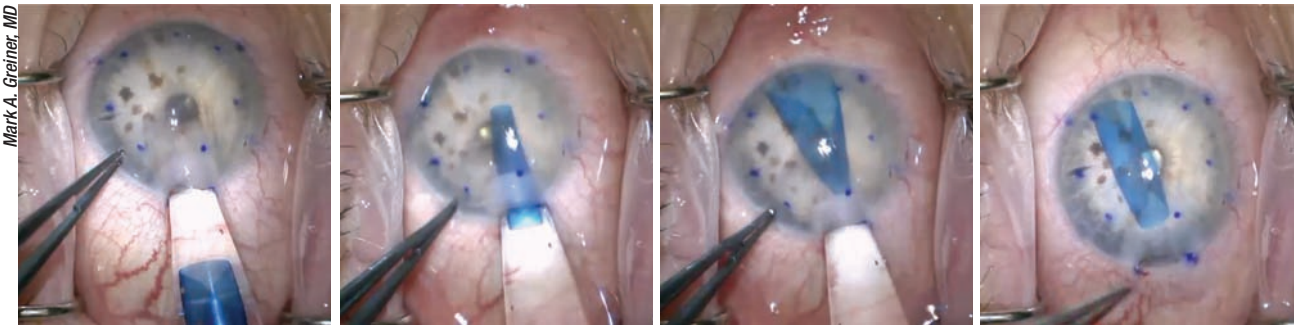
Dr. Culbertson says he doesn't mean to be negative about DMEK. "I think it's a wonderful operation," he says. "When it gets more refined and dependable I think it will be the way to go."

Settling on the Technique

Lack of a gold-standard technique for performing DMEK has been another factor leading surgeons to feel that the procedure might not be ready for prime time. Clearly, determining the most efficacious techniques is something that happens gradually over time as more and more surgeons perform the surgery. Today, an increasing number of surgeons are performing DMEK regularly; as a result, the surgery is gradually becoming safer, simpler and more successful. Many DMEK surgeons now believe a set of gold standard techniques is close to becoming a reality. Dr. Greiner says that from the surgeon's perspective the main concerns are tissue preparation; tissue insertion; making sure that the tissue is oriented properly; and managing the complication of graft detachment, should it occur.

Regarding the tissue preparation, many surgeons worry about whether

Mark A. Greiner, MD



Donor graft tissue is injected into the anterior chamber using a modified Jones tube. The glass tube has an enlarged section before the tip, where the graft floats before injection. The scrolled tissue adjusts to match the size of the space through which it is passing.

they should attempt to prepare the grafts themselves. Dr. Price notes that there are multiple concerns that might influence a surgeon's choice—some technical and some practical. He points out that techniques for preparing the tissue in your own practice have now been refined to the point of having 1 percent tissue loss or less, as is the case at his practice. "That minimal loss rate has been replicated, not just using our technique but several others as well," he says. "Friedrich E. Kruse, MD, in Germany has that level of preparation success, and eye banks are getting close to that. You can have an eye bank do the tissue preparation for you, but you're going to be charged about $1,000 more for the extra processing. So which way you choose to proceed may depend on how you're reimbursed, or if your facility cares about that charge.

"Of course, a lot of transplants are currently done by surgeons who don't do very many," he continues. "One result is that facilities may not even notice if they don't get reimbursed. Sightlife, one of the largest eye banks, located in Seattle, looked at a lot of data from the Centers for Medicare & Medicaid Services and found that hospitals are often not paid for the tissue. Apparently, nobody complains, presumably because they don't do very many grafts. We do more than 600 per year, so if we don't get reimbursed for the cost of the tissue it's a big deal. As a result, I'm always making sure we get paid. If we're not getting paid I talk to the carriers or insurance companies and find out what's going on."

Dr. Greiner and his colleagues have worked closely with their eye bank partners at the Iowa Lions Eye Bank to refine the protocol for preparing DMEK grafts. "They do an excellent job of making prestripped and prepunched tissue available," he says. "When we get the tissue in the OR, it's already been prestripped from the host stroma and laid back down in its native anatomical position. In addition, surgeons can request that their DMEK tissue be subsequently punched with a trephine to their desired size; I like my tissue to be 7.5 mm in diameter."

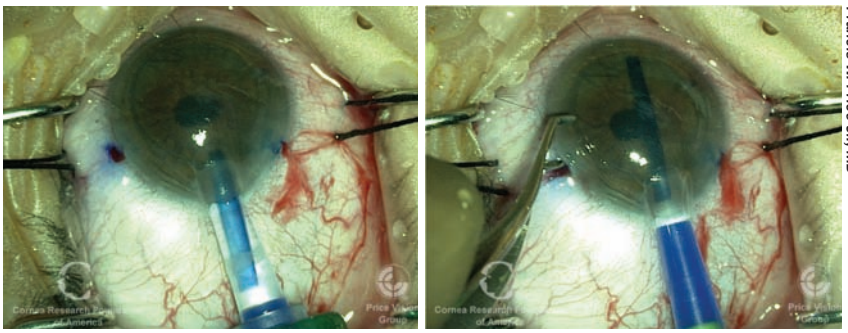
Finding the Best Injector

Another issue that has worried surgeons considering whether DMEK is ready for prime time has been settling on the best way to get the extremely fragile tissue into the anterior chamber. Today, the options appear to have been narrowed down to a few favorites, among which the leading DMEK surgeons seem split.

Dr. Price notes that getting a DMEK graft into the anterior chamber is totally different from injecting an IOL. "There are many different ways to put the graft in," he observes. "Dr. Kruse in Germany and the surgeons at our center like to use IOL injectors—which is off-label, of course. I like that approach because it's a totally closed system, although you have to choose an appropriate injector system. Only certain cartridges work. With the cartridge we prefer to use, we put the tissue into the cartridge and the plunger comes up behind it. It seals with the tip of the cartridge so that when you put it in the eye, you don't have to worry about flow going back and forth." Dr. Price says he prefers not to specify the injector they use, since it's off-label, but surgeons interested in performing DMEK are welcome to ask him about it.

Dr. Greiner says when he was first starting to do DMEK he ran into trouble because the tissue insertion device was suboptimal. "I was using a Microstaar injector designed for IOL insertion with a foam plunger at the end," he explains. "I was filling the back of the injector with a cohesive viscoelastic to get the graft to move out of the cartridge. Because it was an open system, when you advanced the plunger you could have egress of fluid or viscoelastic around the plunger or through the back of the cartridge. You couldn't propel the tissue forward in a controlled way, and you had to use a viscoelastic agent.

"We've switched to the off-label use of a Jones tube," he continues. "This has allowed us to achieve control of the anterior chamber during tissue injection because it's a closed system, which is incredibly important for the fluidics and tissue delivery dur-



Francis W. Price Jr., MD

Injection of donor graft tissue using an IOL injector, a method favored by some surgeons. This injector creates a closed system and allows a controlled injection of the tissue.

ing DMEK. The Jones tube we use can be coupled to a syringe filled with BSS, so we can eliminate the use of viscoelastic. In addition, the glass material is smoother on the inside than the plastic, and it doesn't have as much electrostatic charge as the plastic does. As a result, we get a very smooth delivery."

Dr. Terry, who uses the same glass tube as Dr. Greiner, notes that it was modified by his colleague Michael D. Straiko, MD. "He had the manufacturer change the shape so it would work with DMEK surgery," he says. "A standard Jones tube is a straight glass tube that's used for lacrimal surgery. But when you aspirate tissue into a straight injector, any suction pressure you apply to the other end of the injector will aspirate the tissue very quickly into the syringe. It makes the process hard to control. Dr. Straiko's glass injector has a beveled tip, and it quickly balloons out into a wider tube. This modified tube is attached to a syringe by a coupling section made of standard plastic tubing. Now, when you draw back on the syringe the tissue is pulled into the outpouching area and stabilizes there. The tissue is far less likely to be damaged and the injection process is far smoother."

"In the Petri dish, the graft is scrolled up like a cigar," says Dr. Greiner, adding that the tissue always scrolls with the endothelium on the outside. He notes that the glass tube is tapered to fit into a reasonably sized clear corneal incision. "I use a 2.8-mm keratome and enlarge the wound slightly to accommodate the tip of the glass tube," he says.

Getting the Graft to Stick

Another concern that has discouraged surgeons from making DMEK a part of their armamentarium has been the tendency for the grafts to dislocate—an especially common problem during a surgeon's learning curve. Dr. Greiner reports that significant progress has been made here as well.

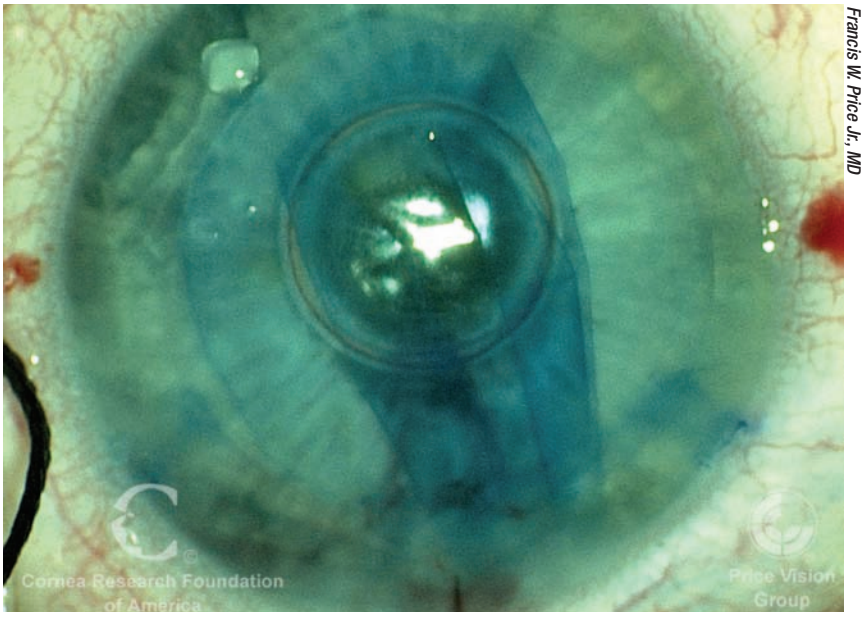
"Once the graft is centered, an air bubble is commonly used to hold the graft in place," he explains. "The bubble presses the graft up against the stroma when the patient is lying on his back, nose to the ceiling. It helps the graft stay physically apposed to the host stroma and begin to self-adhere as the pump function in the graft tissue is waking up. The longer the bubble takes to go away, the longer the assisted apposition time.

"The biggest problem reported during DMEK surgeons' learning curve is dislocation of the graft," he continues. "Typically, this starts with lifting of the edges. Edge lifts can lead to progressive delamination of the graft and require a repeat injection of an air bubble. That certainly frustrated me when I first started doing DMEK surgery.

"As a result of those experiences I made the switch to using sulphur

hexafluoride 20%," he says. "This is a mixture of air and gas, taken from the playbook of our vitreoretinal colleagues. This concentration is typically isoexpansile—it won't expand the way it might at higher concentrations—and it has a longer half-life in the anterior chamber than air alone. An air bubble typically disappears four or five days postop, whereas an SF6 20% bubble is typically still around at week one; it takes about seven to 10 days for these bubbles to fully resorb. That extra time helps to minimize graft dislocation. Our rebubble rate is now very low, and our data has not found any indication of toxicity to the corneal endothelium as a result of using the SF6 20% gas."

Dr. Greiner says he makes sure the anterior chamber is inflated with a bubble of SF6 20% for about 10 minutes to let the graft begin to adhere, although some of his colleagues give it 15 minutes. "After the waiting period we do an air-fluid exchange," he says. "We make sure enough of the air bubble is removed to ensure that there is no air or gas trapped behind the iris, to minimize the chance of pupillary block. Once we're sure no gas is trapped behind the iris, I reinflate with more gas, filling 80 to 90 percent of the anterior chamber."



Francis W. Price Jr., MD

Once the donor tissue is inside the eye and the endothelial side is in the correct orientation, an air bubble can be placed underneath the graft to help it unfold, as above.

Still More Refinements

Dr. Greiner lists additional strategies that have been developed that are making DMEK more surgeon-friendly and helping to maximize the procedure's success rate:

• ***If your grafts come from an eye bank, consider having the tissue stamped for ease of orientation.*** Especially for surgeons first attempting DMEK, determining whether the graft is right-side-up can be challenging. Dr. Greiner points out that some eye banks are now placing an S-stamp on the Descemet's side of the graft. "This may be helpful if you're just starting to do DMEK, or in cases with a challenging view of the eye," he says.

• ***Perform an inferior peripheral iridotomy.*** "This will help minimize the chance of pupillary block from having air or gas trapped behind the iris," explains Dr. Greiner. "I perform an inferior peripheral iridotomy intraoperatively, or in phakic cases, preoperatively with a laser."

• ***Make sure the pupil can dilate and constrict as needed at different points during the surgery.*** "You want the pupil to do what you want it to do, when you want it to do it," Dr. Greiner points out. "In order to facilitate the safe and successful unscrolling of the graft, you want a very constricted pupil. To achieve that, we use miochol, a short-acting miotic. Then, in order to minimize the complications associated with having an air or gas bubble inside the eye, you want the iris to dilate. So we typically avoid using strong, long-lasting miotic agents such as pilocarpine and miostat, precisely because we want to be able to modulate the pupil.

"I tend to apply my dilating eye drops after the tissue is unscrolled and centered, right before I float the graft with the air-gas bubble," he adds. "That's to make sure the dilating drops we use, cyclopentolate 1% and phenylephrine 2.5%, penetrate into the eye effectively. Once an air bubble is in there, it's difficult for the topical drops to diffuse and produce appropriate dilation by the end of the case. So applying them before inserting the air bubble works best."

• ***Consider using a retrobulbar block.*** "I know that many surgeons want to, and do, use topical anesthesia for DMEK, and that's great," says Dr. Greiner. "However, it's very difficult for surgeons who are just making the leap from DSAEK to DMEK to feel comfortable knowing their patients are awake and moving while they may be struggling and less sure of themselves than they will be later on. Here at the University of Iowa, we use retrobulbar blocks for all of our DMEK patients. The retrobulbar block also causes pupillary dilation. That's another reason to use a short-acting agent such as miochol to constrict the pupil before you inject the graft."

• ***Learn multiple techniques***

for unscrolling the graft. Dr. Price notes that there are many ways to get the donor tissue to unfold. "We use different techniques with different eyes," he says. "There are a variety of techniques that work."

The technique favored by Drs. Greiner and Terry is a technique in which the tissue is unscrolled by gently tapping on the anterior surface of the cornea. (This technique was described in a 2013 paper by Efdal Yoeruek, MD, at Eberhard-Karls University in Tuebingen, Germany.[2]) "The anterior/posterior force that results from tapping on the cornea is transferred into a lateral force inside the graft," Dr. Greiner explains. "The resulting fluid movement inside the scrolled graft causes the leaflets to unfold."

Dr. Terry notes that even if you choose this approach, it's important to have multiple tapping maneuvers in your repertoire. "We call those manipulations 'dance steps,' because you're dancing with the tissue," he says. "We teach five dance steps in our DMEK course. For example, you may tap on the side of the cornea, or compress the peripheral cornea, or use two instruments to tap on the surface. With any given piece of tissue one dance step may work; with another tissue that manipulation may not work. Each tissue is a different thickness and different compliance, and may differ in how tightly it's scrolled and how it unscrolls. By having five dance steps to choose from, you'll have at least one strategy that will work for any given piece of tissue."

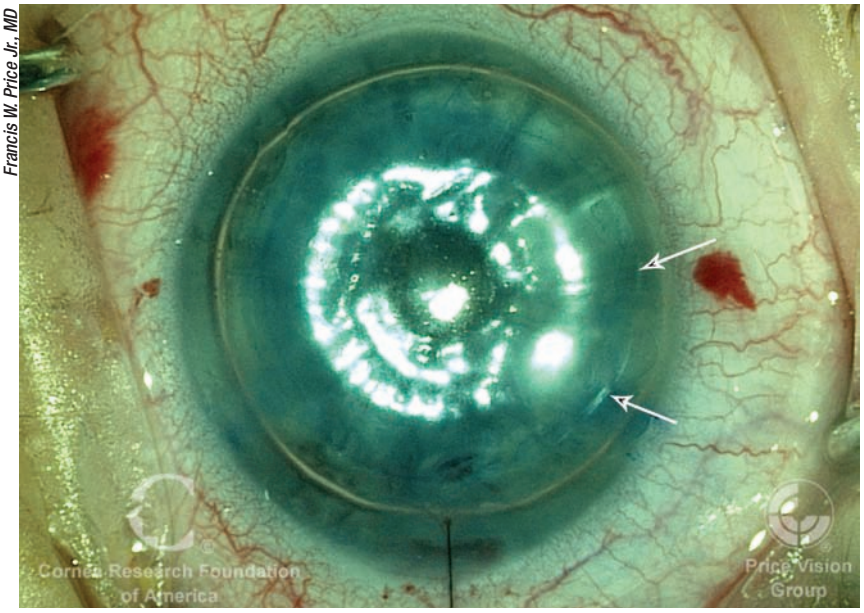
Some surgeons, including Dr. Price, sometimes insert an air bubble inside the scrolled tissue to help it unscroll. Dr. Terry says his group doesn't advocate that strategy. "We don't feel it's necessary if you use the dance steps," he explains. "I know that Dr. Kruse puts an air bubble inside the scroll when the tissue is inside the injector, and that has worked extremely well for him. But that is technically a very difficult maneuver, so we don't teach that option to beginning DMEK surgeons."

What the Future Holds

Of course, whether or not a procedure is already considered ready for prime time, improvements will continue to appear. Dr. Price notes that there are still many ways DMEK can be improved. "Sometimes the donor grafts are nonfunctional," he says. "We haven't figured out why we get some of these primary failures; there's no surgical problem to explain them. And we can always come up with better techniques, such as improving the way we put the tissue into the eye or finding an approach that will ensure that the graft always sticks. Another issue is that there's sometimes a significant mismatch between the shape of the donor cornea and the patient's cornea—which also sometimes happens in DSEK. This may degrade vision or make it harder for the graft to stick. At this point we don't measure or match curvature, and most people do fine anyway, but it's another factor that may eventually be improved. We're working on all of these issues."

Dr. Price believes that as more surgeons perform DMEK, the procedure will continue to improve. "More surgeons doing DMEK means different eyes looking at it and different thought processes," he says. "Each person adds a little bit to the general knowledge. We saw that with DSEK; as more surgeons did it, the procedure got better and better. We're going to see the same thing with DMEK."

Dr. Culbertson agrees that DMEK is improving. "There have been step-by-step improvements in the technique," he says. "DSEK started off the same way, with glitches and problems and rebubbling. But as more and more has been learned about it and the technique has been refined, it's gotten to be much more dependable.



The graft is unfolded and in place; air placed in the anterior chamber helps to hold it there. (Arrows mark the edge of the graft.) Some surgeons now place a longer-lasting mixture of air and sulphur hexafluoride inside the eye, holding the graft in place for additional days.

I expect the same thing will happen with DMEK; and as dependability and technique improve, there will be greater acceptance of it."

Drs. Greiner and Price agree, however, that DMEK is unlikely to ever totally replace DSEK. "Principally, that's because not every patient has normal, straightforward anatomy," says Dr. Greiner. "DMEK is my workhorse for normal anatomy, which most patients have. But I continue to use DSAEK for eyes with abnormal intraocular anatomy, or hardware in the eye from a previous surgery, such as a glaucoma drainage device, or a trabeculectomy, a large peripheral iridectomy or a core vitrectomy. These sorts of conditions can make it very difficult to execute successful DMEK surgery."

So: Is It Ready?

Dr. Terry believes DMEK is ready for prime time. "If we didn't believe that, we wouldn't be teaching our courses," he says. "I think patients should have the best procedure possible. Every surgeon should treat every patient as if he or she were a family member. If a surgeon believes that DMEK is better than DSAEK, and that surgeon would refer his mother or brother to someone else to have DMEK rather than DSAEK, then he should do the same with all of his patients. Simply not offering the surgery because you're not comfortable doing it would be like not offering phaco to your cataract patients because you're only comfortable doing extracap."

Dr. Greiner notes that all of DMEK's surgical details are very nuanced. "It takes a lot of attention to detail to make sure you get a successful outcome," he says. "Nevertheless, I believe this is the surgery to do in cases with straightforward intraocular anatomy. In our group, DMEK is the go-to procedure in cases of straightforward Fuchs' endothelial dystrophy and pseudophakic bullous keratopathy. From our perspective, there's no question—the potential for any downside is worth taking on the calculated risk. The advantages occur far more frequently, and are celebrated by both patients and surgeons."

Dr. Culbertson says that whether DMEK is ready for prime time probably depends on the surgeon's situation. "Some surgeons do a lot of DMEKs and have a setup that makes it easy to manage," he says. "They get very experienced at it and have a high success rate, and it doesn't interfere with the care of other patients in their office. But many surgeons aren't in that situation. So when I weigh the two-line difference in outcomes against the hassle and expense of possibly having to take the patient back for additional procedures at addition cost and inconvenience, I come down in favor of DSEK. Again, I've never seen an unhappy DSEK patient, unless the patient had to have the procedure repeated. My goal is to make patients happy with the least inconvenience."

In any case, Dr. Terry believes the question of whether DMEK is ready for prime time will soon be an obsolete issue. "In a few years we may still rely on DSAEK for complex cases such as anterior chamber IOLs and tubes," he says, "but I think everyone will be doing DMEK for routine cases."

Dr. Price adds that the challenges inherent in performing DMEK surgery are part of what makes being a surgeon enjoyable. "Most people who choose to be surgeons are going for a little gusto," he says. "They get bored doing the same thing. Well, if you want to have adventure and challenges and an exciting time in the OR, DMEK is the procedure for you." REVIEW

Dr. Price has a financial interest in the iBook on DMEK that he co-authored. Drs. Terry, Greiner and Culbertson have no financial interest in any item mentioned.

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Cross-Linking: New Uses and Techniques

Michelle Stephenson, Contributing Editor

Researchers continue to find ways to help patients with corneal collagen cross-linking.

Corneal collagen cross-linking was first used in 1998 to strengthen the cornea through application of riboflavin followed by treatment with ultraviolet A light. The process was originally used to treat keratoconus, pellucid marginal degeneration and ectasia after LASIK, but researchers continue to find new uses and techniques for cross-linking to benefit a larger population of patients. Corneal collagen cross-linking is not FDA-approved in the United States.

X-Linking for a Refractive Effect

Internationally, investigators are conducting studies to determine the efficacy of cross-linking in correcting refractive error. "It became evident when looking at the changes in the corneal shape following cross-linking for keratoconus and ectasia that it is possible to induce refractive changes," says Michael B. Raizman, MD, who is in private practice in Boston. "Especially with some of the newer UV light devices that provide customized light profiles, it became apparent that it might be possible to control more specific changes in corneal curvature that could affect the refractive error. The next step was to consider this for normal corneas, as opposed to corneas that are ectatic from keratoconus or previous laser procedures."

The KXL II unit by Avedro, which is used to perform photorefractive intrastromal cross-linking (PiXL), has been introduced in other countries and uses an active eye tracker to achieve a patterned delivery of UV light. PiXL has the potential to nonsurgically correct myopia and improve cataract surgery outcomes. The device delivers specific light patterns to the cornea based on a patient's topographic data.

"PiXL has a lot of potential," says Rajesh Rajpal, MD, who is in private practice in the Washington, D.C., area. "The concept is that, by differentially cross-linking within different parts of the cornea, the refractive error can be changed. With excimer laser treatment, we are removing tissue. PiXL affects tissue in different patterns, and because the cornea seems to change structure to some degree or at least change the curvature, ultimately, you achieve a refractive effect. This has a lot of potential, but it is still preliminary in terms of outcomes and duration of refractive result."

Dr. Raizman notes that the original devices used for collagen corneal cross-linking just delivered a broad beam of light diffusely to the cornea. "The new Avedro device delivers the ultraviolet light in different patterns, different shapes and different intensi-

ties to different portions of the cornea in a controlled way," he says. "There is still a lot we need to learn about customized UV light delivery with regard to using these patterns for treating keratoconus, for instance. Instead of cross-linking the whole cornea, would it be better if we cross-linked more intensely over certain areas of the cone? We still don't know the answer to that, but it seems likely that we can do better with more specific patterns and perhaps customizing the patterns for different corneas."

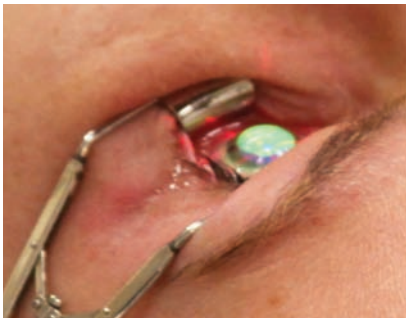
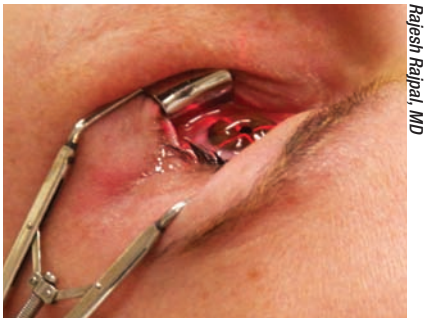


Figure 1. Corneal collagen cross-linking treatment (UV light on).



Rajesh Rajpal, MD

Figure 2. Cross-hairs used for focusing treatment (UV light off).

Epithelium: On or Off?

According to Dr. Rajpal, there are continuing efforts toward better understanding whether epithelium-on or epithelium-off treatments are more effective. "I think it comes down to the type of riboflavin being used to some degree," he says. "If we are using riboflavin that is able to be absorbed through the epithelium, then, hopefully, we are all optimistic that the effect in the stroma of the cross-linking is as good as taking the epithelium off, so we don't have to do epithelium-off treatments. That continues to be an area where there is significant effort. Part of it just comes down to having enough treatments done to be able to analyze that data to see if the effect is as significant as the effect with epithelium-off treatments."

Peter Hersh, MD, who is in private practice in Teaneck, N.J., agrees. "There are clinical studies going on in the United States looking at epi-on cross-linking," he says. "The jury is still out on the efficacy of that compared to standard cross-linking. Epi-on cross-linking may be limited by a few factors, such as absorption of the incoming power by the epithelial cell layer. Also, oxygen availability, in theory, may affect epi-on outcomes. We have learned that oxygen is important in at least one of the pathways of cross-linking. Because oxygen diffusion through the epithelial layer may not be as great as when the epithelium is removed, this may be a limiting factor as well to the efficacy of transepithelial cross-linking. I do think that the ability to get riboflavin into the cornea via transepithelial technique is much improved, and this is much less of an issue than it has been in the past."

A recent study conducted in Turkey has found that transepithelial cross-linking with prolonged preoperative riboflavin application can achieve a similar depth of effect in the stroma with less pronounced confocal microscopic changes as standard cross-linking with complete epithelial debridement.[1] This study included eyes with progressive keratoconus that underwent cross-linking with the standard technique and with a transepithelial technique after prolonged riboflavin drop application for two hours. The depth of the cross-linking effect was similar in both groups (380.86 ±103.23 µm in the standard cross-linking group and 342.2 ±68.6 µm in the transepithelial cross-linking group). In the eyes that underwent standard cross-linking, anterior stromal acellular hyper-reflective honeycomb edema with posteriorly gradually decreasing reflectivity and increasing number of keratocytes and some sheets of longitudinally aligned filamentary deposits were observed on *in vivo* confocal microscopy. The keratocytes repopulated in a posterior-to-anterior direction. In the eyes treated with trans-epithelial cross-linking, there was less pronounced keratocyte damage, extracellular matrix hyper-reflectivity and fewer sheets of filamentary deposits at the posterior stroma.

Accelerated Cross-Linking

Accelerated cross-linking, in which the UV light is delivered at a higher intensity over shorter periods of time, is growing in popularity. Initial published reports indicate that this is a safe and effective alternative to the traditional Dresden protocol, but larger studies are needed to understand the optimal parameters. Combining accelerated treatments with pulsing of light and supplemental oxygen may be even more effective. Three multicenter studies in the United States are looking at the efficacy of accelerated cross-linking. Ultraviolet power is increased typically from 3 to 30 milliwatts, and early results are encouraging.

Dr. Rajpal has been using accelerated cross-linking in the clinical trials he is participating in. "This shortens the amount of UV exposure time," he says. "It is easier for the patient and for the doctor, and because there is less time under the UV light, the total treatment time is shortened. The procedures have similar outcomes, so I think there is little debate

that this is the direction that all treatments are going."

X-Linking with Other Procedures

There have been many reports in the literature about LASIK Xtra, which uses cross-linking as an adjunct to standard LASIK to avoid post-LASIK ectasia and to improve refractive outcomes.

International studies have shown the benefits for patients with high myopia and high hyperopia corrections. A. John Kanellopoulos, MD, recently concluded a long-term study comparing LASIK Xtra to standard LASIK for high myopia corrections.[2]

In this study, 65 eyes underwent LASIK Xtra, and 75 eyes underwent LASIK alone. In the LASIK Xtra group, 90.8 percent of eyes had a postoperative uncorrected distance visual acuity of 20/20 (1.0 decimal) or better, and 95.4 percent had a UDVA of 20/25 (0.8 decimal) or better. In the LASIK-only group, 85.3 percent of the eyes had a postoperative UDVA of better than 20/20 (1.0 decimal), and 89.3 percent had better than 20/25 (0.8 decimal). The differences between the two groups at the 20/20 and the 20/25 levels were statistically significant.

He has also studied LASIK Xtra in patients with hyperopia and hyperopic astigmatism.[3] In this study, 34 consecutive patients with hyperopia and hyperopic astigmatism elected to have bilateral topography-guided LASIK and were randomized to receive a single drop of 0.1% sodium phosphate riboflavin solution under the flap followed by a three-minute exposure of 10 mW/cm^2 ultraviolet A light with the flap realigned in one eye and no intrastromal cross-linking in the contralateral eye.

At two years postop, the mean spherical equivalent refraction was -0.20 ±0.56 D and +0.20 ±0.40 D with mean cylinder of 0.65 ± 0.56 D and 0.76 ± 0.72 D and mean uncorrected distance visual acuity of 0.95 ±0.15 and 0.85 ±0.23 in the cross-linking and LASIK only groups, respectively. Eyes that underwent cross-linking demonstrated a mean regression from treatment of +0.22 ±0.31 D, whereas eyes that underwent LASIK only showed a statistically significantly greater regression of +0.72 ±0.19 D.

According to Dr. Hersh, internationally, topo-guided PRK is being performed adjunctively with cross-linking, and results are encouraging. Dr. Kanellopoulos has studied same-day topography-guided PRK followed by cross-linking, compared with cross-linking followed by topography-guided PRK six months later.[4-6] Procedures performed on the same day have been found to be superior to sequential procedures for visual rehabilitation.

Dr. Kanellopoulos' group found that 27 of 32 eyes achieved uncor-

rected and corrected distance visual acuity of 20/45 or better and had an improvement in uncorrected distance visual acuity and corrected distance visual acuity at last follow-up. Four eyes had topographic improvement, but no improvement in corrected distance visual acuity. Additionally, one eye required a subsequent penetrating keratoplasty, and two eyes developed grade 2 corneal haze.

Additionally, Intacs combined with cross-linking has been found to stabilize the cornea and improve corneal topography and symmetry.[7] "We are continuing our own study of Intacs and cross-linking, and we find that the combination works well. Intacs provides a fairly marked topographic improvement, and there is the adjunctive effect of cross-linking and corneal stability," Dr. Hersh says.

Also, a recent study has found that contact lens-assisted corneal cross-linking is safe and effective for performing cross-linking in corneas of less than 400 µm after epithelial abrasion, and appeared effective based on stromal demarcation line depth.[8] The study included 14 eyes diagnosed with progressive keratectasia with a corneal thickness between 350 µm and 400 µm after epithelial abrasion. Mean preoperative minimum corneal thickness after epithelial abrasion was 377.2 ±14.5 µm (range: 350 to 398 µm). A significant difference in functional corneal thickness was observed intraoperatively, before epithelial abrasion, after epithelial abrasion and with contact lens and riboflavin film. Mean minimum functional corneal thickness after the contact lens was 485.1 ±15.8. Mean absolute increase in the minimum corneal thickness along with the contact lens and pre-corneal riboflavin film was 107.9 ±9.4 µm. Mean depth of the stromal demarcation line was 252.9 ±40.8 µm. No significant endothelial loss was observed, and the corneal topography was stable at the last follow-up visit.

Another procedure of interest is Keraflex, which is performed with the Vedera System by Avedro. It uses a circle or arc of microwave energy to flatten the cornea and adjunctive cross-linking to stabilize the cornea. Dr. Hersh is currently performing Keraflex in a clinical trial. Early results of his study are promising, with significant degrees of flattening seen in some patients.

The Future

Ophthalmologists are eagerly awaiting FDA approval of corneal collagen cross-linking. "Then, I think we can examine treatment optimization, which includes potential changes in the oxygen environment or oxygen delivery, possible pulsing techniques

(continued on p. 63)


Scleral Buckling for RRD: Yes, No or Maybe?

Despite shifts in treatment options, scleral buckle remains an excellent choice to treat rhegmatogenous retinal detachment.

By Nelson A. Sabrosa, MD, PhD, Rio de Janeiro, Brazil, and Chien Wong, MD, London

Rhegmatogenous retinal detachments are encountered routinely in ophthalmologic practice and are among the most common indications for vitreoretinal surgery.[1,2] Predisposing factors for the development of RRD include myopia; increased patient age; significant eye trauma; and prior lens surgery (pseudophakia or aphakia).[3] The first descriptions of surgical RRD repair were by Charles Schepens, Ernst Custodis and Harvey Lincoff.[4,5,6]

Three main techniques are currently used to treat RRD: 1) scleral buckle surgery; 2) pars plana vitrectomy with retinopexy and intravitreal tamponade[1,2,7]; and 3) pneumatic retinopexy. Studies have generally failed to show superior anatomic or visual outcomes with one technique over another.[1] The choice of technique comes down to a combination of surgeon experience and preference, the nature and extent of RRD, and the number, distribution and type(s) of retinal break(s).

While there has been a shift over the past two decades toward PPVs,[8,9] in our opinion, primary SB remains the treatment of choice for certain RRD types, particularly in eyes without an existing posterior vitreous detachment.[10] The techniques of SB surgery have remained largely unchanged for the past 50 years. The goal is to create an inward indentation of the eye wall, thus approximating the retinal pigment epithelium to the neuroretina surrounding the break. Scleral indentation is achieved by the placement of a permanent episcleral explant/buckle at a location corresponding to the retinal break. The buckle is permanently anchored to the sclera, typically with non-dissolvable sutures. Buckle materials include silicone sponge and hard silicone that come in a variety of shapes and sizes. The exact type of buckle required varies according to the desired buckle (scleral indentation) height, and location and number of breaks.

Buckle-induced scleral indentation reduces the magnitude of vitreous traction, alters the direction of vitre-

Dr. Andre Romano

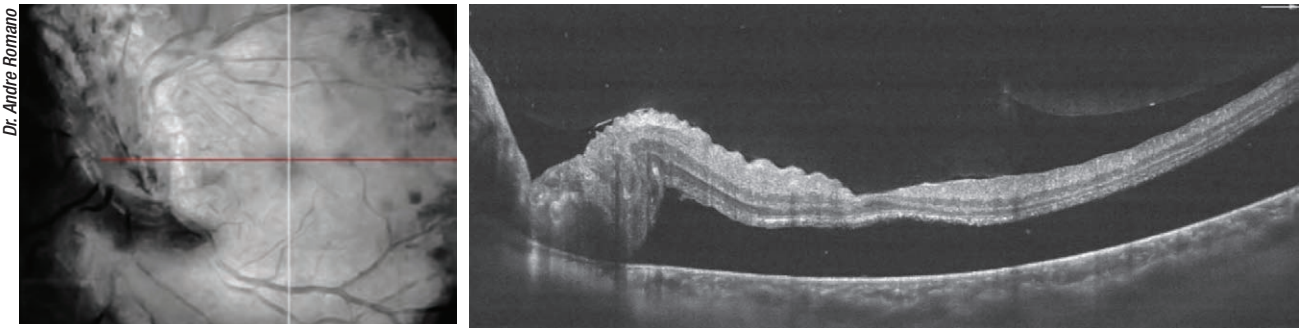


Figure 1. Preoperative examination. Left eye spectral-domain optical coherence tomography demonstrating subretinal fluid, with elevation of the fovea.

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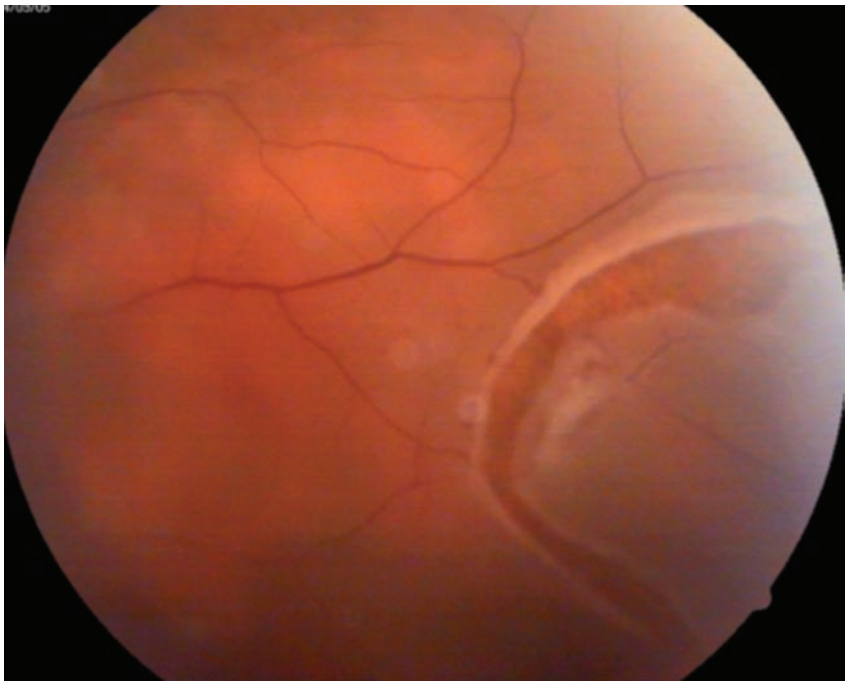

Figure 2. Preoperative examination. Color photograph of the peripheral retina demonstrating a retinal detachment with subretinal fluid and a retinal tear.

ous traction, and reduces the flow of vitreous fluid through the break into the subretinal space, thus shifting the balance towards retinal reattachment. Placement of a buckle alone does not prevent a retinal break from reopening. A permanent adhesion between the neuroretina and the RPE is achieved using either externally applied cryotherapy or laser photocoagulation.[11]

Retinal Detachment

Rhegmatogenous retinal detachment occurs when there is a full-thickness break in the retina, together with a change in the balance of forces favoring neurosensory retinal detachment from the underlying RPE, over physiologic attachment. Importantly, three types of retinal breaks can occur, which can influence the choice of surgical procedure: 1) tear (also known as flap, horseshoe or U-tear); 2) round hole (also known as atrophic holes); and 3) dialysis.

The most common mechanism of RRD is the formation of a full-thickness retinal tear during the development of a PVD.[1,10] Retinal tears account for 90 percent of RRDs, resulting from the traction exerted on the peripheral retina by the posterior hyaloid face, typically at the posterior border of the vitreous base.[8]

Round holes develop as a result of intraretinal abnormalities or in areas of lattice degeneration, and are more common in myopic eyes. For reasons that remain unclear, most round holes do not lead to retinal detachment.

Retinal dialyses occur when the retina detaches from its insertion at the ora serrata together with the vitreous base—often following blunt ocular trauma.[12] A PVD is typically absent unless pre-existing.

With all of the above break types, a full thickness retinal hole enables liquefied vitreous to flow into the subretinal space, separating the neurosensory retina from the RPE.[10,11] Although the initial presentation of patients with symptomatic detachment does vary, common symptoms include:

- PVD-related photopsias (flashing lights);
- a sudden increase in vitreous floaters, due to release of RPE cells and/or blood into the vitreous cavity;
- visual field defects; and
- decreased visual acuity-RRD involving the macula.

Surgical Outcomes

Post-surgical visual outcomes relate to the extent of initial macular involvement.[13] The retina is reattached in 90 percent of cases, with success rates nearing 100 percent in certain case series.[1] However, there is a significant difference between favorable anatomic correction and functional visual outcomes. The presence of macular involvement ("macula-off" RRD) is the most important issue when it comes to success in restoring visual acuity.[13] In macula-off detachments, only 40 to 60 percent of patients have restored visual acuity of 20/50 or better. Visual restoration is much more successful in detachments sparing the macula. In one large series, 90 percent of patients with macula-on detachments had vision of 20/40 or better following surgery.[14] Ocular coherence tomography imaging is important for identifying shallow macula-off detachments *(See Figure 1)*.

The main factors predicting poorer visual function after surgery include:

- poor preoperative visual acuity (reliable predictor);[14]
- increasing extent (clock hours) of RRD;
- increasing number of retinal breaks;
- inferiorly positioned breaks;
- macula-off (or macular-involving) RRD;
- preoperative proliferative vitreoretinopathy of any grade (PVR); and
- intraoperative hemorrhage.

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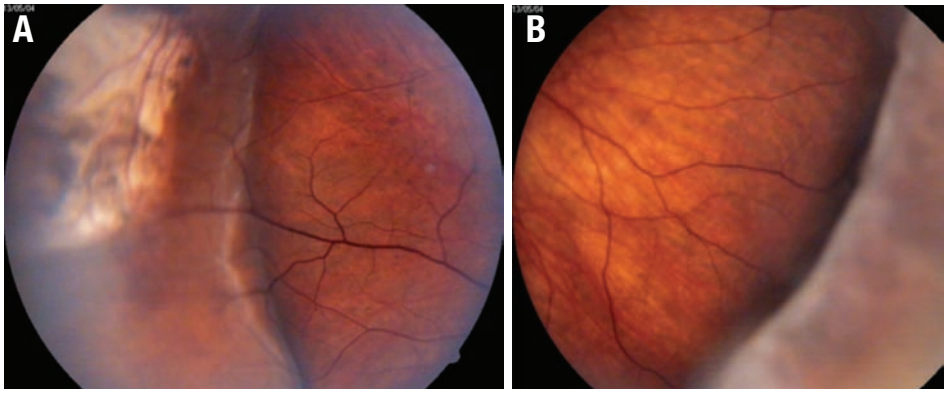

Figure 3. Color photographs of the nasal (A) and inferotemporal (B) retina following placement of a 360-degree encircling band in an eye with a rhegmatogenous retinal detachment and no posterior vitreous detachment. A cryotherapy scar is seen to be supported by the encircling band, the posterior border of which was placed so as to be posterior to the tear and retinopexy treatment (A).

Indications for SB Surgery

While PPV and pneumatic retinopexy are increasingly used for the repair of uncomplicated RRD, SB surgery still has an important role in certain RRD types.[8,10,15] In some cases, vitreous surgery is necessary to relieve vitreoretinal traction that cannot be adequately relieved by scleral buckling and other conventional retinal reattachment techniques.

In our experience, SB is the treatment of choice in patients with uncomplicated RD, in retinal dialysis and for RRDs associated with round holes.

Combined PPV+SB surgery may be associated with a decreased risk for retinal redetachment when compared to PPV for repair of phakic RRD, especially in cases with severe PVR, inferior traction and with incomplete removal of traction. The improved success rate is contributing to the function of vitrectomy, which improves peripheral visibility and reduces the occurrence of proliferative vitreoretinopathy. Some studies showed that in pseudophakic eyes, the anatomic success rate between PPV and combined PPV+SB techniques appears to be similar.[16,17]

In summary, RRDs with any of the following features can benefit from SB surgery:

- no posterior vitreous separation (no PVD): it could be hard to induce a PVD and remove the posterior vitreous in an eye with an RD;
- dialysis: usually no PVD and hard access to the periphery with PPV in a phakic eye (lens touch);
- round or atrophic holes;
- breaks anterior to the equator: easy to place a buckle in the right position and hard access to the periphery with PPV in a phakic eye (lens touch);
- inferior breaks: support of the vitreous base or peripheral retina; and
- certain complex retinal detachments with PVR: 360-degree support of the vitreous base or peripheral retina.

There are three main SB techniques, namely: 1) encircling circumferential buckle; 2) segmental/limited circumferential buckle; and 3) radial buckle. The choice of technique relates in part to surgeon preference and experience, and there is wide international variation.

Encircling buckles confer a permanent 360-degree scleral indent and may be used in cases where there is concern about potentially unidentified and untreated breaks. There is, however, a greater risk of buckle intrusion and anterior segment ischemia with encircling as compared to segmental buckles.

Segmental/limited buckles are useful for breaks that span no more than six clock hours, and are readily identified and treated with retinopexy. All segmental buckle indents fade with time, thus the long-term success is reliant upon permanent retinopexy rather than permanent scleral indentation. This is a technique that is favored over encircling buckles in the United Kingdom. Encircling buckles may be combined with an additional segmental buckle to provide a higher indent over a localized area, together with providing some 360-degree indent.[8]

Radial buckles with a sponge are best for single breaks between recti muscles (for easiest access), particularly highly elevated retinal tears.

Surgical Technique

Scleral buckle surgery can be easily summarized into several discrete steps, as follows:

1. Conjunctival peritomy and isolation of rectus muscles.
2. External localization of all retinal breaks.
3. Decide on buckle type and location.
4. ±External drainage of subretinal fluid.
5. Treat break(s)—cryotherapy, typically.
6. Place and secure buckle.
7. Retinal examination.
8. Conjunctiva and Tenon's capsule closure followed by subconjunctival steroid and antibiotic injection.

However, there are important pearls and pitfalls to bear in mind to optimize the chance for success. The most important aspect of any approach to treating RRD is the ability to localize and treat all retinal tears *(See Figure 2)*, without which any technique is far more likely to fail. Preoperative assessment and planning is the key to success in SB surgery. Evaluate using an

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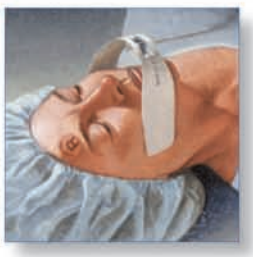

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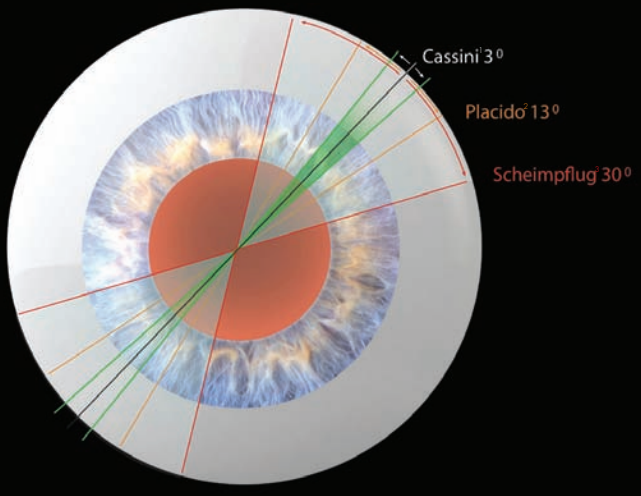

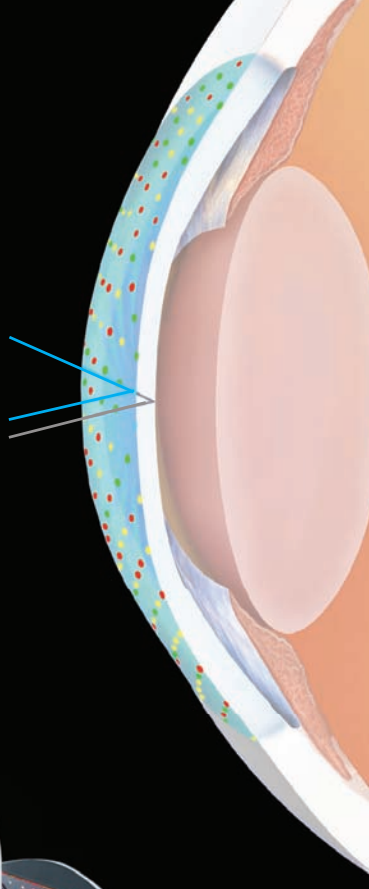

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[1] A. John Kanellopoulos, MD. Clinical Professor Of Ophthalmology New York University Medical School
[2] Karabatsas et al. EJO 2005, [3] McAlinden et al. IOVS 2011

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indirect ophthalmoscope with a condensing lens (20 or 28D), preferably with scleral indentation to optimize the view of the peripheral retina. If the view of the retina is compromised by media opacities, e.g., vitreous hemorrhage, such that the ability to adequately perform SB is compromised, PPV should be considered.[1,18,19]

Once all the breaks have been localized and marked appropriately, retinopexy is typically performed with cryotherapy *(See Figure 3)*. It is difficult to achieve adequate retinopexy with laser photocoagulation alone in the presence of even shallow subretinal fluid.

Drainage of the subretinal fluid may be required in the following situations:

- highly elevated break and detachment precluding adequate cryotherapy to retinal break;
- high scleral indentation of more than six clock hours required subsequent intraocular pressure rise sufficient to occlude central retinal artery despite repeated paracentesis; and
- chronic detachments.

Techniques for external drainage of subretinal fluid include a needle drain and scleral cut down with choroidotomy (laser or needle). Our preference is for a needle drain technique. A spatulated needle with an exposed 2- to 2.5-mm tip is used to create a single stab into the sclera at a site with deep subretinal fluid (elevated retina a long distance away from the RPE). Constant firm external pressure is applied on the globe for several minutes to encourage subretinal fluid egress. If drainage is planned, it is wise to preplace scleral sutures for the buckle, as suturing the sclera in a hypotonous eye is challenging with an increased risk of choroidal hemorrhage.

If a non-drainage technique is chosen, it may be necessary to do an anterior chamber paracentesis to lower IOP, which may be repeated.

The choice of buckle depends on a number of factors, principally the number and location of breaks and desired height of scleral indentation. The choice of encircling versus segmental versus radial buckles has been discussed in the previous section. Explants come in a variety of shapes and sizes. A buckle of sufficient width must be chosen to ensure the buckling element and indent extends past the posterior portion of the retinal break *(See Figure 3)*. Accurate break localization, noting the most posterior extent, is essential. For example, with a large retinal dialysis, the most posterior edge of the dialysis can hang back a surprisingly long way from the ora serrata; a buckle of sufficient width needs to be chosen to provide indentation from the ora serrata to the posterior limit of the dialysis.

Finally, examine the fundus with an indirect ophthalmoscope to confirm that the break is fully supported by an adequate indentation without fish mouthing, and to ensure that the central artery is patent.

Contraindications/Complications

A SB is contraindicated in the following scenarios:

- detachments caused by breaks significantly posterior to the equator; these may be technically difficult to repair using a buckle;
- opaque media (e.g., vitreous hemorrhage);
- significant vitreoretinal traction (such as with PVR and diabetic neovascularization): a PPV approach is usually favored.[20-22]

The potential intra- and postoperative complications of SB surgery are relatively small. The main risks are:

- anatomical failure (e.g., inadequate buckle height, missed breaks and PVR);
- immediate and early postoperative discomfort;
- refractive error, strabismus and double vision;
- glaucoma;
- choroidal hemorrhage;
- buckle infection (now very uncommon with closed rather than opened air cell sponges being used);
- extrusion of the buckle; and
- anterior segment ischemia.

Occasionally scleral buckles need to be removed because of complications, as highlighted above.[23,24]

The surgical treatment for RRD depends largely upon surgeon experience and preference.[25,26] While PPV has been used routinely to treat RRD of all types in recent years, our preference is to use SB surgery for certain RRD break types—specifically round holes and dialyses in the absence of a PVD. REVIEW

Dr. Sabrosa is a retinal specialist in Rio de Janeiro, Brazil. He was a surgical retina fellow at Moorfields Eye Hospital (UK) and is now director of the Medical Retina and Vitreoretinal Services at Santa Casa de Misericordia do Rio de Janeiro (1ª Enfermaria), and is in private practice at Clínica São Vicente, Rio de Janeiro. Contact Dr. Sabrosa at Clínica de Olhos Gávea, Rua João Borges, 204, Gávea, Rio de Janeiro, Brazil, CEP 22451-100. Phone and fax: (+55-21) 2259-5046. Email: nsabrosa@terra.com.br.

Dr. Wong is a retinal specialist in London at Moorfields Eye Hospital and the Royal Free Hospital. He was previously a surgical retina fellow at Moorfields, an international pediatric retina research fellow at William Beaumont Hospital, and most recently a pediatric surgical retina fellow at Children's Hospital Los Angeles. Email: chien22@yahoo.com.

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(continued on page 69)

Thoughts on Healing The Wounded Cornea

A look at the mechanism behind neurotrophic keratitis as well as current and future methods for treating it.

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

An aging population brings with it a dynamic set of clinical challenges; new conditions arise as our patients transition from babies to boomers to card-carrying members of AARP. With advancing age come increases in the incidence of chronic disease, so we see more conditions such as the retinopathy and keratopathy resulting from diabetes,[1] or the inflammation associated with other chronic conditions.

For those of us focused on the anterior segment, we recognize that chronic keratitis comes in many forms, and these present significant therapeutic challenges. From the filamentary keratitis of dry eye and the interstitial keratitis seen in autoimmune diseases to the persistent corneal defects associated with neurotrophic keratitis, there are treatments to alleviate pain and treatments that reduce the risk of disease progression, but there is still much room for improvement in our therapeutic choices.

This month, we'll briefly consider the healthy cornea, discuss some of the worst-case scenarios for keratitis, and describe how these concepts are driving some of the newest ideas in therapies designed to heal the damaged ocular surface.

The Healthy Cornea

The healthy cornea is a unique tissue designed and maintained to transmit and refract light to the lens and the retina. The layered structure of epithelium, stroma and endothelium, along with intervening Bowman's and Descemet's membranes, is key to this function. In addition, there are centripetal aspects to corneal homeostasis. The peripheral cornea interacts with adjacent limbal cells, receives input from surrounding vasculature and is the site of epithelial progenitor cells. The central cornea is an avascular structure with a fully differentiated epithelial layer. Corneal health depends upon the tear film and the aqueous humor for nutritional support and, under normal conditions, exhibits a robust, rapid response to minor surface abrasions and other incidental traumatic stimuli.

While we spend much of our time defining the cause-and-effect relationships underlying corneal pathologies, once in a while it's a useful exercise to consider all the barriers and redundancies built into the cornea and ask what mechanisms and systems are in place to keep the cornea healthy and functional.[2,3] For example, while each of the layers participates as a barrier to environmental and microbial contaminants, they also have specific functions that allow the cornea to conduct the business of light transmission and refraction. The endothelial cells, for example, actively regulate fluid and solute movement into the stromal layer to maintain the deturgescence necessary for corneal transparency.[4] The epithelial layer, in contrast, participates in this process indirectly by maintenance of high resistance, tight junctional barriers at the epithelial basement membrane.

Response to acute trauma on the corneal surface is similar to that seen in any epithelial tissue. The key difference is that as an avascular tissue the response is mediated primarily by tear flow rather than blood flow. The epithelial layer is densely populated with sensory nerve endings (see December 2013's Therapeutic Topics for details) that regulate lacrimation; this normal feedback loop is further stimulated by any physical or chemical insult.[5]

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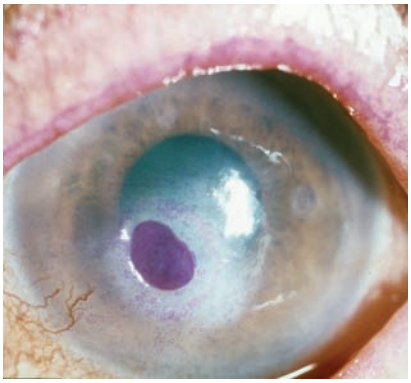
Damaged or necrotic cells and cellular debris are removed by a combination of leukocytes and tear flow, and the tissues at the edges of the wound retract and begin the remodeling process. Reorganization of cytoskeletal filaments is triggered as an early step in remodeling as the leading edges of surviving epithelial cells activate lamellapodia (Latin for "thin feet"), zones of highly mobile areas of membrane adjacent to the wound. These structures use actin filament polymerization dynamics to drive migration of cells, eventually forming a layer of epithelial cells to cover the damaged area.

In cases where tissue damage does not penetrate the epithelial layer (about 60 to 70 µm thick) this process can be completed in as little as 24 hours. More severe traumatic events require epithelial proliferation, migration and reformation of epithelial tight junctions at the basement membrane. With this in mind it's easy to imagine how modest trauma to the corneal surface, such as that which occurs with chronic allergy or dry eye, can have additive effects that challenge the normal repair mechanisms. And when these pathways are further disrupted by defects in tear formation or sensory nerve function, the cornea's ability to respond to any traumatic insult can be significantly impaired.

Neurotrophic Keratitis

Neurotrophic keratitis is a rare, degenerative corneal disease that exemplifies the potential for ocular damage when neural feedback loops are lost or impaired.[6,7] Any condition that reduces the function of the neural pathways emanating from the trigeminal nerve can lead to NK, but most commonly this occurs subsequent to herpes zoster infection, diabetic neuropathy or surgical trauma to the nerve. The resulting loss of corneal sensitivity (anesthesia) leads to a reduction in lacrimation and a decline in metabolism and mitosis of



Recurrent herpetic disease can result in a poorly healing, trophic corneal ulcer.

corneal epithelial cells. NK patients exhibit deficiency in epithelial repair, and can ultimately experience stromal edema, loss of microvilli and abnormal basal lamina homeostasis.

For ordinary subjects, the cornea is constantly responding to environmental insults, but patients with NK are ill-equipped to mount a healthy response to these events. They develop poorly healing, recurrent corneal abrasions or defects that are slow to respond to existing treatments. Most of the current treatments for keratitis simply augment the natural process of corneal remodeling; when this process is compromised, the effectiveness of treatments such as artificial tears, steroids or non-steroidal anti-inflammatories is also compromised.

An important question that remains unanswered is the extent to which neurotrophic action is mediated directly by neural inputs—peptides and other signaling molecules released by epithelial nerve endings—or by their ability to direct the volume of output and constituents of the lacrimal apparatus. Studies dating back a decade or more have suggested that substance P, a peptide secreted by trigeminal nerves in the cornea, exhibited trophic effects and regulated normal epithelial function.[8] More recent research has implicated insulin-like growth factor 1—a known, inducible constituent of tears—as a synergistic regulator of corneal epithelium together with substance P.[9] In addition, elevated levels of IGF-1 binding protein, a negative regulator of IGF-1, have been reported in tears of diabetic patients.[10] Collectively, these data suggest that the combination of neural activity in the corneal epithelial layer and feedback regulation to the lacrimal apparatus work together to modulate corneal epithelial homeostasis.

Treatment Options

Staging for conditions such as NK provides a guideline for both progression of the disease and the types of therapeutic approaches in current use.[6] Stage-1 NK features include: corneal anesthesia; epithelial growth dysplasia; punctate keratitis; tear-film anomalies and rose bengal staining of the conjunctiva. As the disease progresses, patients may also show corneal neovascularization or stromal scarring. Patients with a stage-1 defect are typically encouraged to avoid preservatives in ophthalmic medications and also advised to use an artificial tear to augment the lubrication of the ocular surface.[11] Topical antibiotics are also commonly used to reduce the risk of corneal infection.

A hallmark of the corneal surface defects seen in NK is that they are irregular in nature and may include one or more raised edges that can exacerbate tissue damage. When defects have rounded edges, a tarsorrhaphy or a therapeutic contact lens is a common treatment strategy. Stage-2 NK may also involve stromal swelling. This can ultimately lead to stromal melting and corneal perforation.

Traditional treatments for stage-2 or stage-3 NK also include penetrating keratoplasty in combination with tarsorrhaphy or a soft bandage contact lens. Another strategy to prevent the need for corneal transplant is the use of amniotic membranes, a tissue graft that provides both epithelial do-

nor cells and a basement membrane matrix to support corneal re-epithelialization. As with other severe forms of keratitis, responses to these treatments vary from patient to patient.

Various preparations of artificial tears containing autologous serum have been used to treat a number of corneal defects, including dry eye, graft vs. host disease (GVHD) and NK. It's thought that serum can serve to replenish growth factors and other nutrients typically provided by a healthy tear flow. While there is a wealth of literature to support this strategy, most studies are retrospective or single-treatment studies. There are few masked, placebo-controlled trials of serum-supplemented eye drops for any form of keratitis.[11] One recent study compared artificial tears to cord blood serum or autologous serum for treatment of chemical injury, and showed that cord blood was superior to the other two treatments; despite this, the artificial tears were superior to autologous serum treatment.[12] This result suggests that the method of collection and preparation of serum drops may be critical to their efficacy.

A reasonable alternative to serum treatments would be to identify those serum components responsible for their efficacious effect. Two candidates for this approach are nerve growth factor and thymosin β4. Both of these are polypeptide components of normal serum and tear fluids, and both have significant data to support their use in treatment of corneal defects. NGF is a growth factor that is necessary for survival and differentiation of sympathetic and sensory neurons. It also can enhance the function of injured neurons and has additional effects on both neurons and neuronal target tissues.[13] NGF has been used as an experimental therapy for dry eye[14] and for vernal keratoconjunctivitis. A clinical trial is currently under way examining use of recombinant human NGF as a treatment for stage-2 and stage-3 NK.[15]

Like NGF, thymosin β4 is an endogenous constituent of serum, but Tβ4 is normally found in much higher concentrations. Thymosin β4 is a major constituent protein of platelets, macrophages and polymorphonuclear cells where it acts as a G-actin binding molecule and regulator of actin polymerization.[16] These cell types function in trauma response, and Tβ4 gene expression is among the earliest to be upregulated during the process of wound repair. In addition to regulating actin polymerization, Tβ4 is released into the extracellular environment of wounds where it promotes tissue remodeling and repair in dermal, ocular, cardiac and central nervous system animal models.

Several studies have established the potential for Tβ4 as a treatment for corneal wounds. It was effective in treatment of corneal defects in patients with GVHD, and was also efficacious in a study of severe dry-eye patients. *(Sosne G, IOVS 2013; 54:ARVO E-Abstract 6033)* In a 2010 study of patients with stage-2 or -3 NK, Tβ4 treatment resulted in complete healing of persistent corneal defects in six of six patients studied.[17] It's interesting that a protein that functions as a major regulator of the cytoskeletal protein actin also affects tissue remodeling; whether the two functions are linked remains to be established. Another potential treatment on the horizon for epithelial wound healing that has a clear connection to cytoskeletal function is a peptide mimetic of connexin43. This polypeptide, like Tβ4, has shown promise in treatment of both skin and corneal wound healing.[18]

Perhaps even farther into ophthalmology's future, we may see stem-cell technologies or other genome-based strategies (such as interfering RNA) applied in treatments for corneal wound healing.[19,20] These theoretical treatments are a long way off, but are still in sight, giving patients hope for a lasting solution for their wounds that won't heal. REVIEW

Dr. Abelson is a clinical professor of ophthalmology at Harvard Medical School. Dr. McLaughlin is a medical writer at Ora Inc.

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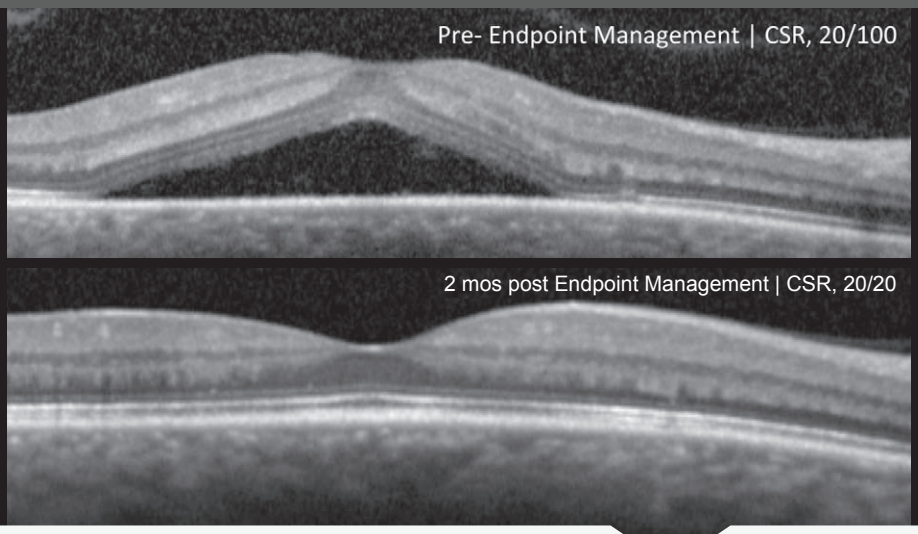

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10 Ways to Optimize Treatment with SLT

This increasingly utilized procedure allows for a significant reduction in IOP without impacting the patient's quality of life.

Hady Saheb, MD, MPH, Montreal

In recent years, selective laser trabeculoplasty has become widely accepted as a means to achieve moderate intraocular pressure reduction in select patients. Here in Canada, this isn't a new idea; SLT has been a popular option since I was a medical student. It's a great way to delay the need for surgery or additional medications, and—unlike drops and surgery—it allows for a significant reduction in IOP without impacting the patient's quality of life.

As you know, the laser used in SLT has a selective effect on the melanotic, pigmented elements of the trabecular meshwork. Randomized, controlled head-to-head trials comparing argon laser trabeculoplasty to SLT have demonstrated that the efficacy of SLT is at least equivalent to that of ALT, yet it causes less coagulative damage and structural change in the trabecular meshwork.

Optimizing Treatment

My protocol for performing SLT is as follows: Preoperatively, I use pilocarpine 1% to 2% with Iopidine. Before starting the laser I use the Latina SLT gonio lens to visualize the angle. The size and duration of the laser spots are standardized at 400 µm and 3 nanoseconds. This spot size is larger than the trabecular meshwork height, so when centered on the trabecular meshwork the laser light overlaps both anterior and posterior to the meshwork. In terms of power I start at 0.7 mJ and titrate upwards, looking for the appearance of small bubbles. My goal is to place 75 to 90 shots over 360 degrees of the trabecular meshwork, which requires adjacent burns. (Some clinicians may choose to apply a small number.)

Here are 10 strategies that will help ensure your SLT treatments are safe and effective:

• ***Choose the right patients***. Patients who are good candidates for SLT include patients with ocular hypertension, primary open-angle glaucoma or pseudoexfoliation glaucoma. Patients I recommend avoiding include those with very uncontrolled IOP; patients with very low target IOPs; and those who have had prior filtering surgery.

My rationale for deciding who is a good candidate for SLT is similar to my rationale for deciding who is a good candidate for microinvasive glaucoma surgery. Like MIGS, SLT optimizes trabecular outflow rather than bypassing it. So for SLT to make sense, you need to believe that the trabecular outflow pathway is not too pathological. Also, once a patient has had filtering surgery and the trabecular outflow pathway is bypassed, optimizing trabecular outflow is no longer likely to be useful.

• ***Don't treat pigment dispersion patients without a trial run first.*** SLT is very effective in eyes with pigment dispersion glaucoma; most PDG patients will get the desired pressure reduction with treatment of just one or two quadrants. However, there's a problem: Eyes with pigment dispersion glaucoma are very susceptible to IOP spikes. One paper described four cases of patients with pigment dispersion glaucoma that required urgent trabeculectomy because of an intractable IOP increase following SLT.[1] If an alternative treatment is available, it may be best to simply avoid treatment of pigmentary glaucoma patients with SLT.

What I recommend when managing

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these patients is to do a test dose: 10 shots at an energy level of 0.3 mJ—much lower than the standard setting I would normally use. Then, do a one-hour and one-week IOP check. If you don't detect an IOP spike, proceed to doing one quarter of the angle at a time. Some physicians may feel that this is too much trouble and prefer to skip SLT in these patients, and that's OK. The point is that SLT can be risky in this group of patients because of the possibility of intractable IOP spikes, so it's a good idea to be cautious. For that reason, I suggest only using SLT in pigment dispersion cases if you and the patient are willing and able to do it gradually, following a protocol like the one described above.

Bear in mind that although my recommendation sounds like five treatments—a test dose and then one-quarter of the angle at a time—these patients may not need to have all four quadrants treated. SLT can work so well in pigment dispersion that many of these patients will respond to one or two quadrants of the laser. However, if you are aiming to treat all four quadrants, I'd still do them one at a time.

• ***When the angle is narrow, make sure your view is clear.*** The better your view, the better your chances of getting a good laser effect. Typically, the cases that will be challenging are the eyes with narrow angles.

One well-known trick to get a better view in this situation is to have the patient look in the direction of the mirror; or, move the mirror in the direction of the targeted angle. I prefer moving the mirror, because given that this is a 360-degree treatment, every time you have the patient move, you have to readjust his gaze for every quadrant. In contrast, if you're manipulating the lens yourself you can control the movement, rather than relying on patient cooperation.

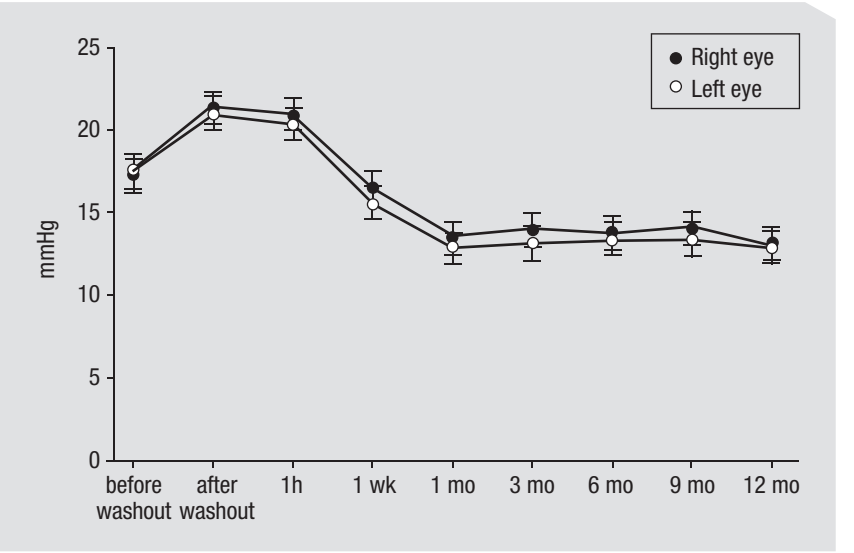
• ***If the cornea is hazy, reduce the size and brightness of the slit-lamp light beam.*** A hazy cornea will also reduce your view of the angle. In this situation, reducing the size and brightness of the light beam reduces the amount of light scatter through the cornea and improves your view. Cleaning and moving the lens may also help to reduce unwanted reflections.

• ***Move a prominent brow posteriorly.*** A prominent brow can lead to difficulty viewing the inferior angle through the superior mirror because any superior movement of your lens is blocked by the brow. In this situation, moving the brow of the patient posteriorly allows better access to the surface of the eye. Patients at the slit lamp have their chin and forehead abutted against the plastic guides; when the brow is prominent, keep the chin in place but tilt the head backwards by pushing the forehead away from the bar. That lifts the eyebrow, and the eye has to turn downwards, allowing the gonio mirror to move upwards a little more easily. It improves your access to the surface of the globe.

• ***During the procedure, move the lens, not the laser.*** When using the laser I have one hand on the lens and one hand on the dial of the laser. To treat the entire trabecular meshwork, you can either move the laser with your hand on the dial, or you can keep the laser in the same place and just rotate the lens to change the direction of the beam. Rotating the mirror in the opposite direction to that of the laser light minimizes the total movement required for the procedure. Make sure you thoroughly understand how movement of the lens and the laser affects the position of the spots in the anterior chamber angle; you will have to move both at some point during the procedure

• ***You don't need to see bubbles with every shot.*** Classical teaching is to aim to generate so-called "champagne bubbles" with every laser shot, but I recommend titrating your laser energy so you see champagne bubbles every two to three burns.

Intraocular Pressure Following SLT



In this study, 61 medically treated POAG patients in St. Lucia underwent a 30-day washout followed by 360° of bilateral SLT. Treatment resulted in prompt, sustained, significant drops in intraocular pressure. Ninety-three percent of successful subjects had IOPs lower than they'd had while on medication. (Five eyes of three subjects had IOP spikes between 5 and 10 mmHg that resolved without treatment.) Chart based on Realini, T. 2013.[6]

• ***Adjust the laser energy as the TM pigmentation changes.*** It's important to remember that pigmentation typically changes throughout the angle; the inferior angle has more pigmentation and so needs less laser energy to effect a change. Conversely, the superior angle is less pigmented, and so may need more laser energy. I usually adjust my energy setting two to three times during my 360-degree treatment.

• ***Check postop IOP more often in certain patients.*** For most patients I do postop IOP checks at one hour and again at one to two months. If a patient has an IOP spike at the one-hour IOP check, I add an extra IOP checkup visit at one week postop. I also add this extra one-week checkup for patients with a history of uveitis, because SLT can lead to a reactivation of the uveitis; patients with advanced glaucoma; patients with pigment dispersion glaucoma; and patients who have highly pigmented trabecular meshworks, such as those with pseudoexfoliation glaucoma.

• ***Don't sweat the steroids.*** There's a theory that the inflammation associated with SLT is useful for helping to generate the hypotensive effect it produces. As a result, some doctors are adamant about not giving steroids because they want that inflammation to facilitate the biomodulation required for SLT to work. However, this theory has not been substantiated, and some studies suggest that steroids make little difference. One randomized controlled trial looked at patients after ALT, randomizing the subjects into two groups, only one of which received steroids. The study found no difference in IOP effect.[2,3] In addition, two other similar, not-yet-published, randomized controlled trials conducted by Drs. Ike Ahmed and Malik Kahook also found no effect on IOP reduction following SLT, given the use or non-use of steroids.[4] Notably, however, in Dr. Kahook's study there was a reduced incidence of pain in the patients that received steroids. (Of course, pain during or after SLT is relatively rare.)

Because of these findings, my routine is to avoid giving postop steroids unless the patient experienced pain with a previous SLT treatment. These findings suggest that it doesn't make a difference whether you give steroids or not; either way it appears you're not helping or harming the patient. Of course, Dr. Kahook's study suggests that there's less pain when the patient has steroid drops, so if a patient comes back with pain, or says the first eye really hurt, then I will give steroids. Otherwise, I don't think it's worth prescribing steroids routinely because of the practical burden for the patient.

MIGS and SLT

Given the current popularity of MIGS in combination with cataract surgery, it's worth mentioning how these options might overlap in a given patient.

Hypothetically, MIGS procedures have a stronger effect than SLT, given that currently approved MIGS procedures bypass the trabecular meshwork. For that reason, if a patient is undergoing cataract surgery, I would choose to add a MIGS procedure to the operation rather than attempt SLT. For the same reason, if a MIGS procedure has been performed during cataract surgery and the result was not ideal, I would not do SLT. They're trying to accomplish the same thing—increase the outflow through the trabecular meshwork. So if a MIGS procedure didn't help, it's unlikely that SLT would have much effect. This has been substantiated by a study looking at SLT following failed combined cataract surgery and Trabectome surgery.[5] However, if a patient has already had SLT without obtaining much pressure reduction, I'd still try a MIGS procedure during the cataract surgery.

A Very Useful Tool

Because SLT allows for a significant reduction in IOP without impacting the patient's quality of life, my preferred timing for SLT is between prescribing a patient's first and second medication. If the patient is using one bottle and needs a second bottle for further pressure reduction, I would aim to do SLT before adding the second bottle, in hopes it might prevent the patient from having to use two medications, with the associated concerns related to side effects and compliance. (Of course, many clinicians still choose to wait until a patient is using several medications before recommending SLT.)

Like MIGS, SLT can't address the specific medical needs of every glaucoma patient you may encounter, but in many situations it's a useful option. I hope the suggestions offered here will help you and your patients gain the maximum benefit the procedure has to offer. REVIEW

Dr. Saheb is assistant professor of ophthalmology and director of resident research at McGill University in Montreal.

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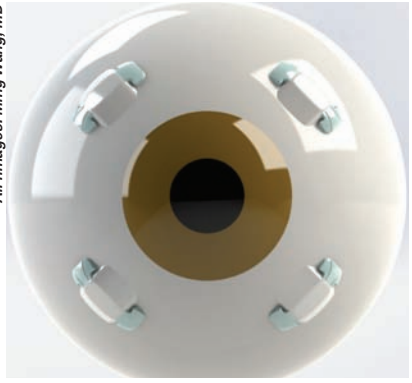
An Update on Scleral Expansion

A user of the technology says updates in instrumentation and imaging have made a difference in the controversial procedure.

Walter Bethke, Managing Editor

As ophthalmologists search high and low for an answer to presbyopia, one of the modalities they're likely to encounter will be scleral expansion segments in the form of the PresView procedure (ReFocus Group). Scleral expansion has had something of a checkered past, with many technology iterations, unpredictable results and critics who questioned its mechanism of action. Proponents say the current scleral expansion procedure, which is in the last leg of a Phase III Food and Drug Administration trial, is different from those of the past, and has been reinvigorated by a couple key technological innovations. Here's a look at where the procedure currently stands, and the main criticisms of its detractors.

All images: Ming Wang, MD



In PresView, four plastic inserts go into the sclera, between the ocular muscles.

The Theory

The PresView procedure involves inserting four plastic segments into the sclera between the ocular muscles. The idea behind this is based on a theory of loss of accommodation proposed by Texas surgeon Ronald Schachar back in the 1990s. In a nutshell, Dr. Schachar proposed that we lose the ability to accommodate because the crystalline lens gradually gets larger over time, eventually crowding the zonules so they're no longer taut and able to exert force on the lens to get it to change shape and allow accommodation. The intrascleral segments are supposed to act like a kind of spacer, pulling the sclera away from the lens, tightening the zonules and allowing them to aid accommodation.

The problem is, not everyone agrees with this relatively new take on presbyopia's mechanism. "I think the theory may have some merit, but it's never been proven that that's the mechanism that's occurring in presbyopia," says Keith Walter, MD, associate professor of surgical sciences-ophthalmology at Wake Forest Baptist Medical Center. Dr. Walter debated the merits of presbyopic treatments, one of which was scleral expansion, at the 2014 meeting of the American Society of Cataract and Refractive Surgery's Cornea Day. "Part of the problem with scleral expansion is we're not sure of the science behind it, how the science explains it's going to work or what magnitude of accommodation we're going to get."

Detractors say the Schachar theory contradicts the only mechanism of accommodation that's been widely documented to exist, that of Hermann von Helmholtz.[1] In terms of the onset of presbyopia, the Helmholtz theory dictates that the primary factor is the increasing rigidity of the crystalline lens that's behind it, not lens growth.[2] Because the theory behind scleral expansion is incorrect, some researchers say, scleral expansion can't work. In one study, an investigator measured accommodative responses of three preoperative presbyopic patients, three post-scleral expansion patients and three young control subjects using

This article has no commercial sponsorship.

an infrared dynamic optometer. He found that none of the postop patients showed any evidence of accommodation.[3] In another study, researchers examined a satisfied scleral expansion patient and found no increase in accommodative amplitude above age-matched controls, and theorize that maybe high expectations for a positive outcome were the cause of his feelings of satisfaction.[4]

Dr. Walter says if it does work, the accommodation restored by it has been low. "I haven't seen any studies yet that show that the patient gets more than 1 D or so," he says. "I haven't done any myself, but I've seen some patients who've had it, and they do seem happy. But I think it has that limitation that we don't really know how it works."

Scleral Expansion Today

Nashville, Tenn., anterior segment surgeon and PresView investigator Ming Wang says that, when it comes to the debate about the basis for scleral expansion's mechanism of action, both sides may be right. "There is a linear relationship between a patient's age and his amount of presbyopia," he says. "That's why a doctor could recommend a reading add for a presbyope over the phone after just hearing her age. However, a doctor can't recommend cataract surgery over the phone based on age. This means that lens rigidity and presbyopia aren't linear with each other. So, there's something in addition to lens rigidity that causes one to lose accommodation or the ability to focus at near. Perhaps the Helmholtz theory only explains half the story." Dr. Wang says the enlargement of the crystalline lens is the other part. "The spacing procedure only addresses this second half," Dr. Wang says. "It's doesn't even pretend to solve the entirety of the problem. It only solves the problem of crowding from the growing lens and the loss of zonular tension."

Dr. Wang says he was skeptical too when he first started looking into scleral expansion. "Initially, there was no ability to fixate the segment exactly in place because there was no locking element," he says. "So the segment could be pushed outward and migrate, causing it to not have an effect. The segments need to oppose each other to create enough tension. Also, in the first years of the procedure, there was no imaging technology to let the surgeon know if the segment had migrated. Both of these factors resulted in the technology's failure for the first seven or so years. In recent years, however, the company has implemented a locking mechanism to keep the segment in place and, critically, optical coherence tomography has become more widely available to allow surgeons to determine where the segments are and refine the technology of fixation."

A fixated guide keeps a scleratome locked into position so the scleral tunnels are created in precise positions in PresView.

In the current iteration of the procedure used in the FDA trial, the surgeon uses a device to create a tunnel approximately 4-mm long, into which it deposits the segment. Then, a locking spacer is placed on one end of the segment to prevent it from migrating back into the tunnel. Currently, the trial has treated its requisite 330 patients, and Dr. Wang says it's now in a two-year period in which the FDA wants to monitor the patients. "At our practice, which is one of the FDA study sites, we achieved about 1.25 D of accommodation," Dr. Wang says. "This is what you'd anticipate achieving in a patient 60 years old or so who has about 2.25 D of presbyopia. We address about half of the problem." Though potential problems include erosion of the tissue above the segment and segment migration, Dr. Wang says his patients haven't experienced any serious complications.

Lingering Issues

Dr. Walter says that even if the procedure works as it's proposed, he wonders if there might be easier approaches for presbyopia. "When I and other doctors look at it, we say to ourselves, 'That looks like a lot of trouble to insert four segments,' though I must admit they've got the procedure down to a very elegant method," he says. "The way they go in the tunnel and then lock the pieces together is very nice. But you're going to have pain with that, so a surgeon would wonder if he needs a nerve block. If I were to put investigative presbyopia treatments on a scale from easy to hard, the Kamra inlay would be easier for a surgeon, especially if he were already doing LASIK. Presby-LASIK, IntraCor [with the femtosecond] or some other multifocal ablation would be easy, especially if you could just use one treatment card. Scleral expansion seems like it would be on the other end of the scale where it would be challenging to do in the office. You'd have to deal with placing them precisely, as well as any hemorrhage and patient satisfaction issues involved with pain and recovery." REVIEW

Neither Dr. Walter nor Dr. Wang has a financial interest in any product or company mentioned in the article.

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Optical Quality of the Cornea After DMEK

In a retrospective study, researchers from the Netherlands determined that anterior and posterior corneal higher-order aberrations and backscattered light were elevated in patients with Fuchs' endothelial dystrophy and remained higher throughout the six months following Descement's membrane endothelial keratoplasty.

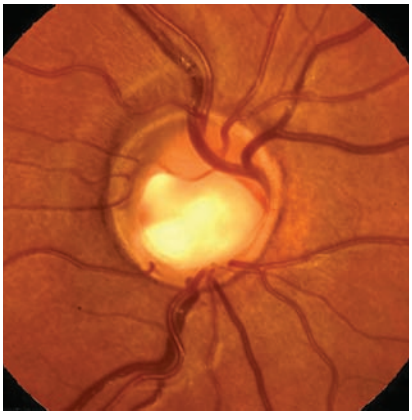
In a total of 118 consecutive eyes of 118 patients who underwent uneventful DMEK for Fuchs' endothelial dystrophy at a tertiary referral center, best spectacle-corrected visual acuity, corneal HOAs and backscattered light were evaluated preoperatively and at six months postop. Outcome data was compared to an age-matched control group with uncomplicated eyes (n=27).

Compared to the control group, Fuchs' eyes, before as well as six months after DMEK, showed higher values of anterior and posterior HOAs and backscattered light ($p<0.033$). Postoperative anterior HOAs and backscattered light (0 to 2 mm) were associated with lower six-month BCSVA (positively related with logMAR BSCVA; $p\leq0.02$). Anterior corneal HOAs did not change from preop to six months after DMEK ($p=0.649$), while total posterior HOAs (RMS third to sixth Zernike order) and haze decreased ($p<0.001$). If present, anterior surface irregularities and anterior corneal haze may be the most important limiting factors in visual rehabilitation after DMEK for eyes suffering from Fuchs' endothelial dystrophy.

Am J Ophthalmol 2014;158:71-79.
Van Dijk K, Droutsas K, Hou J, Sangsari S, et al.

Culture and Adherence to Glaucoma Treatment

In an effort to determine adherence rates and beliefs about glaucoma and its treatments, researchers examined 475 patients using topical eye drops for at least six months in a cross-sectional study. The sample consisted of white Americans (n=133), African Americans (n=58), white Australians (n=107) and Singaporeans of Chinese descent (n=117). Self-reported adherence and beliefs about glaucoma and its treatment were assessed using the Reported Adherence to Medication scale, the Brief Illness Perception Questionnaire and the Beliefs about Medicines-Specific Questionnaire.



Accounting for sociodemographic differences, significant differences in self-reported adherence rates were identified ($p<0.001$). White Americans (65.4 percent) and Australians (67.7 percent) reported significantly higher adherence than African Americans (56.9 percent) or Singaporeans (47.5 percent). Beliefs about glaucoma treatment were predictive of adherence only in Australian and white American samples ($p<0.06$). This suggests that in Western cultures, attempts to improve adherence may benefit from greater examination of individuals' concerns about, and perceived need of, glaucoma treatment.

J Glaucoma 2014;23:293-298.
Rees W, Chong X, Cheung C, Aung T, Friedman D, et al.

Two-year Results from the COPERNICUS Study

New research from the COPERNICUS study, which evaluated the efficacy and safety of intravitreal aflibercept injection for the treatment of macular edema secondary to central retinal vein occlusion, shows that the visual and anatomic improvements after fixed dosing

through week 24 and p.r.n. dosing with monthly monitoring from weeks 24 to 52 were diminished after continued p.r.n. dosing with a reduced monitoring frequency from weeks 52 to 100.

A total of 188 patients with macular edema secondary to CRVO were placed in a randomized, double-masked Phase III trial. Patients (n=114) received IAI 2 mg (IAI 2Q4) or sham injections (n=74) every four weeks up to week 24. During weeks 24 to 52, patients from both arms were evaluated monthly and received IAI as needed (IAI 2Q4 + p.r.n. and sham + IAI p.r.n.). During weeks 52 to 100, patients were evaluated at least quarterly and received IAI as needed.

The proportion of patients gaining ≥15 letters of best-corrected visual acuity was 56.1 percent vs. 12.3 percent ($p<0.001$) at week 24, (the primary COPERNICUS study efficacy endpoint); 55.3 percent vs. 30.1 percent ($p<0.001$) at week 52; and 49.1 percent vs. 23.3 percent ($p<0.001$) at week 100 in the IAI 2Q4 + p.r.n. and sham + IAI p.r.n. groups, respectively. The mean change from baseline BCVA was also significantly higher in the IAI 2Q4 + p.r.n. groups compared with the sham + IAI p.r.n. group at week 24 (+17.3 vs. -4.0 letters; $p<0.001$); week 52 (+16.2 vs. 3.8 letters; $p<0.001$); and week 100 (+13.0 vs. 1.5 letters; $p<0.001$). The mean reduction from baseline in central retinal thickness was 457.2 vs. 144.8 µm ($p<0.001$) at week 24, 413 vs. 381.8 µm at week 52 ($p=0.546$) and 390 vs. 343.3 µm at week 100 ($p=0.366$) in the IAI 2Q4 + p.r.n. and sham + IAI p.r.n. groups. The mean number of p.r.n. injections in the IAI 2Q4 + p.r.n. and sham + IAI p.r.n. groups was 2.7 ±1.7 vs. 3.9 ±2.0 during weeks 24 to 52 and 3.3 ±2.1 vs. 2.9 ±2.0 during weeks 50 to 100. The most frequent ocular serious adverse event from baseline to week 100 was vitreous hemorrhage (0.9 percent vs. 6.8 percent in the IAI 2Q4 + p.r.n. and sham + IAI p.r.n. groups).

Ophthalmology 2014;121:1414-1420.
Heier J, Clark WL, Boyer S, Brown D, Vitti R, et al.

One-year Follow-up of Accelerated CXL for Keratoconus

Researchers from the University of Toronto assessed the efficacy of accelerated corneal collagen cross-linking (irradiance of 9mW/cm^2; 10 minutes) in keratoconus-affected eyes, determining that it is effective in stabilizing topographic parameters after 12 months of follow-up. Improvement in the uncorrected distance visual acuity and stabilization of all tested corneal parameters were noted after the treatment.

Sixteen mild-moderate keratoconus-affected eyes of 14 patients (mean age: 24.9 ±5.8 years; range: 17.1 to 38.3 years) who underwent accelerated CXL treatment and had six and 12 months of follow-up were reviewed retrospectively. Data regarding UDVA, manifest refraction, corrected distant visual acuity and computerized corneal topography data before and post-CXL surgery were extracted and analyzed.

No statistically significant changes were found in the mean CDVA, mean refractive cylinder or mean manifest refraction spherical equivalent at either time point. There was a gain of 0.13 logMAR in the mean UDVA ($p=0.012$) at 12 months. All corneal parameters including K_{steep}, K_{flat}, average K (K_m), corneal astigmatism (K_{cyl}) and maximal curvature reading the corneal apex (K_{max}) were stable at six and 12 months in all patients. No complications were observed during the follow-up period.

Cornea 2014;33:769-773.
Elbaz U, Shen C, Lichtinger A, Zauberman N, et al.

(continued from p. 43)

where the light is turned on and off to allow more oxygen diffusion, and obviously the various alternate epithelial approaches," Dr. Hersh says. "All of these need to be refined. I think the next big leap is going to be topography-guided cross-linking. It really makes sense as a treatment of irregular corneas, and I think it is an exciting potential modality for the treatment of low degrees of refractive errors. We'd also love to get topography-guided LASIK available in the United States so that we can work on combining that technique with cross-linking as well."

He notes that cross-linking is also being used overseas as a treatment of infectious keratitis. "People are trying to optimize protocols to either use cross-linking adjunctively with current antibiotics or potentially to use cross-linking alone for some kinds of infections," he explains.

Dr. Raizman adds that another exciting new area is cross-linking using UV light and alternative molecules other than riboflavin or even cross-linking without the use of UV light. "Perhaps there are better ways to cross-link. It is a rapidly evolving area," he says. REVIEW

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Recently decreased vision and eye pain prompt a hospital ER visit by an elderly patient and soon after, another to the Wills ER.

Jordan Deaner

Presentation

An 82-year-old Caucasian male presented with a three-day history of decreased vision, redness and pain in his left eye. He denied any concurrent headache, diplopia, photophobia, purulent discharge, history of trauma or recent illness. Systemic review was not significant; the patient denied the presence of any rashes, joint pain, abnormal bowel movements or urinary symptoms. The patient initially presented to an outside emergency room two days prior to his presentation at Wills. He was diagnosed with bacterial conjunctivitis and placed on topical ciprofloxacin four times daily without improvement.

Medical History

Past medical history was significant for coronary artery disease, treated with the placement of two stents and a quadruple bypass surgery. Additionally, the patient suffered from myelodysplastic syndrome with isolated thrombocytopenia, hypertension, gastroesophageal reflux disease and hyperlipidemia. His family history was noncontributory. The patient was a former smoker; he drank alcohol socially and denied illicit drug use. He did not have any known drug allergies.

His medication list included: niacin 250 mg by mouth daily; lisinopril 5 mg by mouth daily; metoprolol 20 mg by mouth daily; isosorbide 30 mg by mouth daily; and aspirin 81 mg by mouth daily.

Examination

The patient's vital signs were stable and within normal limits. Ocular examination demonstrated a best corrected visual acuity of 20/25 OD and 20/125 OS. External examination showed periorbital edema of the entire left upper and lower lid, erythema and ptosis *(See Figure 1)*. Hertel exophthalmometry revealed 3.5 mm of left-sided proptosis. Pupillary exam showed no anisocoria, but revealed a trace left-sided relative afferent pupillary defect. Extraocular motility was full in the right eye and reduced in the left eye, with 80 percent motility in all vertical gazes. Horizontal motility was full. Visual fields were full to confrontation OU. Ishihara color plates were full in the right eye and 4/8 in the left.

Anterior slit-lamp examination of the right eye was normal, and revealed chemosis and injection of the conjunctiva of the left eye. The anterior chamber of the left eye was noted to be shallow. Gonioscopy revealed blood in Schlemm's canal of the left eye. Intraocular pressure by Goldmann tonometry was 9 mmHg OD and 12 mmHg OS. Funduscopic examination of the right eye was normal. Funduscopic examination of the left eye exhibited peripheral elevations; a B-scan ultrasound was performed that confirmed the presence of choroidal effusions. Orbital ultrasonography demonstrated thickening of the retinochoroidal region with increased vascular flow, and choroidal elevations anterior, temporal and nasal to the optic disc consistent with choroidal effusions.

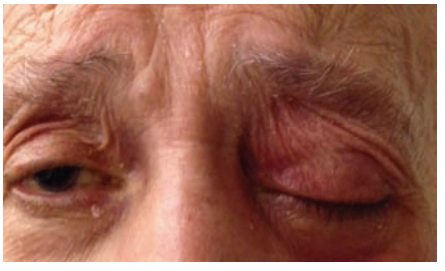

Figure 1. External photograph demonstrating left periorbital edema, erythema and ptosis.

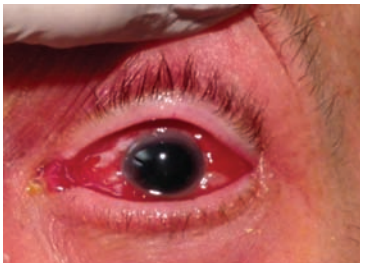

Figure 2. External photograph demonstrating chemosis and injection of the left eye.

What is your differential diagnosis? What further workup would you pursue? Please turn to p. 68

Diagnosis, Workup and Treatment

Given our patient's clinical history and exam, a differential diagnosis was constructed and included conditions that were associated with choroidal effusions such as ocular inflammation, posterior scleritis, orbital tumors and orbital arteriovenous fistula. More puzzling was the presence of blood in Schlemm's canal. Etiologies for blood in Schlemm's canal can be separated into pathologies that cause elevated episcleral pressure (carotid-cavernous sinus fistula, orbital arteriovenous fistula, mediastinal tumors, superior vena cava obstruction, ocular inflammation and orbital congestion), and pathologies that cause a lower relative intraocular pressure (hypotony, iatrogenic pressure from gonioscopy). Although there was no evidence of intraocular inflammation on clinical exam, the aforementioned findings in the context of proptosis, pain and significant injection of the eye made a scleral and anterior orbital inflammatory process the most likely etiology. The presence of a cavernous sinus thrombosis was also on the differential, especially given the findings of ptosis and limited motility of the left eye. Other considerations included orbital cellulitis, metastatic disease and lymphoproliferative disease, as these conditions can mimic a non-infectious inflammatory process.

MRI of the orbit was subsequently performed and showed extensive inflammatory changes involving the preseptal soft tissues, intraconal fat and extraconal fat. Additionally, the left lateral rectus was significantly enlarged. The cavernous sinuses were clear bilaterally. No discrete masses were detected.

The lab workup for targeted autoimmune, infectous and infiltrative diseases (FTA, RPR, ACE, C-ANCA, P-ANCA, ANA, ESR, Rheumatoid Factor, IgG-4, basic metabolic panel) was negative and within normal limits. However, the C-reactive protein was elevated to 3.3 and the CBC revealed a low platelet count consistent with his past medical history.

Following his negative workup for a specific systemic inflammatory disease or infection, the patient was diagnosed with idiopathic orbital inflammatory syndrome with posterior scleritis. He was subsequently treated with oral prednisone 80 mg daily, topical prednisolone acetate four times daily and topical atropine twice daily. The patient followed up in the Oculoplastics Department three days after his presentation to the Wills ER with improvement in pain. His physical exam showed decreased edema, erythema and proptosis. He regained full motility in his left eye. His visual acuity was 20/400 at his follow-up visit in the Retina Department, one week after initial presentation. His choroidal effusions were still present at that time. Unfortunately, no further information is known about this patient's recovery as his medical management was continued in his hometown of Boston. Attempts to connect with the patient to inquire after his visual outcome were unsuccessful.

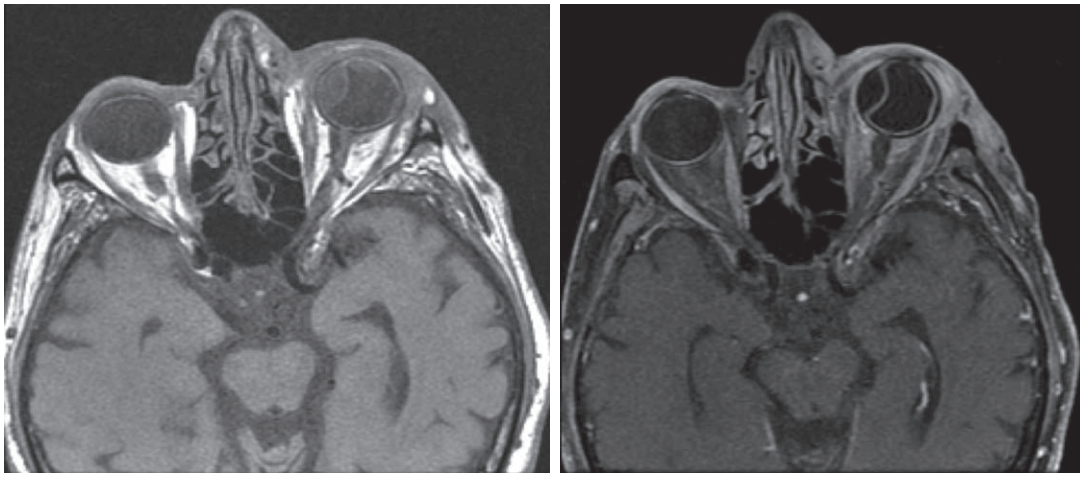

Figure 3. T1-weighted MRI shows extensive inflammation of the left preseptal and orbital tissues, in addition to a choroidal detachment.

Discussion

Idiopathic orbital inflammatory syndrome (IOIS) is defined as a benign, non-infective clinical syndrome characterized by features of nonspecific inflammatory conditions of the orbit without an identifiable local or systemic cause. It is a diagnosis of exclusion that is made when all other causes of orbital inflammation have been ruled out.[1] After Graves' ophthalmopathy and lymphoproliferative diseases, IOIS is the third most common disease to affect the orbit.[2] It is most commonly diagnosed in middle-aged adults and associated with a 2:1 female predilec-

tion, but can also present at the extremes of age.[3]

There have been many theories that suggest the pathogenesis of idiopathic orbital inflammation. A post-viral etiology has been suggested.[4] An association with systemic autoimmune diseases such as Crohn's disease, lupus and myasthenia gravis has also been reported.[5,6,7] More recently, it has been suggested that IOIS is an autoimmune reaction secondary to a molecular mimicry process.[8]

Idiopathic orbital inflammatory syndrome can be considered a continuum of disease with a varying presentation, ranging from rare bilateral diffuse orbital inflammation to the more common unilateral isolated myositis or dacryoadenitis. This spectrum of presentation can also include posterior scleritis. Presenting symptoms usually include edema, pain, injection, proptosis, diplopia and chemosis. If posterior scleritis is present, the patient may also complain of an acute decrease in vision. The progression of symptoms is typically acute, developing within hours to days.[9,10]

Systemic steroids remain the mainstay of therapy, with improvement in up to 76 percent of cases. Patients who are non-responsive, unable to tolerate or dependent on steroids may undergo radiotherapy, but this has been associated with poor response.[5] Individual response to treatment with chemotherapeutics and immunomodulatory drugs has been reported in recalcitrant cases.[11,12] Clinical outcomes of patients who suffer from IOIS are good, and most patients have complete resolution with relapse rates related to the severity and extent of the initial disease. However, patients who present with posterior scleritis as a component of their disease are at serious risk for permanent vision loss. In one study of 99 patients, 30 percent of subjects experienced permanent visual impairment.[10] Myositis has been shown to be frequently associated with scleritis, as demonstrated in this patient. Yet, the presence of concomitant myositis does not worsen the visual prognosis of the scleritis.[13]

In conclusion, IOIS is a diagnosis of exclusion that should only be made after other pathology has been ruled out. Its clinical picture is variable, but typically presents acutely with unilateral pain, periorbital edema and injection. Less commonly, it can present as scleritis that can be more difficult to differentiate from other diseases that cause posterior ocular and anterior orbital inflammation. The etiology of IOIS remains elusive. An autoimmune-mediated process is most likely given the response to steroids and immunomodulatory drugs. Systemic corticosteroids remain the mainstay of treatment. While most patients experience a full recovery, patients with posterior scleritis should be considered at risk for serious vision loss and monitored closely. REVIEW

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

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