REVIEW® of Ophthalmology
March 2016
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CATARACT ISSUE

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IMPORTANT SAFETY INFORMATION

OMIDRIA (phenylephrine and ketorolac injection) 1% / 0.3% must be added to irrigation solution prior to intraocular use.

OMIDRIA is contraindicated in patients with a known hypersensitivity to any of its ingredients.

Systemic exposure of phenylephrine may cause elevations in blood pressure.

Use OMIDRIA with caution in individuals who have previously exhibited sensitivities to acetylsalicylic acid, phenylacetic acid derivatives, and other nonsteroidal anti-inflammatory drugs (NSAIDs), or have a past medical history of asthma.

The most commonly reported adverse reactions at 2-24% are eye irritation, posterior capsule opacification, increased intraocular pressure, and anterior chamber inflammation.

Use of OMIDRIA in children has not been established.

INDICATIONS AND USAGE

OMIDRIA is added to ophthalmic irrigation solution used during cataract surgery or intraocular lens replacement and is indicated for maintaining pupil size by preventing intraoperative miosis and reducing postoperative ocular pain.

References: 1. OMIDRIA [package insert]. Seattle, WA: Omeros Corporation; 2015. **2.** Osher RH, Ahmed IIK, Demopulos GA. OMS302 (phenylephrine and ketorolac injection) 1%/0.3% to maintain pupil size and to prevent postoperative ocular pain in cataract surgery with intraocular lens replacement. *Expert Rev Ophthalmol.* 2015;10(2):91-103. **3.** Hovanesian JA, Sheppard JD, Trattler WB, et al. Intracameral phenylephrine and ketorolac during cataract surgery to maintain intraoperative mydriasis and reduce postoperative ocular pain: integrated results from 2 pivotal phase 3 studies. *J Cataract Refract Surg.* 2015;41(10):2060-2068. **4.** Omeros data on file.

Please see the Full Prescribing Information at www.omidria.com/prescribinginformation.

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REVIEW NEWS
Volume XXIII • No. 3 • March 2016

High-Dose Statin Treatment May Provide Dry AMD Therapy

Researchers at Massachusetts Eye and Ear/Harvard Medical School and the University of Crete have conducted a Phase I/II clinical trial investigating the efficacy of statins for the treatment of patients with the dry form of age-related macular degeneration. Although effective treatments are available for the wet form of AMD, they are currently lacking for the more prevalent dry form. The researchers found evidence that treatment with high-dose atorvastatin (80 mg) is associated with regression of lipid deposits and improvement in visual acuity, without progression to advanced disease, in high-risk AMD patients. Their findings were published in *EBioMedicine*—a new online journal led by editors of the journals *Cell* and *The Lancet*—and not only further the connection between lipids, AMD and atherosclerosis, but also present a potential therapy for some patients with dry AMD.

"We found that intensive doses of statins carry the potential for clearing up the lipid debris that can lead to vision impairment in a subset of patients with macular degeneration," said Joan W. Miller, MD, the Henry Willard Williams Professor and chair of ophthalmology at Harvard Medical School and chief of ophthalmology at Massachusetts Eye and Ear and Massachusetts General Hospital. "We hope that this promising preliminary clinical trial will be the foundation for an effective treatment for millions of patients afflicted with AMD."

Ophthalmologists and vision researchers have long suspected that there may be a connection between dry AMD and atherosclerosis. In dry AMD, physicians often see soft, lipid-rich drusen in the outer retina, similar to the buildup of lipid material in the inner walls of blood vessels in atherosclerosis. Statin use is widespread in middle-aged and older individuals, who also have an increased risk of AMD; however, previous studies have shown very little correlation between regular statin use and improvements in AMD. The authors of the *EBioMedicine* paper hypothesized that, due to the heterogeneous nature of the disease, patients with soft, lipid-rich drusen may respond better to statins prescribed at higher dosages.

"Not all cases of dry AMD are the exactly the same, and our findings suggest that if statins are going to help, they will be most effective when prescribed at high dosages in patients with

Eye Abnormalities Tied to Zika Virus in Infants

Vision-threatening eye abnormalities in infants in Brazil with microcephaly may be associated with presumed intrauterine infection with Zika virus, according to a study published online by *JAMA Ophthalmology*.

An epidemic of Zika virus has been happening in Brazil since April 2015. Six months after the onset of the Zika virus outbreak, there was an unusual increase in newborns with microcephaly. In January 2016, the Brazilian Ministry of Health reported 3,174 newborns with microcephaly.

Rubens Belfort Jr., MD, PhD, of the Federal University of São Paulo, Brazil, and coauthors evaluated the ocular findings of 29 infants with microcephaly (head circumference less than or equal to 32 centimeters) with a presumed diagnosis of congenital Zika virus. The study was conducted during December 2015 and all the children and their mothers were evaluated at the Roberto Santos General Hospital, Salvador, Brazil.

Of the 29 mothers, 23 (79.3 percent) reported suspected Zika virus signs and symptoms during pregnancy, including rash, fever, arthralgia (joint pain), headache and itch. Among the 23 mothers who reported symptoms during pregnancy, 18 or 78.3 percent reported Zika virus symptoms during the first trimester of pregnancy, according to the report.

Abnormalities of the eye were observed in 10 of the 29 infants (34.5 percent) with microcephaly; of the 20 eyes in 10 children, 17 eyes (85 percent) had ophthalmoscopic abnormalities. Bilateral abnormalities were found in seven of the 10 infants (70 percent) presenting with ocular lesions, the most common of which were focal pigment mottling of the retina and chorioretinal atrophy in 11 of the 17 eyes with abnormalities (64.7 percent). There also were optical nerve abnormalities in eight eyes (47.1 percent), along with other findings.

"This study can help guide clinical management and practice, as we observed that a high proportion of the infants with microcephaly had ophthalmologic lesions," the authors wrote. "Infants with microcephaly should undergo routine ophthalmologic evaluations to identify such lesions. In high-transmission settings, such as South America, Central America and the Caribbean, ophthalmologists should be aware of the risk of congenital ZIKV-associated ophthalmologic sequelae."

an accumulation of soft, lipid material," said Demetrios Vavvas, MD, PhD, a clinician scientist at Mass Eye and Ear and co-director of the Ocular Regenerative Medicine Institute at Harvard Medical School. "These data suggest that it may be possible to eventually have a treatment that not only arrests the disease but also reverses its damage and improves the visual acuity in some patients."

Twenty-three patients with dry AMD marked by soft lipid deposits in the outer retina were prescribed a high dose (80 mg) of atorvastatin (Lipitor) and several generic equivalents. Of the 23 patients, 10 experienced an elimination of the deposits under the retina and mild improvement in visual acuity. Other techniques that have attempted to eliminate the deposits have mostly failed with the disease continuing to progress to more advanced dry AMD or a conversion to the wet form of AMD.

As the next step for this line of research, the investigators plan to expand to a larger prospective multicenter trial to further investigate the efficacy of the treatment in a larger sample of patients with dry AMD.

"This is a very accessible, FDA-approved drug that we have tremendous experience with," said Dr. Vavvas. "Millions of patients take it for high cholesterol and heart disease, and based on our early results, we believe it offers the potential to halt progression of this disease, but possibly even to restore function in some patients with dry AMD."

Too Much Screen Time and Too Little Sunlight

The largest study of childhood eye diseases ever undertaken in the United States confirms that the incidence of childhood myopia among American

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REVIEW News

children has more than doubled over the last 50 years. The findings echo a troubling trend among adults and children in Asia, where 90 percent or more of the population have been diagnosed with myopia, up from 10 to 20 percent 60 years ago.

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

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

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

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

From 2003 through 2011, MEPEDS provided free eye exams at USC Eye Institute clinics to more than 9,000 Los Angeles-area children ages 6 months through 6 years. To date, data from the USC study has generated more than 20 academic papers on the prevalence of childhood eye diseases, including myopia, hyperopia, amblyopia and strabismus.

Shire Resubmits Lifitegrast NDA

Shire announced that it resubmitted the New Drug Application to the Food and Drug Administration for its investigational candidate, lifitegrast, for the treatment of dry-eye disease. Shire resubmitted the NDA in response to the complete response letter the company received from the FDA on October 16, 2015.

Addressing the FDA request for an additional study, Shire included in its NDA resubmission package data from OPUS-3, a Phase III efficacy and safety trial with a primary endpoint of patient-reported symptom improvement. The resubmission package also included information requested by the FDA regarding product quality.

"The NDA for lifitegrast now includes data from five randomized controlled clinical trials, with more than 2,500 patients, making it the largest data set for an investigational stage compound in dry-eye disease to date," said Philip J. Vickers, PhD, head of Research & Development at Shire. "Because we believe that, if approved, lifitegrast has the potential to help the millions of U.S. adults living with symptoms of dry-eye disease, we worked diligently to submit our response to the CRL as quickly as possible." The FDA has 30 days after resubmission of an NDA to acknowledge receipt and determine if the submission is a complete response. Upon acceptance, the FDA will provide Shire with a PDUFA date anticipated to be within six months of the date of submission. REVIEW

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INDICATIONS AND USAGE

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

IMPORTANT SAFETY INFORMATION ABOUT PROLENSA®

- PROLENSA® contains sodium sulfite, a sulfite that may cause allergic type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.
- All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including bromfenac, may slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including bromfenac. Use with caution in patients who have previously exhibited sensitivities to these drugs.
- There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery. Use with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.
- Use of topical NSAIDs may result in keratitis. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including bromfenac, and should be closely monitored for corneal health. Patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients. Post-marketing experience with topical NSAIDs suggests that use more than 24 hours prior to surgery or use beyond 14 days post-surgery may increase patient risk for the occurrence and severity of corneal adverse events.
- PROLENSA® should not be instilled while wearing contact lenses. The preservative in PROLENSA®, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of PROLENSA®.
- The most commonly reported adverse reactions in 3%-8% of patients were anterior chamber inflammation, foreign body sensation, eye pain, photophobia, and blurred vision.

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

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

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PROLENSA®
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PROLENSA® (bromfenac ophthalmic solution) 0.07%

Brief Summary

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Recommended Dosing

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

Use with Other Topical Ophthalmic Medications

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

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Sulfite Allergic Reactions

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

Slow or Delayed Healing

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

Potential for Cross-Sensitivity

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

Increased Bleeding Time

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

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

Keratitis and Corneal Reactions

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

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

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

Contact Lens Wear

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

ADVERSE REACTIONS

Clinical Trial Experience

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

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

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

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis and Impairment of Fertility

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

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

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

PATIENT COUNSELING INFORMATION

Slowed or Delayed Healing

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

Sterility of Dropper Tip

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

Concomitant Use of Contact Lenses

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

Concomitant Topical Ocular Therapy

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

Rx Only

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Under license from:
Senju Pharmaceuticals Co., Ltd.
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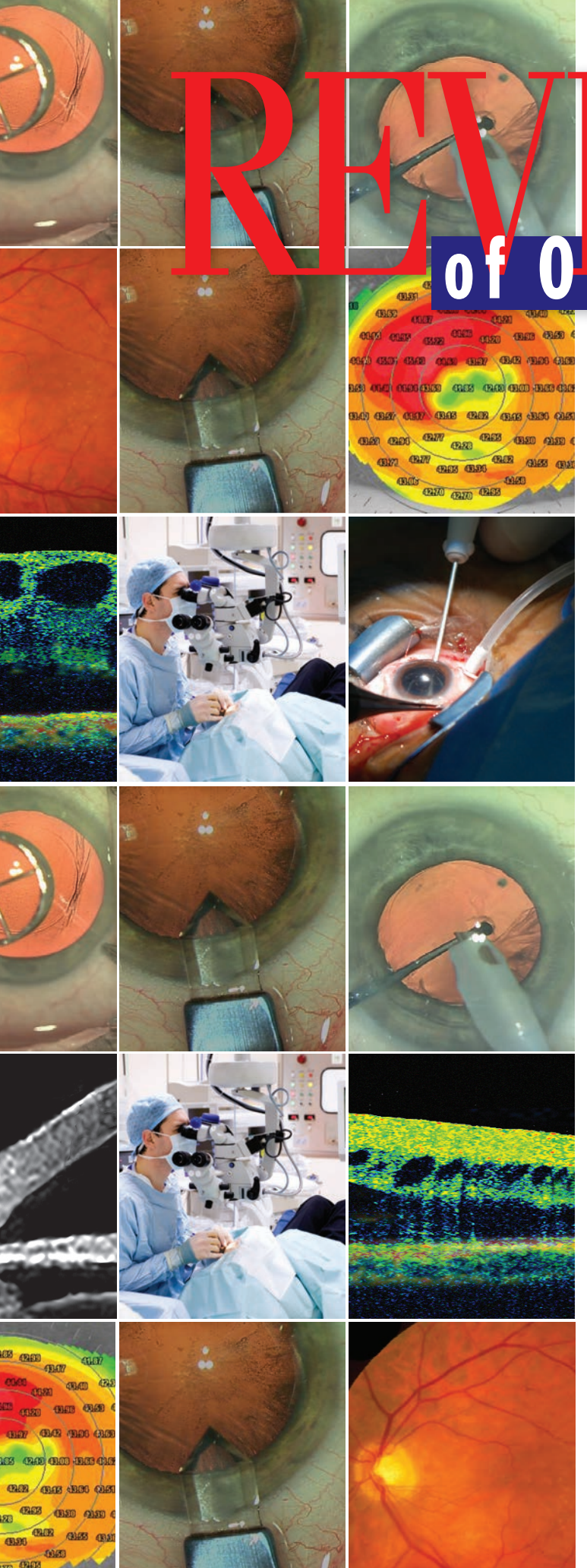

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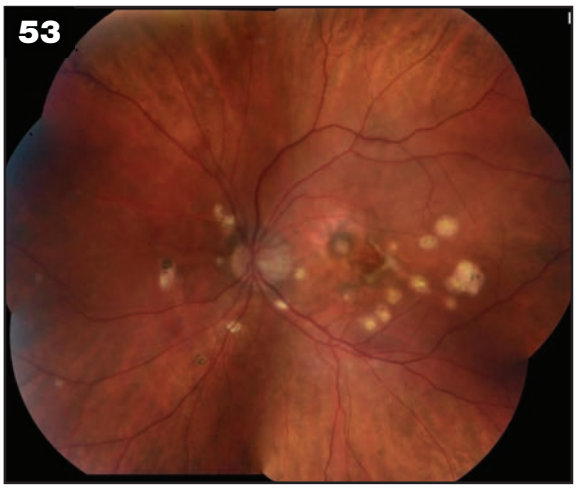

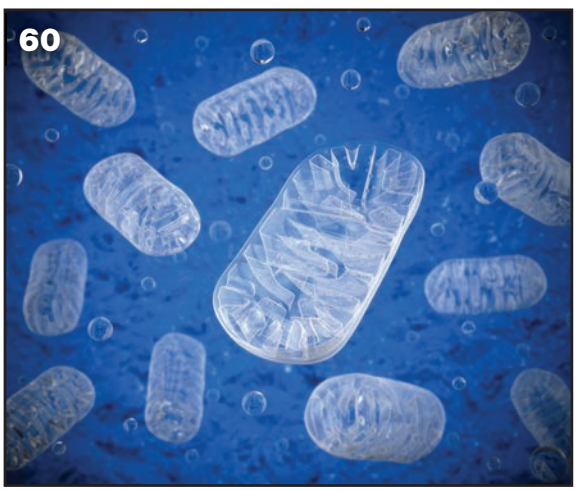

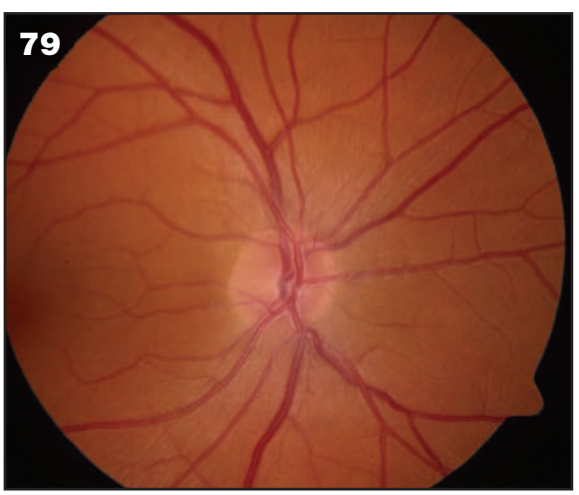

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INDICATIONS AND IMPORTANT SAFETY INFORMATION FOR THE TECNIS® MULTIFOCAL FAMILY OF 1-PIECE IOLs

TECNIS® MULTIFOCAL IOLs
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INDICATIONS: The TECNIS® Multifocal 1-Piece Intraocular Lenses are indicated for primary implantation for the visual correction of aphakia in adult patients with and without presbyopia in whom a cataractous lens has been removed by phacoemulsification and who desire near, intermediate, and distance vision with increased spectacle independence. The intraocular lenses are intended to be placed in the capsular bag. **WARNINGS:** Physicians considering lens implantation should weigh the potential risk/benefit ratio for any conditions described in the Directions for Use that could increase complications or impact patient outcomes.

See additional Important Safety Information on the following page.


Two New Ways to Help Manage Presbyopia

One device allows patients to easily sample multifocal and monofocal options; another may slow the onset of presbyopia.

Christopher Kent, Senior Editor

A cure for presbyopia is one of ophthalmology's holy grails, but until the cure arrives, helping patients manage it is the name of the game. Here, two new ways to help patients deal with presbyopia are profiled by individuals working with them.

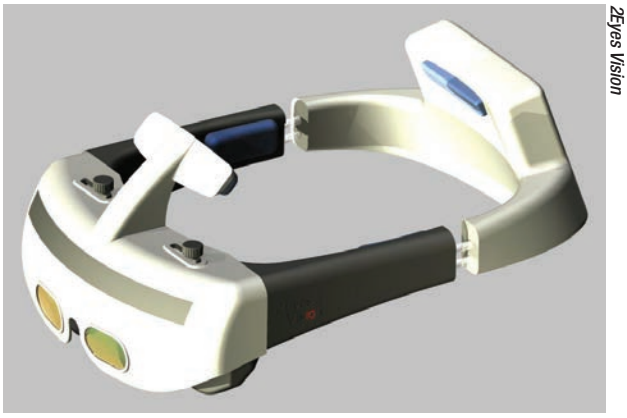
Simulating Visual Options

One of the challenges when attempting to help a patient with presbyopia is allowing the patient to experience some of the treatment options open to him (such as multifocality) before enacting them, to increase the likelihood that the choice the patient makes won't leave him unhappy. As any clinician knows, explaining something like multifocal vision in words to a cataract patient is a poor substitute for the actual experience.

Now, a company spun off from the Visual Optics and Biophotonics Lab at the Institute of Optics in Madrid, Spain, has created a wearable device that allows patients to experience different types of correction in real-life situations, including the improved near vision and reduction in distance visual quality associated with multifocal lenses. Because the device can simulate simultaneous vision, it's called SimVis.

"Our laboratory has long been involved in research and development of adaptive-optics visual simulators, such as devices that allow us to manipulate the optics of the eye through deformable mirrors and/or spatial light modulators," explains Susana Marcos, PhD, professor of research at the Institute of Optics and co-founder of 2Eyes Vision, the company marketing the device. "These instruments allow us to do very useful research on neural adaptation and help us understand vision with new corrections, but due to the reflective nature of the adaptive optics mirrors and their high cost, these instruments tend to be bulky and expensive. Also, the visual stimuli are generally projected as displays inside the instruments.

"In order to reduce the cost and dimensions of visual simulators we turned to the concept of superimposing near and far images—simultaneous vision—to simulate multifocal corrections," she continues. "Our first prototype allowed the simulation of bifocal corrections, with different additions and near/far energy ratios. Our current instrument allows simulation of the clinically available multifocal corrections, including bifocal, trifocal and extended-depth-of-focus designs. The device is compact, wearable and see-through."



2Eyes Vision

The SimVis instrument is a wearable, see-through device that allows patients to experience different visual corrections in the office, including simulated multifocal and monofocal options.

Professor Marcos explains that the device works by superimposition of images focused at different distances. "Different lens designs are pre-programmed and controlled automatically from a portable device," she says. "The current version of the headset is binocular, and in addition to multifocal corrections it can simulate other presbyopia-correcting combinations such as monovision and modified monovision, combining monovision and multifocality. The device corrects for the individual's existing refractive error, so there's no need to use any additional refractive correction.

"Because the instrument is wearable and see-through," she continues, "the patient can visually experience the real world through the different simulated corrections. Patients can perform standard visual function tests, compare the perceived quality across lens designs by rapidly flipping across programmed lenses, or simply walk around the office or other environments wearing the simulated lenses."

Asked how patients react to being able to try different options, Professor Marcos says it has made a difference in their satisfaction with the final result. "We've tested the system on presbyopes and simulated presbyopes in a laboratory environment, as well as in patients with cataracts who were scheduled for cataract surgery," she says. "Patients with normal cataracts were able to perform the test, and they found that using SimVis was tremendously helpful in making the decision about which intraocular lens to implant. The clinical experiments we've conducted included measurements of visual acuity with different simulated multifocal designs. They also tested subjective preference and scoring of corrections that included monofocal, bifocal, trifocal, monovision and modified monovision corrections in realistic visual settings with near, intermediate and far stimuli. The subjects report clear differences in their preferred corrections.

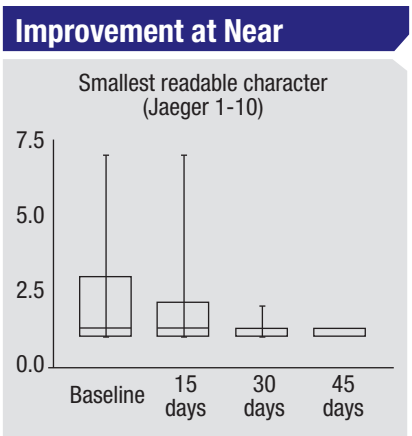
"On average," she continues, "a subject's preference was in line with the expectations we had based on the through-focus optical performance of the lens—i.e., trifocal designs were generally preferred for intermediate distances and monofocal corrections were generally preferred for distance. However, there were important intersubject differences in the subjective preference of one particular design over the others. We're planning several more studies that will hopefully demonstrate that the SimVis improves satisfaction levels and visual performance postoperatively."

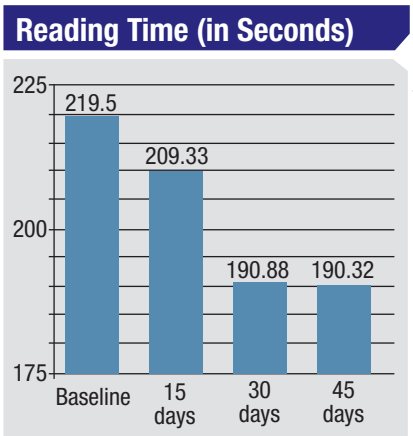
Professor Marcos says the company hopes to have the SimVis on the market by the end of this year. "We have several other technologies licensed to other companies, ranging from diagnostic devices to multifocal lens designs," she notes. "Other technologies in the pipeline include new patented paradigms for accommodating IOLs and for IOL engagement to the capsular bag. We believe these concepts will move presbyopic corrections to new stages of application."

Slowing Advancing Presbyopia

Another new instrument called Ocufit (SOOFT italia, Fermo, Italy) appears to help middle-aged individuals delay the progression of early presbyopia. The device, which has received the CE Mark, uses ciliary body electrostimulation to passively exercise and strengthen the ciliary muscles, significantly improving accommodation in many patients, the company says.

The Ocufit system includes a 20-mm-diameter polycarbonate contact lens containing four 3-mm electrodes, evenly spaced around the periphery. The inside of the lens is in direct contact with the bulbar

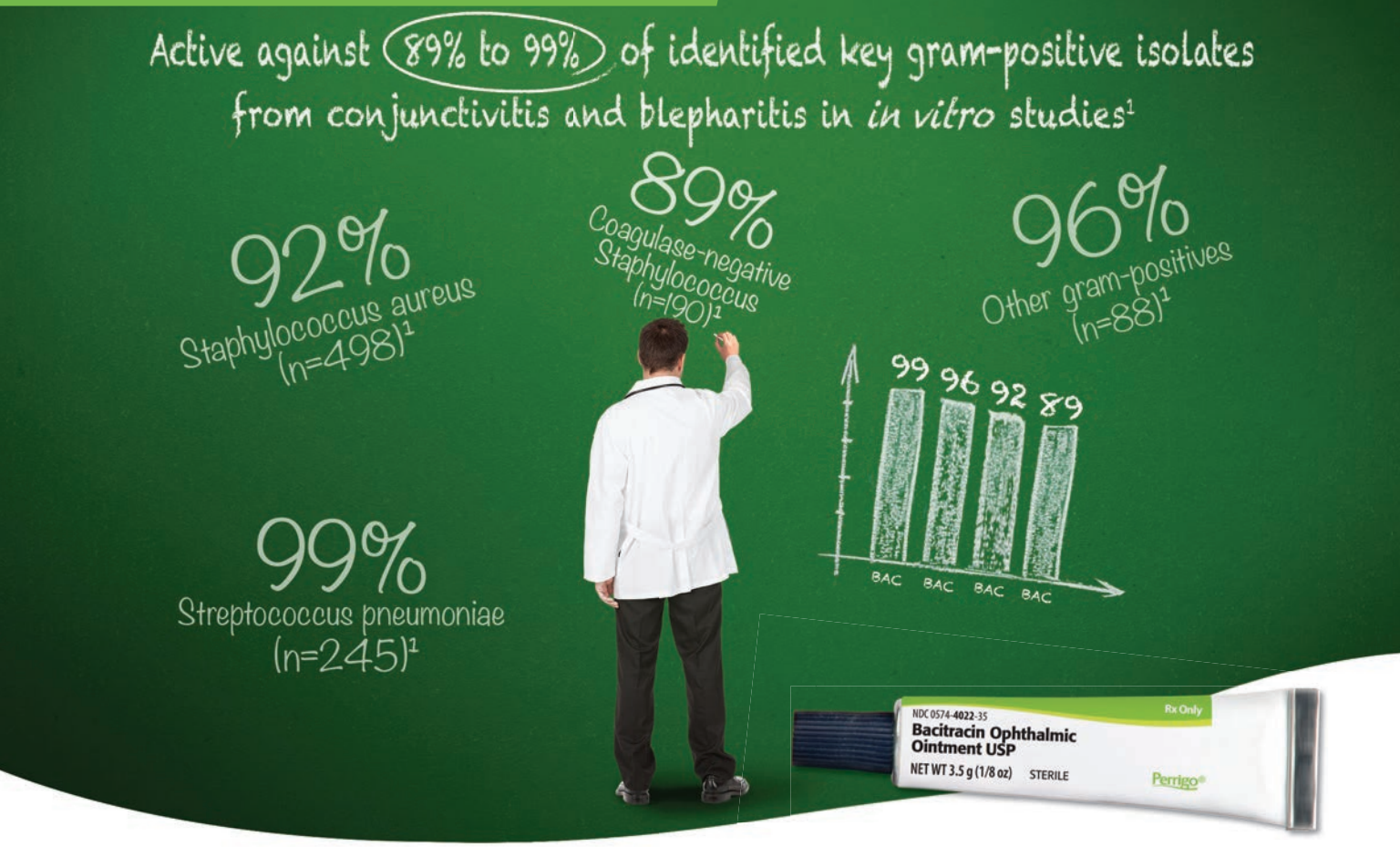




Luca Gualdi, MD

The Ocufit system uses electrodes embedded in a contact lens (above, left) to repeatedly stimulate the ciliary muscles during eight-minute sessions. The repeated contractions exercise and appear to strengthen the ciliary muscles, thus potentially improving accommodation. Early presbyopic emmetropes undergoing the treatment report improvement in near vision and reading speed. The charts above show vision test results for 60 early users; results were statistically significantly improved at 30 days compared to baseline in both datasets.

BACITRACIN OPHTHALMIC OINTMENT USP



***In Vitro* Susceptibility Data Provided Through the University of Pittsburgh Medical Center. *In Vitro* Data Should Not Be Considered Representative of Clinical Efficacy**[1]

Established therapeutic utility in blepharitis, conjunctivitis, and other superficial ocular infections caused by Bacitracin-susceptible organisms

- **Excellent safety profile**—low incidence of adverse events[2]
- Ointment provides **long-lasting ocular surface contact time** and **greater bioavailability**[3]
- **Anti-infective efficacy** in a lubricating base[2]
- **Flexible dosing**—1 to 3 times daily[2]
- **Tier 1 pharmacy benefit status**—on most insurance plans[4]

Indication

Bacitracin Ophthalmic Ointment is indicated for the treatment of superficial ocular infections involving the conjunctiva and/or cornea caused by Bacitracin susceptible organisms.

Important Safety Information

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

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

There is a low incidence of allergenicity exhibited by Bacitracin. If such reactions do occur, therapy should be discontinued.

Please see adjacent page for full prescribing information.

For a closer look, visit www.perrigobacitracin.com

BACITRACIN OPHTHALMIC OINTMENT USP

Perrigo® Specialty Pharmaceuticals

Bacitracin Ophthalmic Ointment USP

STERILE **Rx Only**

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

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

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

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

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

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

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

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

HOW SUPPLIED:

NDC 0574-**4022**-13 3 - 1 g sterile tamper evident tubes with ophthalmic tip.

NDC 0574-**4022**-35 3.5 g (1/8 oz.) sterile tamper evident tubes with ophthalmic tip.

Store at 20°-25°C (68°-77°F)
[see USP Controlled Room Temperature].

Manufactured For
Perrigo®
Minneapolis, MN 55427

0S400 RC J1 Rev 08-13 A

References: 1. Antibiotic susceptibility: conjunctivitis and blepharitis. University of Pittsburgh Medical Center, Charles T. Campbell Eye Microbiology Lab Web site. http://eyemicrobiology.upmc.com/AntibioticSusceptibilities/Conjunctivitis.htm. Accessed December 9, 2015. **2.** Bacitracin Ophthalmic Ointment [package insert]. Minneapolis, MN: Perrigo Company; August 2013. **3.** Hecht G. Ophthalmic preparations. In: Gennaro AR, ed. *Remington: the Science and Practice of Pharmacy*. 20th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2000. **4.** Data on file. Perrigo Company.

conjunctiva on the sclera; the four electrodes are located about 3.5 mm from the limbus, corresponding with the ciliary body region. The center of the lens is dome-shaped, so it doesn't touch the cornea. The embedded electrodes are powered by a handheld battery-operated generator device with wires that connect to a jack on the front of the contact lens. A small tube can be used to induce a small amount of suction to maintain contact between the eye and the lens; the suction (if used) does not affect intraocular pressure during the treatment.

The lens is placed on the patient's eye for a series of eight-minute treatments. Patients feel a tingling sensation during treatment, but it is generally not painful. Early clinical testing indicates that the treatment may improve accommodation and increase reading speed in emmetropes with early presbyopia. *(See charts, p. 16.)*

Luca Gualdi, MD, an anterior segment surgeon at Studio Oculistico Gualdi, in Rome, Italy, has been testing the device on emmetropes with early presbyopia, at the request of the manufacturer, for about a year. "This technique for managing presbyopia is not surgical and there are no side effects," he notes. "The patient doesn't have pain or lose vision after the treatment. The worst possible outcome is seeing no effect from the treatment.

"The company gave us the instrument to test because we have a large practice in a metropolitan area and we own many instruments that are useful for monitoring vision," he continues. "I've performed 300 treatments on 60 patients so far. Among emmetropes between 40 and 50 years old, 95 percent of the patients I've treated are happy because they've seen a positive effect."

Dr. Gualdi explains that the idea for this type of electrostimulation is not new. "In the past this type of stimulation has been used to treat optic atrophy, glaucoma, macular degeneration and progressive myopia," he says. "One scientist demonstrated that stimulating the ciliary muscle moves the trabecular meshwork, leading to a decrease in intraocular pressure after treatment. The Ocufit can also be used to do that, although it requires running a different program."

Luca Gualdi, MD

Patients receiving the Ocufit treatment generally report a tingling sensation but no pain. Treatment intensity is adjustable.

Dr. Gualdi explains that the rhythmic contractions caused by the electrostimulation produce an increase in the efficiency of the ciliary muscle, leading to an increase in accommodative range that can last for several months. Currently, each eight-minute session involves two seconds of electrostimulation out of every eight seconds. The stimulation affects the entire muscle, not just where the electrodes are located, much as it does when this type of electrostimulation is used for other purposes such as physical therapy.

"You have to tell the patient that this is not surgery," Dr. Gualdi notes. "It's exercise, like going to the gym. If you don't train, your muscles get smaller. So, you have to keep training your ciliary muscles if you want to put off wearing glasses. If you keep the muscles in shape, instead of starting to wear glasses at age 41, you might be able to wait until age 50."

Although patients usually feel no pain, Dr. Gualdi notes that the reaction is different from patient to patient. "Some say they feel nothing at all," he says. "Other patients receiving a higher level of stimulation say they feel a little discomfort during the first treatment. You can regulate the power, so if your patient is more sensitive you can reduce the intensity. That will also reduce the effect, but it's important that the patient be comfortable during the procedure. For that reason, we start with less energy for the first treatments and gradually increase it over the course of the treatments. We just keep asking the patient if he or she is OK."

Dr. Gualdi says the company asked him to use the device partly to test the duration of the effect. "We have about one year of follow-up at this point," he says. "Our current protocol is to do a series of three or four treatments during the first two months, one every 15 days or so. After that, one treatment every three months is sufficient to maintain the effect, on average. Younger patients may be able to go for longer than three months.

"The average patient says he can tell a difference after the first or second treatment," he notes. "Some patients don't report a difference after one treatment, but when I check I do find there's been an increase in their visual parameters. By the second treatment most patients say they can tell the difference. They've been able to decrease the size of the letters on their smartphone screen, or they're reading better without reading glasses, especially in dim-light conditions.

"The treatment works especially well on people between 40 and 50 years of age with early presbyopia," he continues. "We tried the treatment on patients in their early 50s, but the effect was reduced. So it depends on the age and the ciliary muscle response. When treating emmetropes,

the prescription of reading glasses they've been using gives us a good idea of how far their presbyopia has progressed and how effective the treatment will be. Patients using reading glasses 1.5 D or lower have a pretty good response to the treatment. When the patient has been using reading glasses more powerful than 1.5 D there's less effect, and most of those patients subjectively can't tell the difference after the treatments, even though testing reveals an improvement. I wouldn't recommend this treatment for those patients."

Dr. Gualdi says the treatment does not appear to cause cataract. "Our studies have shown that the treatment does cause a slight negativization of spherical aberration curvature during accommodation," he says. (Ultrasound biomicroscopy showed a significant increase in lens thickness during accommodation, along with a decreased posterior and especially anterior curvature of the crystalline lens.) "This change, however, does not seem to affect distance vision at all. In fact, that's one of the best things about this treatment. Almost every treatment for presbyopia causes a decrease in distance vision, whether the treatment is monovision, presbyopic inlay, multifocal lenses or presbyLASIK. With this treatment, distance vision is not affected."

In terms of the cost to the patient, Dr. Gualdi notes that his practice is one of the first to offer this service, and they're keeping the cost fairly low. "After three or four months the effect of the treatment wears off, so it can't be too expensive or patients won't opt for it. We're currently charging 100 Euro per treatment. We want to give the world an effective presbyopia treatment that is not painful; we're not doing this to make a lot of money."

Dr. Gualdi says the company is just beginning to market the product in Italy. "They're starting slowly," he says. "They don't want everyone to have the machine at first; some doctors might use it on everybody, people who are too old to benefit, for example, resulting in no effect and the procedure getting a bad reputation. They want to be sure the treatment is in the hands of doctors who understand how to use it, who can help develop the best protocol. The company definitely does plan to market this in the United States.

"I intend to try this on myopes with early presbyopia next," Dr. Gualdi adds. "I want to see whether the increased accommodation will allow those patients to need fewer pairs of glasses." REVIEW

Professor Marcos is co-owner of three patents relating to SimVis. Dr. Gualdi has no financial interest in the Ocufit instrument.

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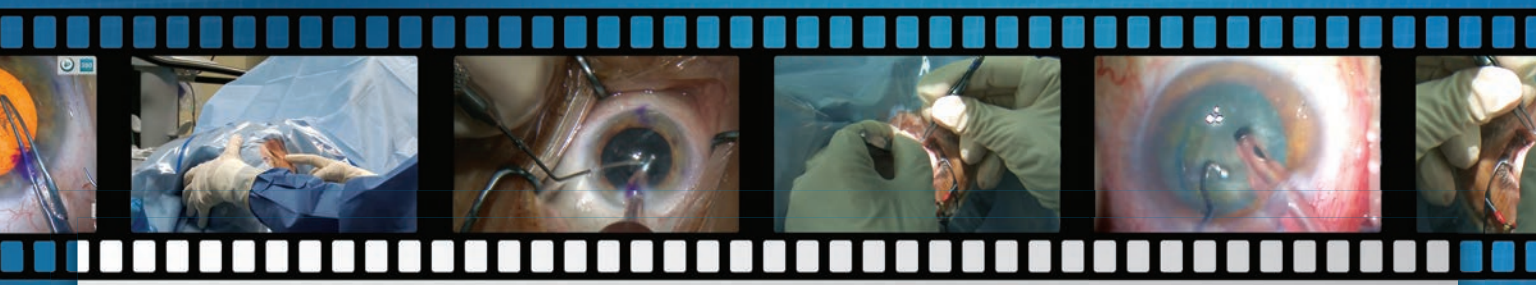

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Episode 3:
"The Deep Set Eye"

Surgical Video by:
Richard J. Mackool, MD

This month I demonstrate the use of the Trendelenburg position in order to gain adequate access to a "deep set" eye during cataract-implant surgery with toric IOL implantation. The pupil dilates only moderately, and possible pharmacological causes of poor dilation are discussed: several techniques that increase and/or maintain pupil size are demonstrated, as are methods to chop the nucleus and protect the posterior capsule during subincisional cortex removal.

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Richard J. Mackool, MD

I would like to welcome you to a new concept in surgeon education, Mackool Online CME.

Demonstrating ophthalmic surgical techniques has long been part of my everyday practice. Now, thanks to educational grants from several ophthalmic companies, you are able to virtually sit at the microscope with me and see the techniques and instrumentation I use with my own patients. The only editing is to show a different camera view or to remove down time – every step of every procedure will be shown just as if you are with me in the OR. We will release one new surgical video every month, allowing you to earn CME credits or simply watch the video.

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Richard Mackool, MD, a world renowned anterior segment ophthalmic microsurgeon, has assembled a web-based video collection of surgical cases that encompass both routine and challenging cases, demonstrating both familiar and potentially unfamiliar surgical techniques using a variety of instrumentation and settings.

This educational activity aims to present a series of Dr. Mackool's surgical videos, carefully selected to address the specific learning objectives of this activity, with the goal of making surgical training available as needed online for surgeons motivated to improve or expand their surgical repertoire.

Episode 3: Learning Objectives

After reviewing the educational video, learners should be able to:

1. Discuss the benefits of using the Trendelenburg position in patients with deep-set eyes.
2. List categories of pharmacological agents that can affect pupil dilation.
3. Describe techniques that can be used to increase or maintain pupil size during cataract surgery.
4. Protect the posterior capsule during cortex removal.

Accreditation Statement
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Institute for the Advancement of Human Behavior (IAHB) and Postgraduate Healthcare Education, LLC (PHE). IAHB is accredited by the ACCME to provide continuing medical education for physicians.

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25 Ways to Maximize Your Cataract Outcomes

Christopher Kent, Senior Editor

Surgeons share strategies that lead to the best possible results when performing cataract surgery.

Cataract surgery may be the most frequently performed surgery in the world, but like any surgery, it can always be done better. (And given the number of surgeries being performed, doing it better can have consequences for millions of people.) Here, with that in mind, four experts in the art and science of getting the best possible outcomes share 25 specific things any cataract surgeon can do to come as close as possible to the desired visual target, while avoiding—and if necessary managing—six of the most common complications.

Performing the Exam

These strategies will get the preoperative process off to a good start:

1. Remember that just because a cataract is present doesn't mean it has to be removed. "The prime directive that we all agreed to when we became physicians is: first, do no harm," says Robert M. Kershner, MD, MS, FACS, professor and chairman of the Department of Ophthalmic Medical Technology at Palm Beach State College, and president and CEO of Eye Laser Consulting, in Palm Beach Gardens, Fla. "Every medical and pharmacological decision we make has the potential to cause harm. Not every cataract needs to be removed. Listen to your patients and hear their complaints, but if it ain't broke, don't fix it."

2. Look for ocular surface disease and treat it before finalizing your measurements. "In my practice I bring about 60 percent of my patients back for a second visit for repeat measurements, because the first measurements may not be as accurate as I'd like," says William B. Trattler, MD, who practices at the Center for Excellence in Eye Care in Miami, and is a volunteer faculty member at the Herbert Wertheim College of Medicine at Florida International University. "The reason is simple: Patients often have ocular surface disease. For example, as demonstrated in the Prospective Health Assessment of Cataract Patients Ocular Surface Study,[1] about 80 percent of patients evaluated for cataract surgery have preexisting dry eye; signs include a rapid tear breakup time and ocular surface staining.

"To ensure that this doesn't impact our outcomes, when patients come in for a consultation for cataract surgery we carefully evaluate them for ocular surface disease at the slit lamp," he continues. "We also perform topography and IOLMaster. I have found that performing a preoperative topography on all patients scheduled for cataract surgery provides helpful information, whether or not the patient is going to

This article has no commercial sponsorship.

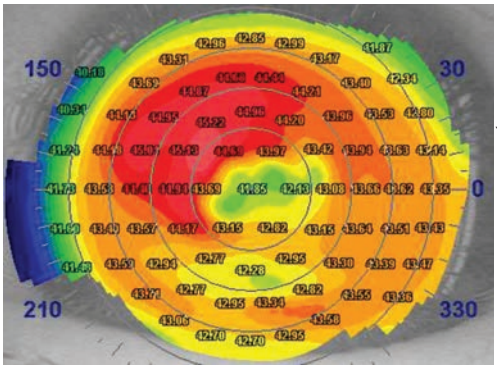
receive a premium IOL. Topography will often pick up dry eye, as well as subtle epithelial basement membrane dystrophy, either of which will impact the visual outcome. Topography can also reveal mild keratoconus that has been undiagnosed.

"If the readings appear irregular and the eyes are dry, I'll place the patient on a topical steroid like Lotemax gel or Pred Forte for two or three weeks," he says. "Then I'll bring the patient back for repeat measurements. This has made a big difference in terms of getting more accurate keratometry, which significantly impacts our cataract surgery outcomes.

"Once you start identifying and treating dry-eye patients aggressively prior to cataract surgery," he adds, "you'll end up doing it more and more, because you'll realize how many patients really have dry eyes, and how treating their condition and repeating measurements can result in improved intraocular lens calculations."

3. Consider treating any epithelial basement membrane dystrophy before performing the surgery. "A lot of patients—more than you may realize—have epithelial basement membrane dystrophy that can significantly impact their visual outcome," says Dr. Trattler. "Just today, for example, I saw a patient who had had surgery with another doctor; he came to me because he wasn't happy with his visual result. The implant looked beautiful, everything was fine, the macula was normal, but the patient had EBMD and some dry eye. That was the source of the reduced vision quality in the eye that had been operated on. The patient did not recall being told about EBMD prior to his surgery.

"EBMD can impact the measured shape of the cornea, and it can therefore impact the postoperative results," he continues. "So, identifying the condition and talking with the patient about whether to treat it beforehand is critical. If a patient has irregularity, enough that you feel it requires treatment, you can perform an epithelial debridement to smooth the corneal surface. Some doctors will use an excimer laser and perform phototherapeutic keratectomy for patients with EBMD. A small percentage of patients who are at risk for delayed epithelial healing may also be treated with an amniotic graft to help the epithelium heal rapidly after debridement.



Epithelial basement membrane dystrophy is more common than many surgeons realize; left untreated, it can degrade a patient's cataract surgery outcome.

William B. Trattler, MD

"Following epithelial debridement or PTK," he adds, "one should advise the patient that she'll need to wait about two months to re-take the keratometry measurements, to ensure that they're relatively accurate."

4. Perform a careful preoperative retinal exam and take steps to minimize the risk of cystoid macular edema. "Although CME with retinal detachment is a much-less-frequent complication of cataract surgery today, it still occurs, and is often the cause of a poor outcome and the basis for a lawsuit," says Dr. Kershner. "The best way to prevent this is a thorough preoperative retinal examination. I've seen too many referred cases where preexisting lattice degeneration, maculopathy, vitreoretinal degeneration or a retinal tear or hole was missed. Worse, I've seen cases where these were recognized and charted but not addressed prior to surgery.

"Don't become a legal statistic," he continues. "You can never be faulted for being safe and thorough, but you'll have to answer for a poor surgical outcome caused by something that could have been eliminated as a complicating factor—if only it had been addressed before surgery. Consider what any prudent ophthalmic surgeon would do under similar circumstances, and if you don't think you're doing that—whatever is truly in the best interest of the patient—then get outside help. If you fail to meet the standard of care, you'll be answering to a lawyer."

"Patients who are at increased risk of developing CME," adds Dr. Trattler, "include patients with various retinal conditions such as epiretinal membranes, a history of retinal vascular occlusions, diabetic retinopathy or uveitis. The key to managing the risk of CME is prevention. Using topical nonsteroidals for three days prior to cataract surgery appears to reduce the risk of developing CME, and combining therapy with a topical corticosteroid can also help. These anti-inflammatory medications are often used for four weeks postoperatively, and in some cases are prescribed for an additional month or two."

Choosing the IOL

Selecting the optimum type and power of IOL is essential to a great outcome:

5. If multiple technologies are used to measure astigmatism, make sure they agree. "If one device suggests there is 1 D of astigmatism at 85 degrees and a second device says there is 1.8 D of astigmatism at 95 degrees, consider initiating a treatment for ocular surface disease," suggests Dr. Trattler. "Then bring the patient back for repeat measurements."

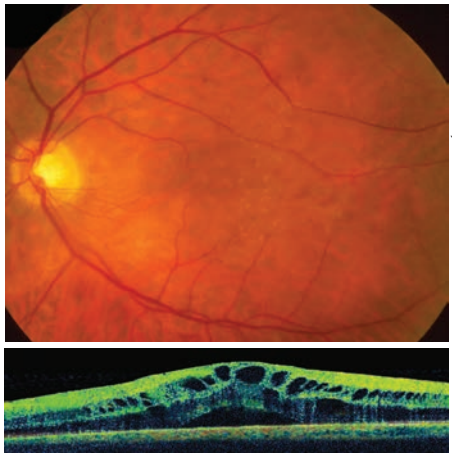
6. Use aspheric lenses. "Aspheric lenses correct the spherical aberration

in the cornea," notes Jack T. Holladay, MD, FACS, clinical professor of ophthalmology at Baylor College of medicine in Houston. "That translates to improved vision. Studies have shown that aspherical IOLs improve vision by about one line and improve contrast sensitivity by about 30 percent.[2-5] Most doctors have embraced this idea, but many of them don't realize that there's a second benefit to reducing residual spherical aberration: Residual spherical aberration not only reduces your quality of vision, it also causes your refraction to change as a function of pupil size. With positive spherical aberration, your vision will tend to shift toward nearsightedness when your pupils are larger in darker conditions. So, aspheric IOLs not only provide you with better-quality vision, they also give you a more constant refraction at various light levels.

"At this point," he adds, "using an aspheric lens has become the standard of care."

7. Use equi-convex lenses. "This refers to a lens design in which both surfaces have the same curvature," explains Dr. Holladay. "This design does a better job of maintaining image quality in the face of lens tilt and decentration, and the principal planes don't shift as a function of power. Most of the popular lenses in use today incorporate this design. If you're using one that does not incorporate this design, you should consider switching to another lens."

8. Reconsider your habitual choice of IOL. "Just because you've implanted a particular IOL thousands of times with excellent results does not mean that it's the best choice for a particular patient," says Dr. Kershner. "Also, it's important to revisit your routine IOL choices frequently—at least twice a year. Technology changes. Your IOL rep may be a longtime friend, but there might be better options out there that you have not considered. In fact, the best choice may not be necessarily be the latest and greatest; sometimes IOLs that have been available for decades will be the best choice for your patient."



Robert M. Kershner, MD

A thorough retinal exam before surgery can catch problems that may lead to cystoid macular edema—and potential lawsuits—later.

9. Don't use a two-variable formula when calculating lens power. "If you're using a two-variable formula to predict the lens position, you're behind the times," says Dr. Holladay. "The formulas that use two variables are mostly older ones. The Haigis formula, for example, uses axial length and anterior chamber depth, while SRK/T, Hoffer Q and Holladay I use axial length and Ks. With a two-variable formula you'll get about 60 percent of your cases within 0.5 D. That's not very good, and it puts your outcomes in the bottom 50 percentile.

"Today there are three formulas that use up to seven variables: The Holladay II, the Olsen II and the Universal II formula from Graham Barrett," he continues. "Those formulas use axial length, K-reading, horizontal white-to-white distance, anterior chamber depth, lens thickness, refraction and age of the patient. Using any of these formulas will result in 70 to 75 percent of your cases being within 0.5 D of your target. ASCRS did a study that showed that between 60 and 70 percent of doctors are now using a seven-variable predictor formula, because they have access to the Holladay II formula in the IOLMaster, the LenStar and the Verion system.

"If you're not using one of these advanced formulas, you need to catch up," he says. "It's not hard to do because the Holladay II is available on all of these instruments."

10. Personalize your lens constant. "Probably 30 percent of surgeons still don't personalize their lens constant," notes Dr. Holladay. "Manufacturers' constants are based on averages and numerous assumptions that may not apply to any given surgeon. Also, your surgical technique and choice of IOL will affect the value of your ideal constant. The only way to pin down the constant that will give you the best outcomes is to measure your patients' postoperative refractions and check that against the constant you're currently using. *[For more about how to personalize your constants, see "Another Step Closer: Lens Constant Customization" in the January 2010 issue of Review.]*

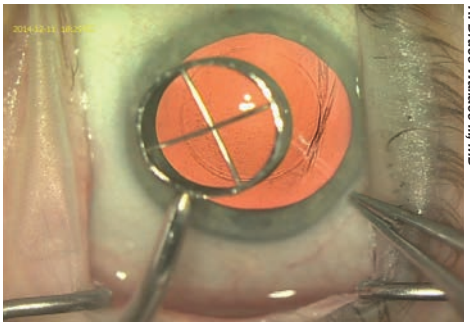
"If you use one of the advanced multi-variable formulas and also personalize your lens constant, you can get up to 82 percent of cases within 0.5 D of your intended target," Dr. Holladay continues. "That's what you should be doing, because with today's premium lenses, if you're not within 0.5 D 80 percent of the time, more than 20 percent of your patients will be unhappy."

Dr. Kershner agrees. "It's important to make sure the formula you use is backed up by solid data demonstrating reproducible results from your own outcomes analysis," he says. "Many a surgeon has quoted the thought leaders or literature results, but not as many can quote their own statistics. Just because Dr. X can achieve 20/10 results with his lens constant and his own tweaked formula, does not mean that you will get the same results as he does. You need to carefully track and monitor your own outcomes and adjust your formula accordingly.

"Furthermore, even if your formula is correct, it won't ensure reproducible results unless the same people in your practice are taking the same measurements every day and inputting the data the same way," he adds. "In other words, you need to avoid the inadvertent introduction of other variables into your measurements simply because on Tuesdays, Tom takes the measurements and Sally makes the calculations, and on Thursdays the new person does it all. To maintain the integrity of your data, you need to control as many factors that could introduce errors as possible."

11. When calculating the astigmatism correction, use an advanced calculator that takes IOL power and effective lens position into account. "One of the pitfalls of using some online calculators is that they are only accurate for a 22-D lens," notes Dr. Holladay. "They assume the ratio of the lens toricity that you'll need to correct the corneal astigmatism is 1.5 to 1, but that's only true for a 22-D lens. For example, a 3-D toric lens will correct 2 D of astigmatism at the cornea when the lens is 22 D. But if you have a 10-D lens, you need almost 3.5 D of toricity in the lens to correct 2 D of corneal astigmatism. And if you have a 30-D IOL, you'll only need about 2.25 D of toricity to correct 2 D of corneal astigmatism."

Dr. Holladay explains that the less-precise calculators produce good results in the majority of eyes because about 70 percent of the lenses in use today are within 3 D of 22 D. "About twice as many 22-D lenses are used as any other curvature because refractive errors are clustered around emmetropia," he says. "So the unusual eyes—30 to 40 percent of eyes—are not as common. They don't push the curve enough to make it look wrong. However, some calculators now do take the curvature of the lens into account. The AMO Express calculator takes this into account; the Verion System from Alcon corrects for this, and they're upgrading their online calculator to do the same. The Holladay IOL Consultant also takes this into account. In fact, I wrote the software for all three. Bausch + Lomb should also have this in their calculator upgrade sometime this year.



R. Bruce Wallace III, MD

Using a device to make a capsulotomy diameter mark on the cornea can provide the surgeon with a visual guide that will help create a capsulotomy very close to the intended size.

"For now, doctors need to be aware that not every calculator compensates for this," he concludes. "Using an older calculator will result in undercorrecting the astigmatism when using low-power lenses and overcorrecting astigmatism when using high-power lenses. That's why you're more likely to end up with more than a half diopter of residual astigmatism as the lens curvature gets farther from 22 diopters."

12. Be aware that the lens may shift differently following manual capsulorhexis than following femtosecond capsulotomy. "If you perform manual capsulorhexis there appears to be a slight forward shift of the lens between the first week and month six," says Dr. Holladay. "If you perform a femtosecond laser capsulotomy there may be a slight posterior shift in the IOL in the same time frame. The reason for this shift in opposite directions—and exactly how great the shift is likely to be—is still under investigation. But this may impact your outcomes, depending on which technology you're using, so personalize your lens constant."

Planning Your Approach

To avoid losing the advantages gained with the previous steps:

13. Make sure you don't induce a refractive change with your planned incision. "There is simply no such thing as 'One incision size and location fits all,' " says Dr. Kershner. "As the great Spencer Thornton, MD, has taught us, all incisions in the cornea will act as if tissue has been added. That means there is no such thing as a 'refractive-neutral' incision. And remember that where you cut—not how you cut—will determine the incision's effect on the overall power of the cornea. So, monitor your incision placement, whether the incision is made with a diamond keratome or a femtosecond laser. You want to leave the patient with less than 0.5 D of astigmatism and less than 0.25 D of spherical error; that means not inducing a refractive change with your incision. If you don't know how to minimize the refractive impact of your incision, take a course and read a text on the surgical correction of refractive error."

14. Make sure all of your patients end up with less than 0.5 D of residual astigmatism. "Any more than half a diopter of astigmatism will result in diminished quality of vision at distance," says Dr. Holladay. "To accomplish this you need to know how much astigmatism your surgical technique will induce, and you need to use toric lenses to maximum advantage. Toric lenses come in step sizes that are 0.75 D, which converts to about 0.5 D at the corneal plane. So if used properly, the farthest you can be from the perfect astigmatic correction is about 0.25 D.

"To get the very best result from a toric lens," he adds, "intraoperative aberrometry is ideal, since it narrows the alignment error far more than manually marking the eye can."

15. Take posterior capsular astigmatism into account. "As Doug Koch,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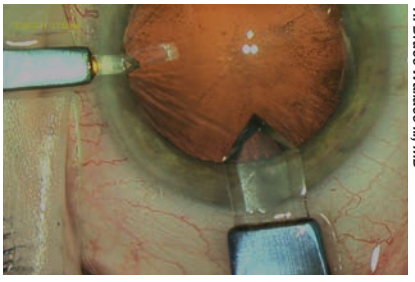
MD, first pointed out, the posterior surface of the cornea in most people contributes about 0.5 D of against-the-rule astigmatism to our vision," says R. Bruce Wallace III, MD, FACS, founder and medical director of Wallace Eye Surgery in Alexandria, La., and clinical professor of ophthalmology at Louisiana State University and Tulane Schools of Medicine in New Orleans. "That's enough to have an impact on your outcomes. Generally speaking, if you're making a 2.5- to 3.0-mm temporal corneal incision, then posterior corneal astigmatism won't have a big impact on your outcome; your incision will produce a compensating effect. On the other hand, if you're making a superior incision you have to take this into consideration because your incision will add to the against-the-rule astigmatism. So if you're making a superior incision, adjust your astigmatism correction accordingly."

Performing the Surgery

Once you're in the OR:

16. Before surgery, verify that the patient data is correct—multiple times. "Make sure your system protocol and pre-flight checklist incorporate a series of checks and balances to verify that the patient's data is correct; that the data you are using is the data belonging to the patient you are about to operate on; and that no fewer than three different individuals have verified this," says Dr. Kershner. "I've often appeared as an expert witness to help defend a physician because of a poor outcome, when the office had the best intentions and the doctor had the right skills but the data used was from the wrong patient. Take nothing for granted. Verify, verify, verify."

17. Make sure your anterior capsulorhexis is the size you intend. "Getting the size of your anterior capsulorhexis right helps with IOL centration and stability," says Dr. Wallace. "I find two strategies useful. First, when I want to make a 5- to 5.5-mm diameter anterior capsulotomy, I create what's called a capsulotomy diameter mark—an indention on the corneal surface marking the edge of a 6-mm optical zone. Using that as a visual guide, I stay just inside that mark when I'm creating the 5- to 5.5-mm anterior capsulotomy. It's easier to size the capsulotomy accurately with that as a reference point.



R. Bruce Wallace III, MD

Making a sutureless incision that's as square as possible, rather than logitudinal, can help prevent leakage. To create a square incision, stay in stroma as long as possible when creating the incision. Using a diamond knife makes this easier to do.

"A second strategy that helps is fixating the globe during the capsulotomy using a cyclodialysis spatula through the sideport incision," he says. "This stabilizes the globe so that when you're making the capsulotomy with forceps the process is easier to control, resulting in the most accurately-sized and most complete anterior capsulotomy."

18. If possible, use intraoperative aberrometry. "When Alcon bought WaveTec," notes Dr. Holladay, "it was on condition that WaveTec would do a controlled study demonstrating that their intraoperative aberrometry technology—the ORA—could statistically improve outcomes, even when a surgeon was using the latest formulas and personalizing his constants. And they did. About 20 surgeons went from having 82 percent of their outcomes within 0.5 D, using the Holladay II formula and a personalized constant, to 92 percent within 0.5 D by also using the ORA.

"Today, many surgeons are buying the VerifEye for that exact reason: It reduces the number of patients you have to bring back for a lens exchange or laser surgery, which costs a lot more than the per-case cost of using the VerifEye," he continues. "The reality is, this is the level of performance that doctors are being measured against today. If you use the seven-variable predictors, personalize your lens constant and do intraoperative measurements you can get upwards of 90 percent of your patients within 0.5 D of the intended target.

"Of course, purchasing the equipment to perform intraoperative aberrometry costs money, and surgeons early in their practice may not have that option," he adds. "But you can get close to that by using the more advanced formulas and personalizing your constant. That's the standard of care today."

19. Don't just look at where your implanted IOL has ended up, measure it. "Today's anterior segment OCT can give you excellent data on the anterior-posterior position of the IOL you've implanted, as well as lateral displacement," notes Dr. Kershner. "If the lens ends up farther back than you had expected with your calculations, your patient will be undercorrected. The patient won't be able to accommodate to make up the difference. So check to make sure that the IOL has ended up where you intended it to be." *[For more on this, see #22, below.]*

Managing Complications

Obviously, the best planning and surgical execution may not lead to the best outcome if a complication occurs.

20. Take steps to prevent incision leakage. Dr. Wallace notes that a leaking incision can lead to a host of other complications (including endophthalmitis), so it's crucial to ensure that your incisions are watertight. "I've found that the best way to prevent leakage

(continued on page 71)

ADVERTORIAL

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SUN OPHTHALMICS: RE-ENERGIZING THE MARKET

A passion for delivering on eye care professionals' needs.

Sun Ophthalmics has burst into the ophthalmic pharmaceuticals arena with the energy and enthusiasm of a company with a focus. Its mission is to launch innovative ophthalmic products that integrate seamlessly into the professional's office. To achieve this, Sun Ophthalmics is building its reputation on strong R&D support and a philosophy of customer-centric service delivery.

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Sun Ophthalmics' parent company, Sun Pharma (Mumbai, India), has a global presence in 150 countries, a $35 billion market cap, and a strong foundation of research and innovation. Sun Pharma, and its partners employ approximately 2,000 PhDs to conduct research and development, and has brought more than 2,000 products to market within the healthcare field during the past 30 years. Thus, Sun Ophthalmics, the US eyecare division, has the agility and enthusiasm of a startup, with the support of a world-class pharmaceutical powerhouse.

CONCIERGE CUSTOMER CARE


JASON MENZO

Sun Ophthalmics is building a "concierge level" of customer care by teaching its sales representatives to be hyperfocused on eye care professionals. "We intend to invest significantly in our reps' training," said Jason Menzo, Vice President of Sales & Marketing, Ophthalmic Business. This training will include a mandatory number of hours each year observing surgery and shadowing eye care professionals in clinic. Furthermore, Sun Ophthalmics' reps will receive training on billing and reimbursement so they can understand the needs of administrators, and thereby create value-added services for their clients. Moreover, its reps will have fewer targeted doctors in their "call on audience" than the industry standard, so that they can give each one more time and attention and learn about each clinic's operations intimately.

Mr. Menzo believes that thoroughly preparing and educating its reps is the key to differentiating Sun Ophthalmics in the current marketplace. "Within the ophthalmic marketplace today," he explains, "I see that reps have lost some passion and enthusiasm about catering to their customers." He wants to foster loyalty and motivation within the Sun Ophthalmics sales force that will translate to strong relationships with provider-clients. "I want it to be obvious to our customers that Sun Ophthalmics hires ethical, passionate, energetic people who love what they do and the company they work for, because it cares about them and invests in their training."

Mr. Menzo believes that his team's passion for addressing customers' needs is what sets Sun Ophthalmics apart from its competitors. "The partnership between eye care professionals and industry has become more distant in recent years. That is where we see an opportunity to re-energize the space. Our goal is to be seen as the preferred partner by the Ophthalmologists and Optometrists we serve."

PIPELINE

Sun Ophthalmics plans to launch two novel products in 2016, an ocular drop for managing glaucoma, and one for preventing inflammation after cataract surgery. Both represent new delivery options for currently available molecules.

The glaucoma product is called Xelpros (latanoprost BAK-free eye drops), which is a unique, preservative-free formulation of latanoprost in a multi-dose bottle. The second product is BromSite (0.075% bromfenac), which features the DuraSite delivery system.

SUN OPHTHALMICS' FORWARD VISION

Mr. Menzo's focus for Sun Ophthalmics in 2016 is to build a national footprint of sales reps. He has assigned key positions within its sales and marketing force in order to have a powerful network in place for the anticipated product launches later this year. With this goal framing its efforts, 2016 promises to be a busy and exciting year for the company. ●

Power Calculation: How to Up Your Game

Walter Bethke, Managing Editor

Surgeons discuss ways to take advantage of new IOL formulas or optimize the ones you already use.

In many aspects of life, there's a constant tension between the forces that push us toward the latest gadget or way of doing something and those that pull us back to the tried-and-true devices and methods we've come to trust. These forces are currently at work in the realm of intraocular lens calculation, with new fourth- and fifth-generation IOL formulas competing with the battle-tested third-generation formulas for surgeons' attention. In this article, IOL experts discuss the potential benefits and drawbacks of switching to one of the newer IOL formulas, and they also share tips for making the most of the formula you're currently using.

The Generation Gap

Some surgeons think their colleagues should begin to break away from using third-generation IOL formulas and move toward fourth- and fifth-generation ones. They argue that the newer formulas use more variables, or key variables that purport to get the elusive effective lens position, which impacts the final refraction so heavily. Here's a look at what some of these formulas might bring to the table.

• ***More measurements to use for calculation.*** The popular third-generation formulas, the Hoffer Q, Holladay I and the SRK/T use two input variables, keratometry and axial length, to try to predict effective lens position and, ultimately, the IOL power that should be used. The fourth- and fifth-generation formulas (the Holladay II, the Olsen formula and the Barrett Universal II formula) can use as many as seven variables (keratometry, axial length, anterior chamber depth, lens thickness, horizontal white-to-white measurement, age and preop refraction in the case of the Holladay II, for example). Some surgeons think more variables on the front end will mean fewer errors on the back end. "The older formulas were based on normal eyes," explains Rockville Centre, N.Y., surgeon Eric Donnenfeld. "They looked at eyes without evaluating the effective lens position, the anterior chamber depth and the white-to-white measurement, for instance. When a patient's eye was very short or very long, then, they got somewhat imprecise."

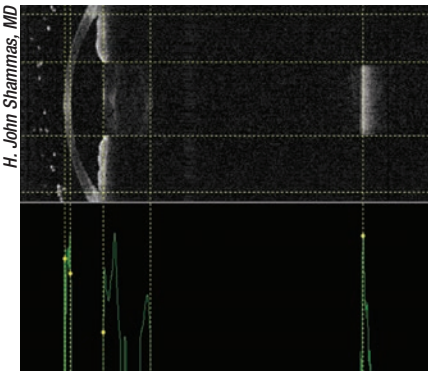
H. John Shammas, MD, clinical professor of ophthalmology at the University of Southern California Medical School, says that this is true, but surgeons got used to working with the third-generation formulas' idiosyncrasies and got good results. "For the past few years, the best formulas available have been the third-generation for-

mulas," he says. "Multiple articles have shown that, while the Holladay I works best for the average eye, the SRK/T works best for long eyes and the Hoffer Q works best for short eyes. After these three came out, Wolfgang Haigis, PhD, introduced the Haigis formula, which depends on axial length and the anterior chamber depth to determine where the implant sits. The Haigis is as good as the others in different categories of eyes, such as short, medium and long." Specifically, surgeons now know that the Holladay I trends toward better outcomes in eyes between 22 and 26 mm long, the SRK/T toward better results in eyes over 26 mm, and the Hoffer Q in eyes shorter than 22 mm.[1]

Even though the newer formulas use more variables, that doesn't necessarily mean they'll be clearly superior in all cases to the older ones, however. In a study of eyes longer than 26 mm in which the IOL was at least -6 D, the SRK/T, Hoffer Q, Haigis, Barrett Universal II, Holladay II and Olsen formulas all met the benchmark of at least 71 percent of eyes within ±0.5 D of the predicted refraction and 93 percent within ±1 D. In long eyes with an error of less than 6 D of myopia, the Barrett Universal II, Holladay I and Haigis formulas using an anterior-length adjustment met those criteria.[2] Also, in a small, retrospective study of eyes with small axial lengths, the researchers say none of the latest-generation formulas significantly outperformed the older ones.[3]

• ***More accurate ocular measurements.*** To get the most from many of the latest-generation formulas, you also need to have an optical biometer such as the IOLMaster 700 or the Lenstar. This is because two of the newer formulas, the Holladay II and the Olsen, require a measurement of the lens thickness that these types of cutting-edge machines can provide. Though this is a significant expense for the surgeon who is content using a combination of immersion ultrasound and keratometry, proponents of the new formulas point out that using optical biometry will bring better outcomes in the long run. "Since around the year 2000, optical biometry has been the standard of measurement for the eye," says Dr. Shammas. "So, if any surgeon is still using ultrasound to measure the eye, upgrading to optical biometry would improve his results tremendously. Optical biometry's accuracy is within 0.01 mm, while with immersion it's 0.1 mm, so it's 10 times more accurate."

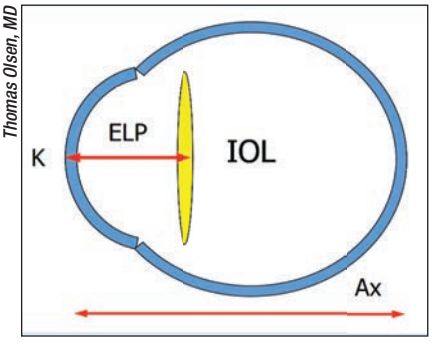
H. John Shammas, MD



New devices, such as the swept-source OCT Argos by Movu, may be able to help surgeons predict IOL powers better. From left to right, the vertical dotted lines indicate the anterior and posterior corneal surfaces, the anterior and posterior lens surfaces and the retinal surface.

• ***A better predictor of ELP?*** This possible benefit is still undefined because the jury is still out on whether formulas that require the measurement of lens thickness—primarily the latest Olsen formula and the Holladay II—are truly better at predicting where the IOL will finally sit in the eye (the knowledge of which allows you to choose the right power for it). Proponents say the measurement does make a difference, however.

Thomas Olsen, MD



Surgeons are trying to improve on the so-called thin-lens method of IOL calculation, which uses the K reading and axial length to try to predict the effective lens position.

In the new Olsen formula, which is available on the Lenstar device and through the website phacooptics.com, the ELP is predicted primarily through a concept called the C constant. "The holy grail of any IOL power calculation is the ability to predict the ELP," says the formula's inventor, Thomas Olsen, MD, of Aarhus, Denmark. "I've spent many years researching this, and I got the idea of the C constant because we can now get better measurements of the anterior segment, specifically the anterior chamber depth and the lens thickness by way of ray tracing. The latter will make a difference, in my opinion, because if you have accurate measurements of lens thickness together with anterior chamber depth, then you have a very accurate method of predicting the physical location of the IOL after surgery. This is what the C constant is about.

"In cataract surgery, you take out the crystalline lens and replace it with an artificial one," Dr. Olsen continues. "The artificial one will be in a certain location in the empty capsular bag. The C constant, then, is actually a fraction of the lens thickness by which the center of the IOL will locate itself postop. For instance, say the C constant is 0.5. In that case, the IOL will locate itself exactly in the center of the crystalline lens—or actually the middle of the empty capsular bag. So, if I take a measurement of the lens thickness and I have the anterior chamber depth, I can add half the lens thickness to the anterior chamber depth and that will tell me where the center of the IOL should be after cataract surgery." It might seem counter to the spirit of the new generation of formulas that the

new Olsen formula only uses a couple of variables—mainly anterior chamber depth and lens thickness—rather than seven, but Dr. Olsen argues it's not so much the number of your variables as having the right ones. "There have been a lot of multiple-variable formulas, and I have used them myself," he says. "I once thought, 'If I just put another variable in this formula, then I might get a better result. But it turned out to not be the case. Using the C constant gets down to the basics. The target of our surgery is the crystalline lens, and if we get the measurements right, we get the predictions right." In terms of results, Dr. Olsen says in his practice the formula is enabling him to get his mean absolute error of his lens predictions to an average of 0.3 ±0.4 D.

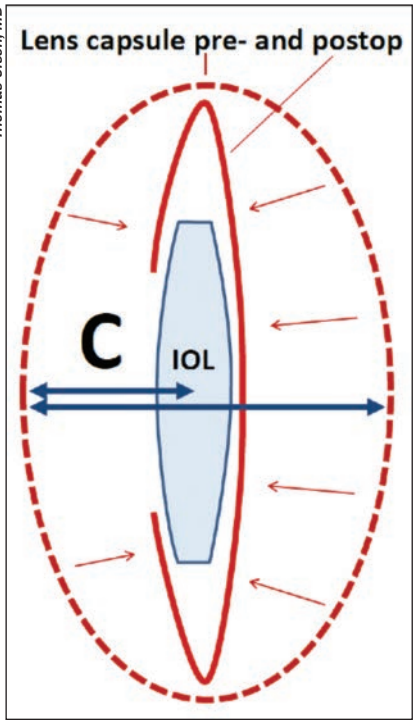
Use What You Have

For surgeons who aren't convinced they need to jump into the latest IOL formulas, and possibly have to make a new capital expenditure in the process, some experts say that, by optimizing the constants they use in their third-generation formulas, ophthalmologists can still get very good results.

• ***The Aristodemou method.*** Limassol, Cyprus, cataract and retinal surgeon Petros Aristodemou has published a method for optimizing third-generation formulas' constants.[1,4]

In Dr. Aristodemou's method, you track preop axial length, preop keratometry, the IOL model and power and the current IOL constant you use. Postop, you subtract the refraction from the predicted refraction to get each eye's prediction error. Then, when you've calculated the average prediction error for a sample of 100 eyes, you increase your IOL constant if the average prediction error is hyperopic and decrease it if the average error is myopic. The amount of increase or decrease is determined like this: For each 0.1 D of hyperopic error, for instance, you increase the Hoffer Q's personalized ACD constant by 0.06, the Holladay I's surgeon factor by 0.06 and the SRK/T's A constant by 0.12. An example given by the researchers uses an IOL with an average prediction error of +0.53 D achieved using a pACD of 4.97, a SF of 1.22 and an A constant of 118. To optimize the surgeons' constants in this case, the new pACD would be increased by 0.318 to 5.288, the SF would be increased by 0.318 to 1.538 and the A constant would be increased by 0.636 to 118.636.[1]

Thomas Olsen, MD



The Olsen formula uses ray tracing to get the preop lens thickness and anterior chamber depth to derive C, which can be thought of as a fraction of the preoperative lens thickness. This C constant is then used to determine where the IOL will come to rest in the eye.

• ***The grid method.*** Champaign, Ill., ophthalmologist Samir Sayegh says this method can be helpful if you've got enough surgical volume. "Create a 3 x 3 grid with axial length on one axis—with 'short, medium and long' as each column's label—and K reading on the other axis, with the labels 'flat, medium and steep,' " he explains. "This creates nine categories of eyes, one in each box of the grid. You can then optimize your constant 'locally' in each box. One problem, however, is that your number of cases is going to be divided by 9, and that's assuming an even distribution over the grid, which is not likely. Instead, you'll probably wind up having many eyes in the middle squares. However, at this point in their surgical careers, I believe many surgeons will have been using consistent techniques with their third-generation formulas and IOLs for a decade, so it's likely that they will have a sufficient number of patients for the extremes of the grid to do a local optimization in those boxes. This method is preferable to taking someone else's constant that was derived in another practice, using different devices from yours, with different methods of measuring values such as the K reading."

Tips for Special Cases

In addition to advice for normal cases, surgeons also have some insights on how to improve your IOL results with particular patient presentations.

• ***The post-refractive surgery patient.*** Li Wang, MD, PhD, associate professor of ophthalmology at the Baylor College of Medicine in Houston, has published on how to approach cataract patients who have had refractive surgery, and she helps update the American Society of Cataract and Refractive Surgery's online post-refractive IOL Calculator. "For the preop measurements of corneal curvature in post-refractive surgery eyes, we recommend doing as many scans as possible in the office with all the devices you have," she says. "Then, input the results into the ASCRS IOL Calculator. If you get different measurements, you can use the average. If there is an obvious outlier, ignore it."

Dr. Wang has recently begun studying a new method for predicting IOL powers in post-refractive eyes using

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optical coherence tomography with the Optovue's RTVue machine. The OCT formula uses net corneal power, posterior corneal power and central corneal thickness, and is showing some promise in initial studies.[5]

• ***Correcting for an error in the first eye.*** In some instances, your IOL calculation for a patient's first eye may turn out to be incorrect. Surgeons say there's an algorithm you can use to help get the second eye on-target.

Dr. Shammas says you can base your second-eye prediction on a fraction of the first eye's error, an approach that has been published in the literature.[6] "What we advise is to account for half the error that was produced in the first eye and correct for that in the second eye," he says. "So, if the first eye was off by 1 D, you'd correct for an additional 0.5 D in the second eye. This approach showed the best statistical results in a study. This approach makes sense because the error that occurred could be a combination of things, such as the measurements, the way the surgery was performed or even the movement of the implant to its final position. It's hard to tell exactly what causes an error. So, by accounting for half of it, it brings the error closer to zero."

• ***Use a variable toricity ratio with toric lenses.*** Dr. Sayegh, who has developed an IOL calculator of his own, thinks surgeons should be aware that using a fixed toricity ratio when implanting a toric lens can result in errors. "A fixed-toricity ratio has a similar effect on toric lenses as assuming a fixed effective lens position does on spherical lens calculations," he explains. "This has been described in the literature.[7,8] The toricity ratio is a conversion ratio from the astigmatism of the IOL to the astigmatism that will be corrected at the corneal plane, and the fixed toricity ratio that's used by Alcon's toric lens calculator and many others is roughly 1.5. This works fine for normal eyes, but if an eye is long and has a steep cornea the conversion ratio should be almost 2. So, for example, say you want to correct 1 D of corneal astigmatism in a very long eye. If you assume a fixed toricity ratio and use the 1.5 value, you would choose a 1.5 D toric lens, which, in a normal eye, would yield 1 D of treatment at the cornea. However, since this is a long eye and the factor is actually 2, you'd get only 0.75 D of correction, so the patient would have 0.25 D of residual astigmatism just from this alone. If you use a variable toricity ratio, you can avoid these astigmatic errors."

Data will continue to emerge on the new formulas, and the push-pull forces will continue to exert themselves on surgeons. In the meantime, surgeons will have to sift through the literature and their data to get the best results. "When you get good or bad results, it's hard to know exactly why," says Dr. Sayegh. "Was it because your K readings were off by 0.75, or were they perfect and it was your calculation that was off? It's a complex issue." REVIEW

Formulas on the Rise

In addition to the fourth- and fifth-generation formulas, there are other formulas emerging as well, which should be making their way into general use this year.

• ***Hoffer H-5.*** Developed by Santa Monica surgeon Kenneth J. Hoffer, the H-5 uses gender and race to change the average mean values in the Holladay-II and Hoffer Q formulas. By using gender and race to alter the predicted IOL power, the formula may be more customizable for a particular patient. The H-5 is licensed to the IOLMaster 700.

• ***Radial basis function formula.*** Mesa, Ariz., lens calculation expert Warren Hill, MD, developed this mathematical approach with the assistance of engineers. In discussing the formula, Dr. Hill has commented that going outside the world of ophthalmology let them approach intraocular lens power selection in a different way that didn't rely on traditional vergence formulas or estimation of the effective lens position. The RBF method will be added to the Lenstar, and will also be available as a web-based calculator. More information about the formula can be found at rbfcalculator.com. *(Both Dr. Hoffer's and Dr. Hill's formulas were highlighted in the February 2016 installment of Technology Update.)*

• ***The Ladas Super Formula.*** Designed by Silver Spring, Md., surgeon John Ladas and Los Angeles surgeon Uday Devgan, the Super Formula makes a 3-D computer model based on five popular IOL formulas: the Hoffer Q; Holladay I; Holladay I with Koch adjustment; Haigis and SRK/T. It then uses the model and the formulas to help pick the ideal lens.[1] *(For an in-depth look at the Super Formula, see* Review*'s January 2016 cover story.)*

— W.B.

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Dr. Donnenfeld is a consultant to Zeiss and Dr. Olsen is a consultant to Haag-Streit. Dr. Shammas's post-refractive IOL formulas are licensed to most biometry units. Drs. Sayegh and Wang have no financial interest in the products mentioned.

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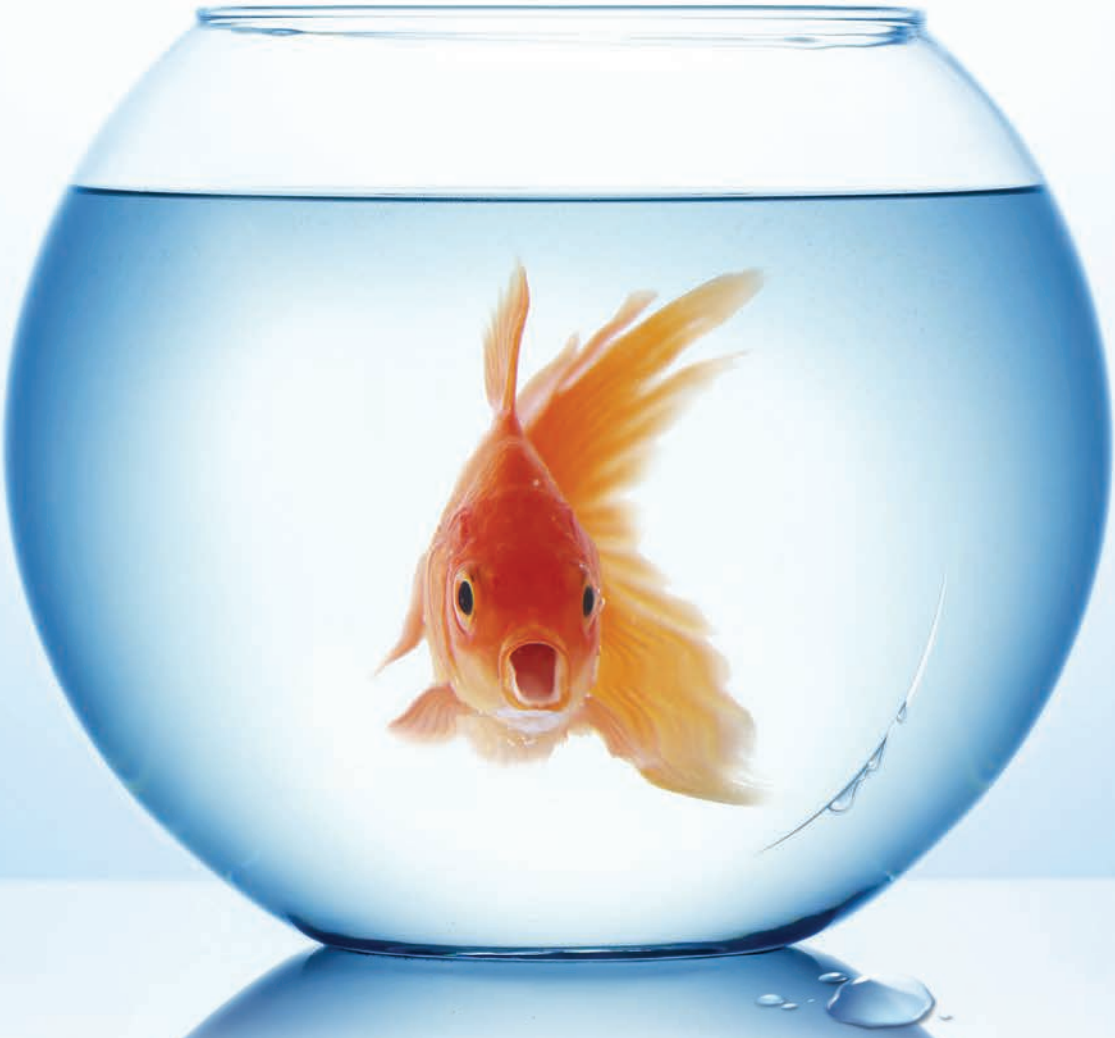

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Cataract Surgeons Wait On New Technology

Walter Bethke, Managing Editor

After the predictable rush of early adopters, surgeons are taking their time with new tech.

As many of us have heard before, whenever a new technology arrives, there will be an initial wave of early adopters who jump right on it, bugs or complications notwithstanding. Following that furious start comes a longer period of deliberation by the rest of the group, as individuals decide whether or not this new device will truly make a difference for them. Judging by the recent responses to our annual e-mail survey on cataract surgery, it appears ophthalmic technologies such as femto cataract and intraoperative aberrometry might be in the second phase, with many surgeons sitting on the fence, weighing their options.

Surgeons' views on new technology are just one aspect of the survey, and respondents also shared their opinions on cataract surgical techniques, as well. This month's e-mail survey was opened by 902 of the 8,500 subscribers to *Review*'s e-mail service (an open rate of 11 percent) and, of those, 91 completed the survey. See how your go-to cataract techniques and maneuvers compare with theirs.

Going Easy on Innovation

The survey touched on several new modalities in the cataract realm, including femto cataract and intraoperative pupil dilation injection (Omidria). Though it's only been a year since surgeons weighed in on a couple of these innovations, their enthusiasm for them seems to have leveled off a bit.

• ***Femtosecond cataract.*** In last year's cataract surgery survey, 31 percent of surgeons said they used the femtosecond laser for at least one aspect of cataract surgery. This year, that number has held steady at 32 percent. The most popular use for the femtosecond during cataract was in correcting astigmatism, chosen by all of the femto-cataract surgeons. Next came the creation of the capsulotomy and nucleus fragmentation, chosen by 97 percent each. Fifty-seven percent also use the laser for the entry wound and 43 percent for the paracentesis. "Despite being very proud of my nearly perfect capsulorhexes done with the Utrata forceps by hand, no human alive can reproduce the precision and accuracy of placement and reproducibility of the femto!" enthuses Robert P. Lehmann, MD, of Nacogdoches, Texas. "That it adds perhaps one or maybe two minutes to my overall case and its increased cost are the only downsides. Fact is, many patients are still not willing or able to afford it." Richard D. Ten Hulzen, MD, of Jacksonville Beach, Fla., says though he appreciates what the femto brings to

his practice, there are downsides, too. "The pros are the precision—the laser being more precise than manual—and the higher reimbursement potential," he says. "The cons are the expense, the extra chair time for the surgeon and staff due to the counseling required, the multiple options that tend to put stress on patients when they're trying to make a decision, the extra procedure time and the fact that the surgical outcomes are the same as conventional cataract surgery, as per the studies and my own experience."

A surgeon from Nevada says the femto offers a "consistent rhexis, and it can correct small amounts of astigmatism for patients getting multifocal IOLs." He adds, however, that it's "expensive, adds additional time to the case, and the cortex is more difficult to remove." A Texas surgeon thinks the positives outweigh the negatives, however. "It adds time, but it seems to give better results." And an ophthalmologist from Maryland has also had a good experience with the technology. "It's gentler and more accurate," he says. "It also allows flexibility when customizing it, and is safer in some situations."

Looking down the road a bit, three-quarters of the respondents who don't use the femtosecond in cataract surgery say they're unlikely to start using it within a year. A lot of their reservations about the lasers center on the perceived cost/benefit ratio.

"It involves an unnecessary increase in the cost of the procedure compared to standard phaco," says Peter Libre, MD, of Norwalk, Conn. "Yet, I perceive no net improvement in the quality of the procedure." A surgeon from California feels similarly, and is also concerned about having to relearn something that she already does well. "Femtosecond cataract seems as if it's too costly for such minor advantages," she says. "Also, I don't want to go through a difficult learning curve when I'm already happy with my current procedure."

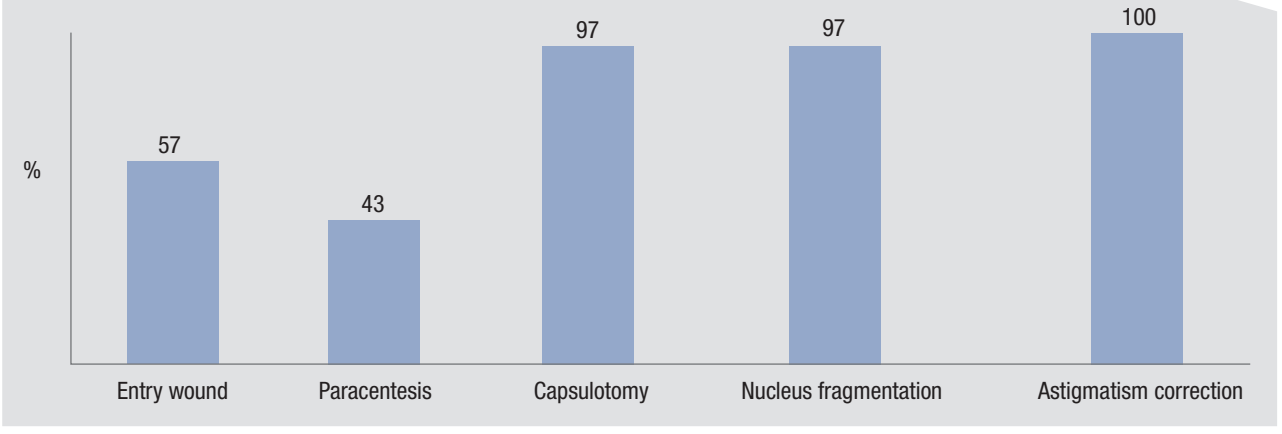
One physician is among the quarter of respondents who are looking forward to using the femtosecond. "It's an excellent technology for astigmatism and capsulorhexis," he says. Richard Wieder, MD, of St. Louis says it's only a matter of time before he takes the plunge. "I have not used femtosecond laser yet," he says, "but I'm planning to later this year."

• ***Intraoperative aberrometry.*** Even fewer of the survey respondents (15 percent) use this technology than use femtosecond cataract devices. Sixty-eight percent of the surgeons who don't use it say they're not likely to do so in the coming year. Cost and added surgical time are often cited as the main roadblocks. "The advantage is that it provides an intraoperative estimation of the IOL power and astigmatism axis," says Robert Bullington Jr., MD, of Phoenix. "The disadvantages are that it adds time and expense and doesn't give a definitive answer." A Texas physician agrees about the pros and cons involved with using the technology. "It helps with the confirmation of difficult IOL calculations," he says. "However, you can't always trust the cylinder adjustment assessments. It also takes time, sometimes requiring multiple attempts at capture."

Some surgeons, however, think it's been a good addition to their practices. "Poor patient fixation can be an issue," avers a surgeon from Florida. "However, it's very helpful with toric IOLs, post-refractive surgery patients, high hyperopes and high myopes."

• ***Pupil dilation strategies.*** Surgeons say a well-dilated pupil is one of the keys to smooth surgeries and good outcomes, and many are interested to see where the new intraoperative agent from Omeros, Omidria (an injection of phenylephrine and ketorolac), might fit in their practices. On the survey, half of the surgeons use an intracameral injection of a mixture of BSS, epinephrine and lidocaine (the so-called "epi-Shugarcaine" first proposed by the late surgeon Joel Shugar); 17 percent don't take any extra steps to promote a wide pupil, 12 percent use Omidria and 23 percent say they use some other meth-

Surgeons' Use of Femtosecond for Cataract Surgery



od to ensure dilation, such as iris hooks or Malyugin rings. "Shugarcaine is adequate for most patients," says Glenn Sanford, MD, of Washington, Mo. "I manage floppy irises with the Malyugin ring." Luther Fry, MD, of Garden City, Kan., has begun using Omidria, and likes his results. "Omidria works well in preventing intraoperative miosis—it has markedly reduced my use of the Malyugin ring," he says. "I don't use it for adequate pupils, though."

• ***Postop inflammation/infection management.*** Surgeons also weighed in on the new approach to postop management that involves replacing a postop drop regimen with a single postop injection of a combined antibiotic/steroid, such as the TriMoxi-Vanc combination sold by Imprimis. Though some surgeons see the benefit of this, drops still rule the survey, with 92 percent of surgeons choosing them over the injection. Six percent of surgeons administer the injection and the rest use another method. "I gave the intravitreal 0.2 cc of TriMoxiVanc a trial in over 140 cases and stopped," recounts Dr. Lehmann. "Now, I will go with either prescription drops or the compounded triple drops. The rising cost of prescriptions is making it hard for many patients—but I won't get into a discussion of politics right now." Another surgeon from Texas is sticking with the injections. "The savings are huge with TriMoxi injection, both for the system and for the patient," he says. "The acceptance by the patient is easy. The biggest hurdle to adoption is surgeons' fear of the unfamiliar."

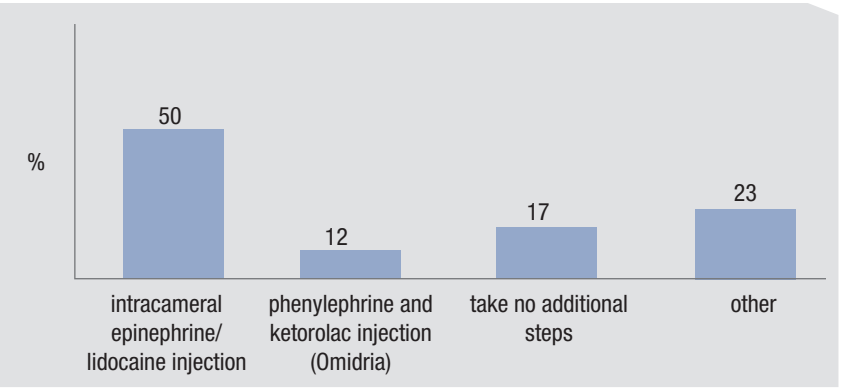
Managing Astigmatism

When surgeons approach a patient's pre-existing astigmatism, the toric IOL remains the single most popular option, chosen by 48 percent of the respondents. The next most popular choice is to combine the toric lens with the placement of the entry wound on the astigmatic axis (16 percent), followed by the toric lens combined with AK incisions (10 percent). The rest of the surgeons' options appear on the graph on p. 40.

"In my hands [toric IOLs] have provided the best and most predictable patient outcomes," says Dr. Sanford. "I gather greater than 90 percent of my one-month refractions and continue to optimize my surgeon constant, and have found that my corneal incision induces less than 0.1 D of corneal change." Charles Colombo, MD, of Rochester Hills, Mich., agrees, saying, "Toric IOLs give effective results." A surgeon from Texas says his choice is often based on the amount of astigmatism to be corrected. "Toric IOLs are the most consistent method for moderate to high cylinder," he says. "LRIs are the most consistent for low cylinder." Robert Pode, DO, of Peru, Ill., is among the surgeons who prefer to combine the toric lens with an on-axis entry wound. "I don't like the irregular topography induced by AK and limbal relaxing incisions," he says. A surgeon from North Carolina says the lens/on-axis incision approach gives the "most predictable and reliable result."

Dr. Lehmann chooses to combine the toric lens with AK incisions, but says he's flexible based on the patient presentation. "I implant a huge percentage of toric IOLs," he says. "Yet, I also use femto corneal relaxing incisions. For the non-premium patients I will do limbal relaxing incisions with a blade at no additional cost. It's always best to put the patient's outcome over all else."

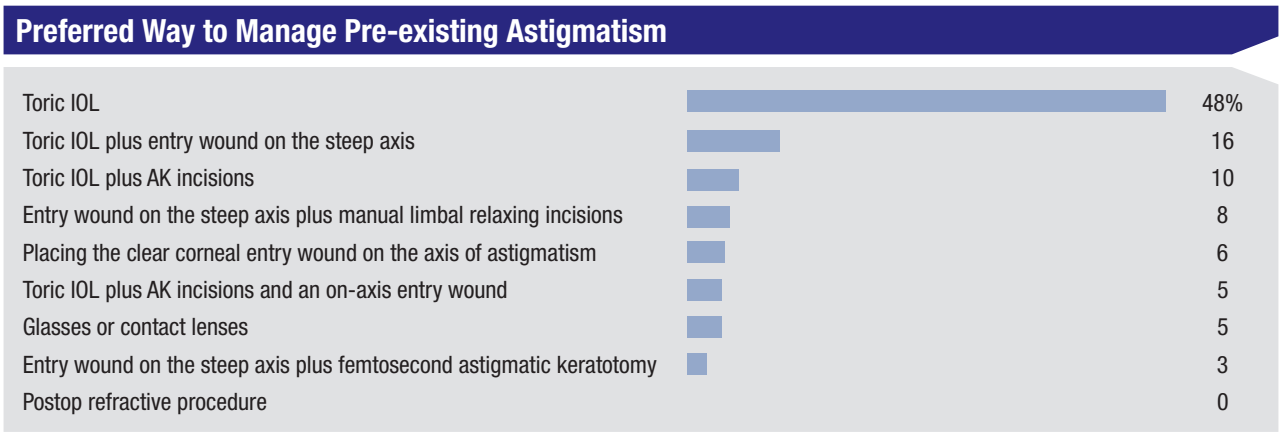
Preferred Way to Promote Pupil Dilation Intraop



Phaco Techniques

Attacking the nucleus is where the rubber meets the road in the cataract procedure, and 52 percent of surgeons surveyed say they prefer to use a quadrant-division approach. Following quadrant division, 16 percent prefer stop-and-chop, and 15 percent prefer a phaco-chop technique. Phaco flip/tilt, sculpting and dividing the nucleus in two were each chosen by less than 10 percent of the respondents.

Florida's Dr. Ten Hulzen is in the quadrant-division camp. "I'm a comprehensive ophthalmologist and glaucoma subspecialist," he says. "I have a lot of patients with pseudoexfoliation, dense cataracts, poorly dilating pupils/IFIS, retinal pathology from AMD and/or diabetes. Maintaining posterior capsular integrity is paramount in these patients as well as in the premium (toric and multifocal) IOL patients. Therefore, I minimize any stress on the capsular bag and zonules. I groove and use a nucleus splitter to achieve a clean split while maintaining equal-and-opposite forces within the capsular bag." A surgeon from New York also says he likes quadrant division because it keeps him in control. "It



gives me full control of the procedure," he says. "There's no blind instrument passing."

Jeffrey Lander, MD, of York, Pa., prefers stop-and-chop. "It's safe and controlled," he says. "Much of the phaco is done away from cornea." Robert B. Taylor III, MD, of Las Vegas agrees, saying, "It's simple, efficient and works in most types of lens densities."

A surgeon from Florida, however, says phaco chop is preferable to the other methods. "It's safer and uses less energy," he says. "It also offers faster postop recovery." Phoenix's Dr. Bullington also prefers it. "In my hands," he says, "it's the most efficient technique for emulsifying the lens with minimal phaco time."

Surgical Pearls

With many decades of combined experience under their belts, the survey's respondents were happy to share their best surgical pearls.

In terms of discrete techniques, several surgeons offer ideas. Carol Johnston, MD, of Jacksonville, N.C., says, "Preop pledgets and the use of bridal sutures in eyes with difficult exposure are helpful." Dr. Pode advises: "If you think you may need a Malyugin Ring for a difficult case, always put it in. You'll never be upset that you used the device. It'll make your surgery easier, quicker and safer." A surgeon from Texas says to sweat the small stuff. "Each step builds on the one before it," he says. "So even things like positioning the patient are of utmost importance." Dr. Wieder focuses on astigmatism with his advice. "Utilize multiple different testing modalities to manage preoperative astigmatism," he says. "This will provide the most predictable results postop."

Dr. Ten Hulzen shares his own medical regimen: "My number-one surgical pearl is called the Beaches Eye Slurry," he says. "It was born out of frustration with other slurries I've tried online. Most slurries add too many different drops, which ends up diluting all the active ingredients to sub-therapeutic—and sub-optimal—levels, or they require supplemental drops before or after slurry instillation to achieve the desired effect. My patients get topical antibiotic, NSAID and steroid drops for four days prior to surgery, so there's really no need to add those drugs to the preop slurry, in my opinion. The slurry is also a cost-saving measure for any ASC or hospital outpatient department (e.g., phenylephrine is over $100 per bottle), and the preop nurses love the simplified regimen and documentation: For example, it's 0.1 to 0.2 ml aliquots from the 1 ml TB syringe for each dose. As long as the slurry is instilled about an hour before surgery, the pupils are maximally dilated and anesthetized and, for cataract surgery, the larger the pupil, the easier the cataract surgery is to perform. It also uses less time and materials."

Several surgeons emphasized the importance of getting things done correctly rather than getting things done quickly. "Don't hurry," says a surgeon who preferred to remain anonymous. "Take the time to prevent complications." Dr. Colombo feels similarly. The clock stops in the OR," he says. "Work carefully and never rush—no wasted steps. Keep calm."A surgeon from Massachusetts highlights the importance of preop checks. "Just as there is an in-the-room pre-surgical checklist with lens verification and a time-out, a preop checklist for every patient is useful," he says. "Make a list of the things that you want to know before surgery and look out for any outliers and plan ahead. For example, you'll obviously note things like pseudoexfoliation or poor dilation, but note also the white-to-white distance and AC depth. If there are asymmetries, they can direct you toward other steps that can be taken to prevent complications. There are times I have said I wish I had used Trypan Blue or iris hooks, but there's never been a time when I used them and wished I hadn't."

Finally, a surgeon from Texas says that, above all else, make sure you keep your surgical options open. "Always have a plan B available for your technique," he says. "Be flexible about approaching each case differently. If all you have is a hammer, everything looks like a nail." REVIEW

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New Alternatives in Post-Cataract Pharmacology

Michelle Stephenson, Contributing Editor

Some surgeons have given up drops completely, while others are injecting antibiotics and using topical anti-inflammatories.

Cataract surgeons agree that postoperative eye drops are not ideal for many reasons, including lack of compliance; low bioavailability; potential toxicity; and expense. So, many surgeons are exploring new ways to deliver postop medications. Some are choosing to use fewer drops, while others are choosing to forego topical medications altogether and inject medications instead.

"When it comes to infection prophylaxis, there isn't evidence that topical agents are effective," says Samuel Masket, MD, who is in private practice at Advanced Vision Care Los Angeles and a clinical professor of ophthalmology at the Jules Stein Eye Institute, UCLA. "Moreover, patients often instill drops incorrectly. And, with medications that need to be used as frequently as four times a day, compliance drops off. Also, some patients are sensitive to the preservatives, particularly if they have been on medication a long time. Some patients develop punctate keratopathy, which impacts negatively on comfort and vision. I think all of us realize that there are problems with drops. Another frequent annoyance occurs at the pharmacy if branded meds are switched by the pharmacist for a generic eye drop or if the patient's insurance doesn't cover a given medication. This alone is a thorn in our sides and reason enough to move away from eye drops."

One option is to inject the medications instead of instilling them topically. "Injecting drugs ensures delivery of the medicine, and it's a great convenience to the patient," says Neal Shorstein, MD, an ophthalmologist and associate chief of quality at Kaiser Permanente in Walnut Creek, Calif. "In a recent study, when elderly patients were videoed trying to put in the drops, there was a high incidence of failure to instill the drops correctly and with good hand hygiene, and I worry about that."

The Canadian study found that cataract patients who were inexperienced with eye-drop use demonstrated poor instillation technique by failing to wash their hands; contaminating bottle tips; missing their eye; and using an incorrect amount of drops.[1] The study included 54 patients. Subjectively, 31 percent reported difficulty instilling the eye drops, 42 percent believed that they never missed their eye when instilling drops, and 58.3 percent believed that they never touched their eye with the bottle tip. Objectively, 92.6 percent of patients demonstrated improper administration technique,

including missing the eye (31.5 percent), instilling an incorrect amount of drops (64 percent), contaminating the bottle tip (57.4 percent), or failing to wash hands before drop instillation (78 percent).

Injections

Additionally, a growing body of evidence is showing that intraocular administration of antibiotics is safe and effective for infection prophylaxis.

In 2008, Dr. Masket co-authored a study that found no increased safety risk associated with intracameral injection of moxifloxacin compared with balanced salt solution.[2] In this prospective, randomized, open-label study, 57 eyes of 47 patients were treated with intracameral moxifloxacin or an equal amount of balanced salt solution after cataract surgery. Visual acuity, intraocular pressure, endothelial cell counts, corneal pachymetry, corneal clarity and edema, and anterior chamber cells and flare were evaluated preoperatively and for three months postoperatively. At both time points, optical coherence tomography results showed no statistically significant differences between the two treatment groups.

"Since that investigation, I've used 0.05 mL nondiluted Vigamox right out of the bottle in every cataract case, and I have not noted any toxicity," says Dr. Masket. "That study did not address efficacy owing to the larger number of necessary cases, but we found that intracameral Vigamox was not toxic when masked against BSS with regard to corneal edema, endothelial cell counts, anterior chamber inflammation and macular edema."

Dr. Shorstein and colleagues at Kaiser Permanente in California found that intraocular administration of antibiotic is more effective for preventing postoperative endophthalmitis than topical antibiotic.[3] In their study, they identified 315,246 eligible cataract procedures performed at Kaiser between 2005 and 2012 and confirmed 215 cases of endophthalmitis (0.07 percent). The researchers found that intracameral antibiotic was more effective than topical antibiotic alone for preventing endophthalmitis; and they found that combining topical gatifloxacin or ofloxacin with an intracameral agent was not more effective than using an intracameral agent alone.


istock

"The problem as I see it, however, is that presently we don't have an appropriate delivery system to include anti-inflammatory as well as anti-infective prophylaxis," Dr. Masket says. "The injection of a long-acting intraocular steroid may induce elevated intraocular pressure. I look forward to the day when we have delivery systems that can emit low-dose medication over a long period of time to manage the anti-inflammatory component of postoperative treatment. I believe that it needs to take the form of both a steroid and a nonsteroidal agent because there is strong evidence that NSAIDs are more effective at preventing cystoid macular edema than are steroids."

Currently, Dr. Masket uses 0.05 mL of Vigamox intracamerally in every eye, and he continues to use topical agents as well. "I am very much in favor of the concept of moving away from drops, but I am awaiting newer delivery methods. In the near future, our office will be participating in an investigation of a combination of injected dexamethasone and moxifloxacin at the time of surgery, combined with a topical NSAID postoperatively," he says.

Other surgeons are comfortable injecting both anti-inflammatory and anti-infective agents postoperatively. Dr. Shorstein began injecting antibiotics in 2008. "Once we had set up onsite compounding with our integrated pharmacy at our surgery center and felt comfortable inject-

ing it, we then took the next step of stopping perioperative antibiotic drops because we felt that there really wasn't any strong evidence in the literature that they reduce the rate of endophthalmitis," he says. "Given the strong evidence for intracameral antibiotics, we didn't feel that topical drops added any substantial benefit to intracameral antibiotic injection. After all, we are injecting right into the space where one would want to have the antibiotic. In the latter half of 2008, we began to think about an alternative delivery of corticosteroid to prevent postoperative macular edema. There were a couple of articles in the literature showing the effectiveness of injected triamcinolone subconjunctivally, and we started doing that in late 2008."

A few months ago, Dr. Shorstein published a study that examined the relationship between chemoprophylaxis and the occurrence of acute, clinical, postoperative macular edema.[4] The study included 16,070 cataract patients who underwent phacoemulsification at Kaiser Permanente between 2007 and 2013. There were 118 confirmed cases of macular edema. The study found that adding a prophylactic nonsteroidal anti-inflammatory drug to a postoperative topical prednisolone acetate treatment was associated with a reduced risk of macular edema with visual acuity of 20/40 or worse. The risk and safety of triamcinolone injection were similar to those of topical prednisolone acetate alone.

"An interesting and somewhat surprising finding was that the patients who were treated with a topical NSAID in addition to topical prednisolone had half the rate of macular edema," says Dr. Shorstein. "We looked at over 16,000 eyes, so this is one of the very few large studies that has shown a statistical difference in the reduction of macular edema with an NSAID. Those of us who were injecting the triamcinolone began asking if we should be adding NSAID drops routinely for patients who undergo phacoemulsification. Interestingly, only 0.73 percent of our group's phacoemulsification eyes were diagnosed with clinically relevant, OCT-validated macular edema. That's a small percentage. We felt that, given the overall low incidence of macular edema and given that it's a fairly benign complication of phacoemulsification cataract surgery, we didn't see a compelling reason to alter our dropless, intracameral antibiotic injection practice."

He adds that, if dropless administration is equally effective and sufficient, surgeons may be doing patients a favor by reducing the risk of endophthalmitis by limiting the manipulation of the eye after surgery. "It is a few dollars per eye to compound the intracameral antibiotic. The pharmacy prices for late-generation fluoroquinolone drops could run

A Different Take on Going Dropless

Omidria (phenylephrine and ketorolac injection 1%/0.3%) can be added to irrigation solution preoperatively and is the only Food and Drug Administration-approved product for intraocular administration that prevents intraoperative miosis and reduces postoperative pain. In a recently published study, it was found to maintain mydriasis, prevent miosis and reduce early postoperative pain when administered in irrigation solution during intraocular lens replacement, with a safety profile similar to that of placebo.[1]

According to Robert Weinstock, MD, many of the challenges that surgeons face during cataract surgery are related to intraoperative pupil size and maintaining good visualization during surgery, and inflammation after surgery. "Omidria is a combination of a dilating agent and a nonsteroidal and has a dual mechanism of limiting inflammation and maintaining dilation of the eye," says Dr. Weinstock, who is in practice at the Eye Institute of West Florida in Largo. "It allows the surgery to go more smoothly because the pupil stays larger during the case. This is extremely important in patients who have had previous laser peripheral iridotomies and glaucoma and in patients who are taking alpha-2 antagonist medications for urologic or cardiovascular conditions, because these are the patients who develop floppy iris syndrome intraoperatively."

Johnny Gayton, MD, of Eyesight Associates in Warner Robins, Ga., says, "Omidria is a novel way of delivering a nonsteroidal. No other product, compounded or commercial, offers an intraocular nonsteroidal. The nonsteroidal, in combination with phenylephrine, a very potent dilator, helps us a great deal in maintaining the pupil during cataract surgery. It is well-known that if the pupil drops below 6 mm during cataract surgery, visualization decreases, your surgical time increases and your complication rate increases."

He notes that Omidria is also beneficial in femtosecond laser cases. "This product offers us an incredible tool to help us maintain patients' pupils with both traditional and femtosecond-assisted surgery and to help control patients' discomfort during and after the procedure," Dr. Gayton says.

Omidria was approved by the FDA in 2014. Dr. Weinstock says that he is only using Omidria in select patients currently, because it is not covered by all insurance companies. "The number of patients in my practice who are receiving Omidria is growing because insurance coverage is just getting ramped up," he says. "As more insurance plans are starting to cover this, we will expand our usage. I will consider using it in all patients who have insurance coverage, because you never know who is going to have floppy iris syndrome. I'm in favor of anything we can do safely to help that pupil stay dilated."

—M.S.

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several hundred dollars a bottle," Dr. Shorstein says.

Currently, for those surgeons who opt to go "dropless" but prefer not to compound their own injections, Imprimis markets TriMoxi, which is a mixture of moxifloxacin and triamcinolone, and TriMoxiVanc, which adds vancomycin. "The mixture is intended to be injected into the vitreous via a transzonular cannula. Downsides include reduced vision in the early postop period from the triamcinolone suspension, potential damage to the zonule and absence of an NSAID," Dr. Masket says. "I'm genuinely looking forward to improved delivery systems, and there is much investigation regarding nanotechnology delivery of medications."

"Less Drops"

However, some surgeons are reluctant to give up drops completely. "Dropless injectable antibiotic/steroid combinations are a great idea, attain good results and may be especially useful in non-compliant, physically challenged and/or indigent patient populations. However, there are four difficulties with this approach," says Lance Ferguson, MD, who is in private practice in Lexington, Ky.

Dr. Ferguson cites the challenges and the drawbacks to injection:

- *Technique.* "Although there is a short learning curve, the surgeon must be able to get an adequate dosage into the vitreous cavity via a transzonular approach or be comfortable with pars plana injections," he says.
- *Floaters.* With refractive cataract surgery, the immediate "wow" factor has become increasingly more important to patients and as a practice builder through word of mouth and social media, and the prednisolone stranding is bothersome to many patients. "Good preoperative counseling, controlling expectations, and patient selection will help, but when patients are still struggling in the first week and their drop-using friends extol their immediate great vision, patients sometimes forget this preoperative session. Moreover, that session takes time and staff hours," he adds.
- *Edema.* "Even with great delivery, an occasional patient will need supplemental steroid/NSAID drops, and this again can be addressed preoperatively. However, the reality of expensive drops in addition to the injection (that they paid for) will be a sore spot for many patients, and they will wonder why they elected for the dropless approach when they ultimately need and pay for 'additional' drops. Again, this is a time sink for staffers and makes these patients less than enthusiastic ambassadors for the dropless approach," he explains.
- *Depot medicine.* "Once onboard, the steroid cannot be withdrawn, which presents patient safety and medicolegal issues, particularly if the patient is far away from the practice and has difficulty visiting even a comanaging optometrist/ophthalmologist. If the patient is a steroid responder, then many additional visits, meds, expense, and family inconvenience will be required for IOP control. With drops, the medication is simply discontinued, and the problem resolves," he says.

Dr. Ferguson's practice uses the "less drops" approach espoused by Imprimis. They compound antibiotic/steroid drops or antibiotic/steroid/NSAID drops and find them particularly appealing to a wide range of patients. "Less drops patients enjoy the convenience and cost savings (we mark up the cost of these meds only about 5 percent) of obtaining their drops at the practice site, precluding pharmacy stops, hassles and insurance issues," he explains.

Additionally, Dr. Ferguson says that there is a simpler schedule and ease of administration, adding up to improved patient compliance—only one bottle, four times a day, with a scheduled taper, and there is safety in the event of an untoward reaction to any of the components.

Also, there is no potential for disappointment, because patients understand from the start that they will need to use the drops for three to four weeks postoperatively.

"Practices who use the 'less drops' approach enjoy markedly less counseling, paperwork permits and staff time consumed with dealing with pharmacies, unavailable meds and generic-only substitutes, etc," Dr. Ferguson believes. "And they have happy patients who share their positive (and simpler) experience with others."

Additionally, according to Dr. Ferguson, there is less medicolegal risk in the event of a steroid responder or possibly a patient with a retinal complication (which, although unrelated to the injection/pars plana injection, may, in the patient's mind, be forever related).

"The 'less drops' program has really helped us," he says. "It is much less expensive for patients, and it is much simpler for them from a compliance standpoint. I'm very happy with this new compounding. And let me reiterate, because it provides the option of discontinuing or altering components, it avoids the risks of depot medicine. I don't take boats into harbors that I can't get them out of." REVIEW

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Technology Making Patient Care Personal

Jan Beiting, Contributing Editor

The 'Internet of Things' has the potential to increase access to ophthalmic care, while at the same time making it more personalized and cost-effective.

The Internet of Things is the network of interconnected objects embedded with software or electronics that allow them to collect and exchange data. The IoT ranges from the simple (your washing machine telling your dryer what cycle to run) to the sophisticated (regional electricity smart grids).

And it's beginning to revolutionize health care. In 2015, approximately 5 million people were already using connected mobile health (mHealth) devices to help their doctors monitor their cardiac rhythms, blood glucose or other metrics, and that is expected to rise to 15 million by 2018 and to 36 million by 2020.[1]

Much of that growth will likely come from smartphone-enabled home medical monitoring. With widespread access to cellular networks and high-speed image and data processing capabilities, today's smartphones are orders of magnitude faster than many of the medical diagnostic devices used in the 1990s. And cell phone use is becoming nearly ubiquitous, even among older adults. Americans now spend an average of 5.6 hours daily using some form of digital media, more than half of it on a smartphone or tablet *(See Figure 1)*.[2]

"At the same time as this boom in smartphone usage, we were facing huge changes in vitreoretinal care, with more patients requiring frequent injections for the treatment of macular degeneration and other diseases," says Mark S. Blumenkranz, MD, a retinal specialist, professor and former chair of ophthalmology at the Byers Eye Institute at Stanford University School of Medicine. "I was looking at my iPhone one day and thought how great it would be if there was a phone-based eye test so I could track how my patients were doing between visits." That was the genesis of the idea for an app that he and Stanford colleague Daniel Palanker, PhD, would develop over the next several years, eventually cofounding DigiSight Technologies.

Monitoring Acuity and More

The visual acuity test, which is now available for a variety of iOS and Android devices, is simple to perform. Holding the phone at approximately 14 inches, the patient chooses the letter he or she sees from among six options or selects "Not Sure" *(See Figure 2)*. Letters corresponding to 20/70 vision are presented initially; they get smaller or larger with right or wrong answers. Visual acuity is determined by two correct responses followed by two incorrect responses at the next-smaller letter size.

To ensure that the test was well-correlated to in-office vision testing, the developers spent a lot of time making sure the on-screen letters accurately corresponded to lines of Snellen acuity. "We also had to adjust for the higher contrast of a screen compared to a standard eye chart," says Dr. Blumenkranz. Extensive testing revealed that it didn't matter very much whether the person tended to hold the device at 12 or 14 or 16 inches. "As long as they hold it the same way every time—and our data suggest that people naturally do this—the reproducibility is very high," Dr. Blumenkranz says.

The test has been clinically validated[3] and was recently listed with the Food and Drug Administration as part of a suite of tests called Paxos Checkup.

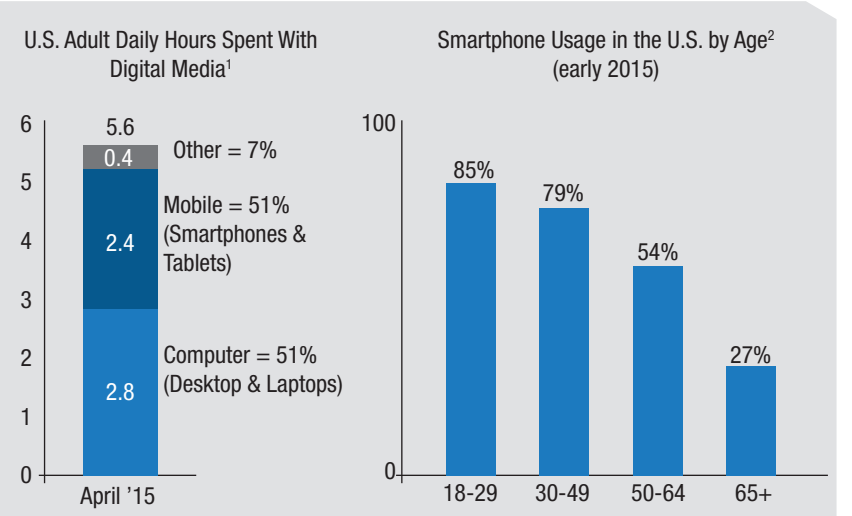
The other tests that patients can take from the Paxos Checkup app include contrast sensitivity and contrast acuity, inverse acuity, low-illumination contrast acuity, Amsler grid and a proprietary grid test (DigiGrid) and color discrimination. Patients can take one or more tests daily, weekly or as directed by their physician, with whom they must register prior to using the app. Test results are transmitted and stored in compliance with HIPAA privacy and security guidelines for protected health information. The physician's office receives alerts when patients hit triggers set by physicians, such as losing two or more lines of vision, but doctors can also review all the test results for an individual patient plotted in a graph.

"It completely changes what I look at," says Dr. Blumenkranz, who uses the app for home monitoring of his patients with age-related macular degeneration. "Instead of trying to make a decision from two data points—the visual acuity at the last two exams—I see a curve. The more often they test, the smoother the curve. At a glance, I can tell if the patient's vision over the past month has been stable, trending up or down or fluctuating. It makes it much easier to pick up on subtle changes."

The goal, he says, is to intervene before the patient's vision "falls off the cliff." He also believes having this kind of data can serve as a valuable safety net for patients, because it helps him identify which patients need to come in sooner than planned for their next injection.

"Patients love it," Dr. Blumenkranz says. "It gives them something they can proactively do towards managing their disease, over which they otherwise have no control. I think it really reinforces the doctor-patient relationship."

Increasing Hours Spent on Digital Media



Adapted from: 1. Allen R, Smart Insights. 2. Goldman Sachs. "The digital revolution comes to US healthcare" Internet of Things. Vol. 5. June 29, 2015.

Figure 1. Smartphones make up a significant portion of adults' daily digital media use in the United States. Smartphone usage is growing across all age groups.

Mobile Imaging

Beyond at-home monitoring, the mobile diagnostics suite also includes Paxos Scope, a smartphone hardware add-on and app that together allow users to create and securely transmit

Figure 2. The most popular test within Paxos Checkup is the visual acuity test. Pictured here, it is simple and intuitive, even for patients who are illiterate or have limited English proficiency. Patients need only match the letter in the white box to one of the letters below or select "Not Sure."

anterior and posterior segment images. The Paxos Scope is registered with the Food and Drug Administration as a Class II 510(k) exempt medical device and launched commercially in November. It was recently deployed as part of the Himalayan Cataract Project's efforts to provide eye care for villages in Nepal *(See sidebar)*.

The device is lightweight and inexpensive. It was developed by two Stanford ophthalmologists, David Myung, MD, PhD, and Robert T. Chang, MD, who serve on the faculty at the Byers Eye Institute at Stanford. The two started working on the project together nearly four years ago when they saw the need for a better way for residents and physicians on call to send photos to their colleagues.

There were already a number of adapters available to connect a phone or camera to a slit lamp, but Dr. Myung said he felt that these didn't meet the need at large. "There are many settings where there is no slit lamp available, such as a nursing home, primary-care setting or in many rural settings," he says. "And even in the emergency department, there might not be anyone who is completely comfortable in the use of the slit lamp, or has the time to spend troubleshooting it if there are any problems."

Figure 3. The Paxos Scope device enables both anterior and posterior imaging of the eye. Its universal, spring-loaded mounting system fits and aligns with virtually any smart phone, regardless of its size and camera lens location.

Ultimately, Drs. Myung and Chang—who published their original design in March of 2014— determined that they wanted a device that could be used on any phone.[4,5] A variable-intensity external light source was necessary to provide light for fundus photos. That way, they wouldn't have to rely on the phone's internal flash (which can vary from one smartphone model to the next) and could take many photos without draining the phone battery. The intensity of the light can be adjusted for patient comfort and eye color. The mounting and lens-alignment system is also designed to adapt to nearly any size and dimension phone *(See Figure 3)*.

Dilation is required to obtain the fundus photos, so it is anticipated that this capability will be mostly used by ophthalmologists, optometrists and trained ophthalmic nurses and technicians as an adjunct to their current practice. But non-eye-care providers could easily use Paxos Scope to send pictures of a red eye or traumatic injury for a preliminary ophthalmic consult. "One could imagine a situation where photos of a ruptured globe could result in a quick decision to call for a helicopter transport, when a verbal description alone might not have adequately conveyed the urgency of the situation," says Dr. Myung.

Young ophthalmologists in training are already using their phones to share photos with an attending surgeon, he said, but may be doing so in ways that are not HIPAA-compliant. Paxos Scope securely transmits images to a Cloud server over WiFi or cellular signals without storing them on the phone.

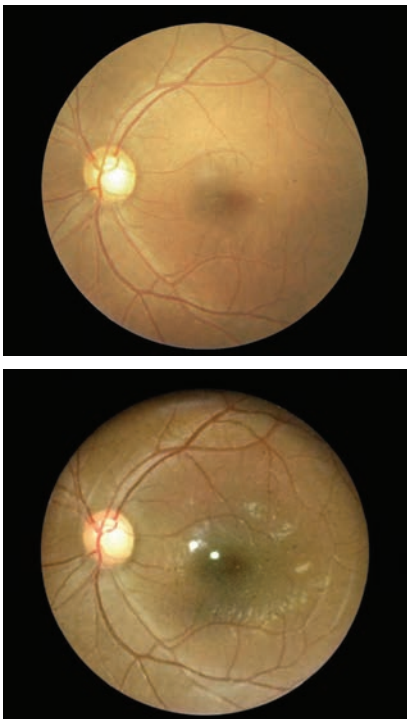


Figure 4. A recent study found that Paxos Scope's smartphone-acquired fundus photos demonstrated 91 percent sensitivity and 99 percent specificity to detect moderate nonproliferative and worse diabetic retinopathy, with good agreement between fixed camera and smartphone-acquired photo grades.

A recent study that is forthcoming in the journal *Retina* found that the smartphone-acquired fundus photos demonstrated 91 percent sensitivity and 99 percent specificity to detect moderate or worse nonproliferative diabetic retinopathy, with good agreement between fixed-camera and smartphone-acquired photo grades ($p<0.001$).[6] *(See Figure 4)*

The device is capable of capturing retinal images with up to a 56° static field of view. "Although the quality of the images is quite impressive given the modern smartphone camera quality, our goal was not to re-

place a fundus camera, but instead to obtain images quickly and easily that are good enough to aid referrals to specialists or remote recommendations," says Dr. Chang. "In this way, we can augment communication and triage capabilities with additional photographic information." Moreover, he said, "People were already taking photos with their smartphone but the magnification and lighting were not optimized for the eye; we wanted to improve this."

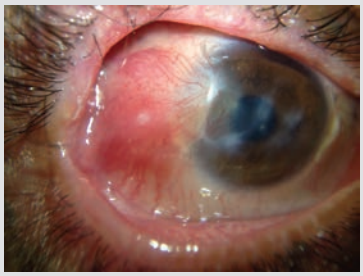
Dr. Chang believes less-expensive, on-demand, mobile imaging holds the potential to expand access to care everywhere, particularly in underserved populations in the United States and abroad. Some examples include helping other health-care workers obtain photos in patients in nursing homes who haven't been getting regular dilated exams, facilitating various eye disease screening camps, and even coupling photos with other parts of the eye exam that can be performed remotely. "The ultimate dream of a portable, full basic eye exam on a smartphone platform using a few small adapters is moving one step closer to reality," he said.

Big Data

A third element of the platform that will soon launch is Paxos Analytics, which will give pharmaceutical companies real-time insights into their clinical study outcomes. In fact, it's the data analysis part of the platform that is expected to provide much of DigiSight's initial revenue.

As part of a clinical trial, or a home-monitoring arm of a larger study, subjects would take the appropriate tests at home, via the app, in between their study visits. "The resulting data will provide a much clearer and more detailed picture of the pharmacodynamics of a new drug," says Doug Foster, CEO of DigiSight Technologies. "High-frequency datasets will

Scaling Mountains to Provide Eye Care



John Welling, MD, using the Paxos Scope in Nepal on a cataract mission with the Himalayan Cataract Project. Bottom: Photo of an inflamed pterygium taken with the anterior adapter.

In the mountainous regions of rural Nepal, a trip to the capital, Kathmandu, can be very challenging. Many patients go without specialist care, and the rate of cataract blindness is high.

The nonprofit Himalayan Cataract Project has been working to change that by improving eye-care training, infrastructure and the provision of high-quality care in Nepal and elsewhere. The organization supports a training center, the Tilganga Institute of Ophthalmology, that serves as a center of excellence for the developing world. It trains many teams of doctors and nurses from Asia and Africa, in an attempt to alleviate blindness by increasing local capacity and efficiency.

HCP Board Director Matthew S. Oliva, MD, says the work provides a strong sense of shared values and commitment. "While I have really focused on expanding our sustainable development model, I still love sharing that moment of sight restoration with individual patients," he says.

Mobile health technology may help his organization overcome a major challenge. "It is often difficult for ophthalmic technicians and doctors in underserved areas to decide which patients would benefit from a trip to Kathmandu to receive subspecialist care," he says.

Dr. Oliva and his colleagues at HCP, including its co-founder Geoff Tabin, MD, fellow John Welling, MD, and David Chang, MD, have been collaborating closely with David Myung, MD, PhD, from Stanford and ophthalmologists at the Tilganga Institute of Ophthalmology in Kathmandu to deploy free Paxos Scope adapters in rural Nepal through a partnership between HCP, DigiSight and the American Society of Cataract & Refractive Surgery Foundation *(See images, above)*.

Given that most doctors at rural-health care centers in Nepal use cell phones and text messaging as their primary means of communication, he is convinced that a smartphone based technology can be an effective aid to telemedicine. "The Paxos Scope offers an elegant way to share patient information so that rural health providers can seek advice on patient care or facilitate a referral for follow-up care. We are optimistic this will lead to improved, comprehensive care for patients in Nepal," Dr. Oliva says.

—J.B.

make it easier to understand how people are responding to the drug and to characterize the exact onset of action, the half-life of the drug, and the stability of vision over time."

Eventually, physicians may also find the data analytics aspect extremely valuable for day-to-day patient care. "Once you aggregate a lot of data, we think there are some very compelling and interesting things that can be done with it, such as developing more sophisticated predictive capabilities," says Mr. Foster. Analysis of the data could potentially lead to new insights about disease progression or therapeutic efficacy and allow doctors to more precisely personalize care to the individual patient.

"There is significant pressure on health-care systems in the United States to be accountable for high-quality care, while at the same time containing rising costs," says Mr. Foster. "One way to accomplish this is to give expensive treatments like anti-VEGF injections only when patients actually need them, rather than on an arbitrary schedule that overtreats some patients, increasing costs through overutilization, while undertreating others and potentially increasing costs through higher rates of visual impairment."

Although it seems at first blush that more information could overwhelm physicians who are already stretched to provide care to a growing senior population, Mr. Foster says more information can actually help doctors work smarter. The company's internal analyses suggest, for example, that physicians spend only about 10 minutes per week reviewing the Paxos Checkup dashboard for all the patients doing at-home monitoring. "But in that short time, they can actually enable patients to engage more in their own care, and potentially create a more pleasant workflow experience and potentially improve outcomes," Mr. Foster says. REVIEW

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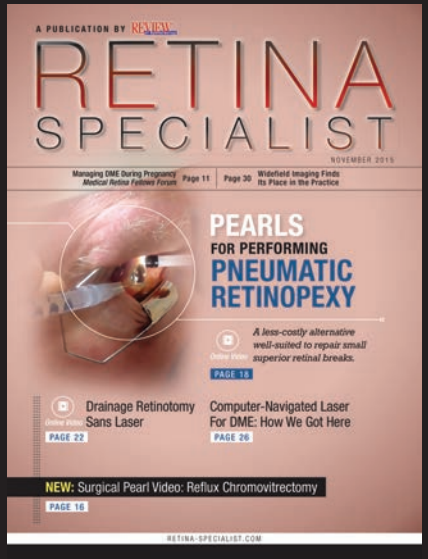

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Spectral-Domain OCT in Managing Uveitis

Advances in imaging have led to improved quantitative and qualitative assessment of uveitis-related pathology.

Wen-Shi Shieh, MD, Jayanth S. Sridhar, MD, and James P. Dunn, MD, Philadelphia

Optical coherence tomography is a safe, non-invasive modality that allows for high-resolution, cross-sectional imaging of the retina through detection of relative changes in reflectivity at optical interfaces by infrared light.[1] Compared with time-domain OCT, spectral-domain OCT has allowed for improved visualization of retinal morphology with its ability to achieve axial resolutions of 5 to 7 µm. Clinicians can choose between radial (a series of B-scans separated at regular angular intervals) and raster (a series of parallel B-scans) OCT patterns. Pairing the OCT with a scanning laser ophthalmoscopic image allows for precise determination of the exact location of the scan.

Given its high degree of reproducibility, SD-OCT is an invaluable technique for characterizing pathologic features of the retina, including the retinal pigment epithelium, and in assessing disease activity and therapeutic response. Enhanced-depth- imaging OCT now allows better visualization of the choroid. This review summarizes the applications for SD-OCT imaging in vari-

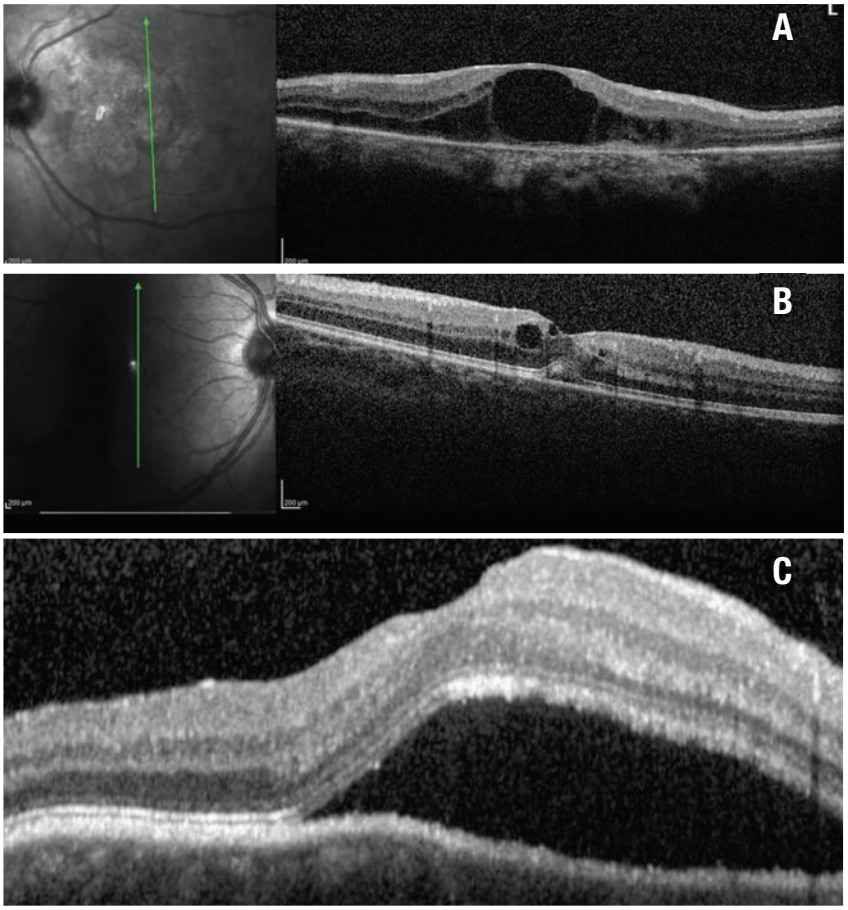

Figure 1. Different forms of macular edema in uveitis. 1A (top). Cystoid macular edema in serpiginous choroidopathy. 1B (middle). Diffuse macular thickening with cystic changes in chronic uveitis. 1C (bottom). Subretinal fluid in Vogt-Koyanagi-Harada disease.

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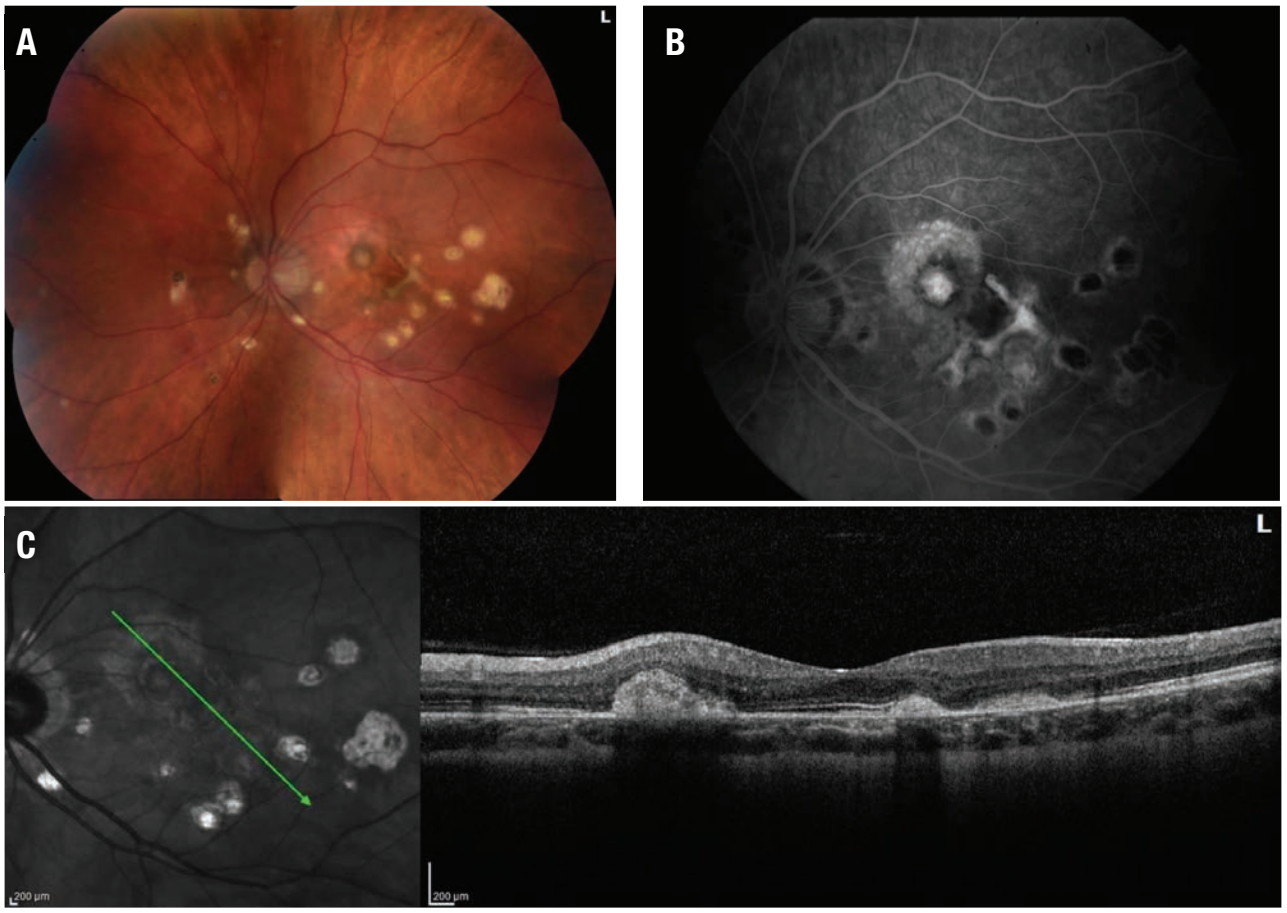


Figure 2. Punctate inner choroidopathy with choroidal neovascularization, left eye. 2A (top, left). Color fundus photo. 2B (top, right). Fluorescein angiogram. 2C (above). Spectral-domain showing choroidal neovascular membrane.

ous ocular inflammatory diseases.

Edema, ERM and CNV

Detection and monitoring of uveitic macular edema using SD-OCT has been extensively studied. The 12-line radial and 25-line raster scans are comparable in their ability to detect intraretinal and subretinal fluid. Three different patterns of fluid distribution in the macular have been described: cystoid macular edema *(See Figure 1A)*; diffuse macular edema *(See Figure 1B)*; and serous retinal detachment *(See Figure 1C)*. CME appears as low reflective intraretinal spaces that are separated by thin retinal tissue with high reflectivity. DME shows small areas of hyporeflectivity and a spongy appearance to the retinal layers, thus resulting in increased macular thickness. Lastly, serous retinal detachments are characterized by a separation between the neurosensory retina and RPE.[1] Isolated anterior uveitis usually causes non-cystic retinal thickening that correlates well with disease activity.[2]

OCT can be used to quantitate response to therapy. One study that showed a 20-percent change in retinal thickness correlated well with a 10-letter change in visual acuity, suggesting that changes in SD-OCT could be a meaningful measure of treatment success in macular edema related to uveitis.[3]

Epiretinal membrane formation is common in uveitis and appears on SD-OCT as jagged hyperreflective lines adherent to the inner-most layers of the retina. ERM formation is often found in conjunction with vitreoretinal traction, and a tractional mechanism may contribute to the onset of macular edema in uveitis.[1] The vitreomacular interface may also affect response to therapy for uveitic macular edema, with eyes having posterior vitreous detachments showing greater and faster response to intravitreal corticosteroids or bevacizumab than eyes with vitreomacular adhesion.[4]

Choroidal neovascularization is a leading cause of impaired vision and blindness in eyes with uveitis, and SD-OCT is a useful way to detect it and monitor treatment *(See Figure 2)*.

White Dot Syndromes

SD-OCT can identify hyperreflectivity, thinning, loss of or edema of retinal and chorioretinal interface layers in white dot syndromes, which may provide more accurate case definitions of these disorders and better prognostic clues. For example, restoration of retinal architecture at the IS/OS junction following systemic immunomodulatory treatment has been reported in birdshot chorioretinopathy.[5] In contrast, there is no anatomic or visual field improvement in regions with initial photoreceptor loss in acute zonal occult outer retinopathy (AZOOR).[1]

However, OCT findings may not predict visual outcomes. In acute posterior multifocal placoid pigment epitheliopathy, for example, photoreceptor atrophy and continued disruption of the IS/OS junction or RPE can still be seen in later phases despite visual recovery.[6]

Peripapillary IS/OS junction (ellipsoid) defects are a common finding in eyes with an enlarged blind spot, often found in AZOOR, multiple evanescent white dot syndrome (MEWDS) *(See Figure 3)*, and multifocal choroiditis and panuveitis (MCP-PU).[7] AZOOR often has more severe outer retinal changes and can be associated with thinning of the inner nuclear layer. One differentiating feature of MEWDS is the restoration of the IS/OS junction line during the recovery phase; this phenomenon occurs only in areas where the outer nuclear layer (ONL) initially had normal thickness in AZOOR. Similarly, loss of the IS/OS line in MCP-PU is seen overlying the classic chorioretinal scars, along with drusen-like deposits between the RPE and Bruch's membrane.

SD-OCT of macular lesions in punctate inner choroidopathy shows elevation of the RPE with sparing of Bruch's membrane and choroid. Bands corresponding to photoreceptors also appear compressed during active phases and return to normal caliber with clinical stabilization.[8] Both active and inactive serpiginous lesions demonstrate increased reflectivity in the choroid and deep retinal layers in addition to disruption at the IS/OS junction. In MEWDS, multifocal debris centered at and around the ellipsoid layer, protruding toward the outer nuclear layer corresponds to the location of dots seen with photography, indocyanine green angiography, and fluorescein angiography. *(See Figure 3)*[9]

Posterior Uveitis

Although occlusive retinal vasculitis is a cardinal finding in Behçet's disease, choroidal thickening may be related to vasculitic processes affecting choroidal vasculature. Studies using SD-OCT to focus on foveal changes during remission of Behçet uveitis have revealed better visual acuity and greater foveal thickness in eyes with an intact IS/OS line compared with those with poorly defined architecture.[10]

SD-OCT can easily identify structural changes of the retina and choroid in VKH disease. Intraretinal fluid accumulation in serous retinal detachments causes outer segment detachment from the photoreceptor layer. The subsequent fibrin precipitation in the fluid space of the outer photoreceptor layer forms membranes and the cystoid spaces that are typically seen in active disease.[11]

Enhanced-depth imaging has made it possible to visualize the choroidal involvement in VKH disease. A reduction in the number of hyperreflective dots at the inner choroid compared to normal controls has been attributed to non-perfusion of small choroidal vessels due to inflammatory cell infiltration and stromal

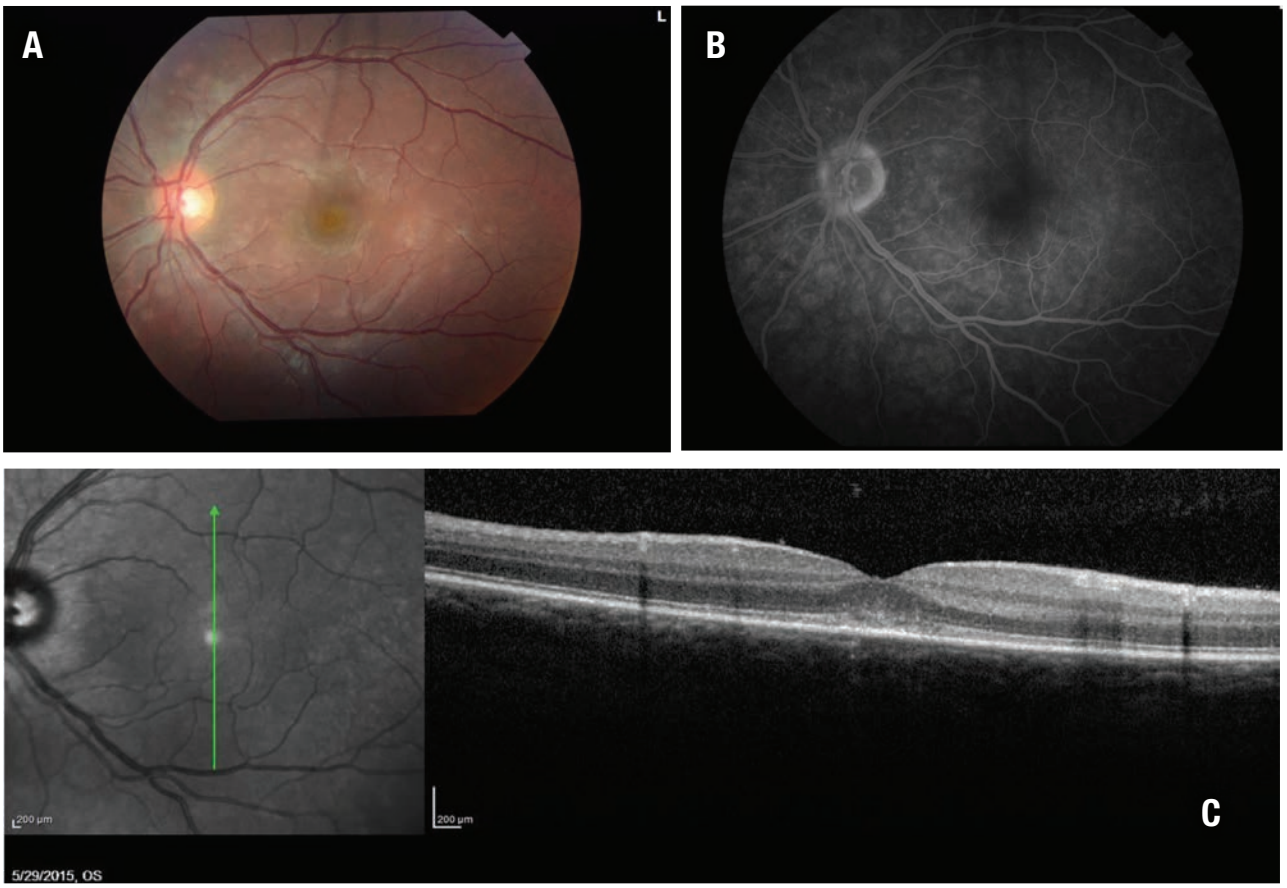


Figure 3. Multiple evanescent white dot syndrome. 3A (top, left). Color fundus photo, left eye. 3B (top, right). Fluorescein angiogram, left eye. 3C (bottom). Spectral-domain optical coherence tomography, left eye. Note the disruption of the subfoveal ellipsoid region.

scarring-induced dropout of similar vessels in the active and convalescent stages of VKH disease, respectively.[12] An increase in choroidal thickness during the acute phase has been well-documented, as has the return to normal values upon effective treatment with corticosteroid therapy.

Infectious Posterior Uveitis

Acute syphilitic posterior placoid chorioretinopathy assessed by SD-OCT in one study demonstrated transient sub-foveal fluid one to two days after presentation in nearly half the eyes that were examined. After seven days, irregular hyperreflectivity and nodular elevations between the photoreceptors and RPE as well as segmental loss of the IS/OS band were consistently noted *(See Figures 4A & 4B)*. In some cases, loss of the external limiting membrane and punctate, hyperreflective spots in the choroid were observed. With the initation of neurosyphilis therapy, all of these findings were resolved by one-month follow-up.[13]

Ocular toxoplasmosis is the most frequent cause of infectious posterior segment inflammation. In one series of patients with active toxoplasmic retinochoroiditis, SD-OCT exhibited increased retinal thickness with and without sub-retinal fluid accumulation. Inner retinal layer reflectivity also resulted in RPE and choriocapillaris shadowing. Other pertinent findings include persistent disorganization of retinal layers secondary to scar formation and a trend toward separation of the hyaloid at six-week follow-up.[14]

Anterior Uveitis

Slit-lamp examination remains the standard method for evaluating anterior chamber inflammation, but suffers from limited interobserver agreement, lack of a non-linear grading scale and variability in illumination from one slit lamp to another. While SD-OCT currently has limited applications in anterior uveitis, SD-OCT has axial and transverse resolution finer than the diameter of a white blood cell (7 to 9 µm), and can be modified to create three-dimensional images of the anterior chamber. Using these techniques, grading of cells by anterior segment OCT has been shown to correlate strongly with clinical grading.[15] A potential limitation of this technique is the misidentification of pigment in

the anterior chamber for white blood cells, although this can be a problem in slit-lamp grading as well.

Limitations

There are limitations of OCT include potential lack of reproducibility when normative values may not be known (e.g., children with uveitis) or there is more inherent variability of the tissue being assessed (e.g., optic nerve head and choroid vs. macula). Uveitis may affect the interpretation of OCT in other disorders such as glaucoma. Uveitis may cause falsely elevated estimates of retinal nerve fiber layer thickness; continued thinning of the RNFL and increased cupping, despite good intraocular pressure control in such eyes, may occur from resolution of edema of the RNFL as the uveitis resolves.[16] Therefore, screening for glaucomatous RNFL changes should be performed only when the uveitis is inactive. Finally, despite its many advantages, OCT has not replaced fluorescein angiography for evaluation of macular edema. OCT (preferable for assessing macular thickness) and FA (preferable for assessing macular leakage) show only moderate agreement regarding macular edema status in uveitis. Macular leakage cannot be ruled out if macular thickness is absent, so that FA may be necessary if the OCT is normal when detection of leakage would alter management.[17]

Recent Advances

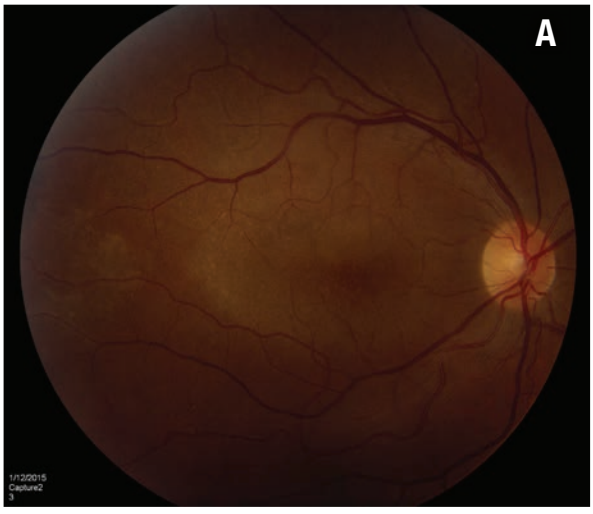
Three-dimensional OCT can produce volumetric renderings with excellent resolution of the retina and retinal pigment epithelium. While such images have been mostly used in the evaluation of vitreoretinal interface disorders, central serous retinopathy and ocular tumors, they may eventually be useful in diagnosis and management of infectious chorioretinopathy (e.g., fungal, tuberculous).

Swept-source OCT uses a longer wavelength and faster scan speed than SD-OCT, providing even finer resolution (as little as 1 µm) with wider and deeper scans. SS-OCT also allows imaging of the retina through moderately dense cataracts. Simultaneous imaging of the macula and optic nerve is possible, as well as enhanced visualization of the choroid. However, interpretation of images is presently limited by inherent variability in choroidal thickness due to age, axial length and even time of day.

"En face" OCT is a new technique with particular applicability for imaging of disorders involving the IS/OS photoreceptor junction and the inner choroid. In one case report of a patient with MEWDS, en face OCT showed attenuation of these layers in a pattern that mirrored hypofluorescent spots seen with ICG angiography.[18] En face OCT highlighted confluent areas of middle retina hyper-reflectivity corresponding to these lesions. Three distinct en face OCT patterns were observed: arteriolar; fern-like; and globular. Microperimetry demonstrated relative scotomas mapping to the area of middle retinal hyperreflectivity seen on en face OCT.

OCT of the optic nerve and peripapillary retina is frequently used in the assessment of disorders such as papilledema, optic neuritis and glaucoma. One group described the use of OCT to measure peripapillary RNFL thickness and optic nerve central thickness in monitoring resolution of inflammatory papillitis.[19]

OCT angiography is a non-invasive means of assessing retinal and choroidal blood flow and can detect and quantify neovascularization and capillary dropout without the use of dye. Four layers are assessed en face: the superficial retinal vascular plexus



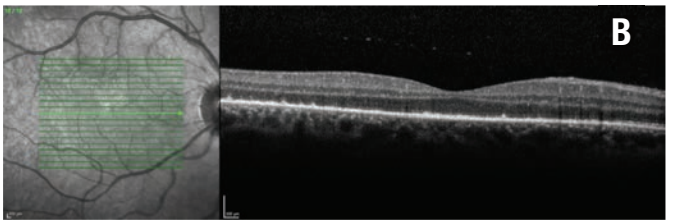


Figure 4. Placoid syphilitic retinitis, right eye. 4A. Color fundus photo. 4B. Spectral-domain optical coherence tomography showing outer retinal changes.

(similar to the traditional fluorescein angiogram view); the deep retinal vascular plexus; the outer retina; and the choriocapillaris. Currently, OCTA is limited by its ability to image only the posterior pole. However, the combination of high-definition SD-OCT and OCTA has allowed a detailed understanding of variable areas of capillary dropout within the superficial and deep retinal capillary plexi in the inner retina in patients with vascular disorders causing paracentral acute middle maculopathy.[20] Additional experience will show to what extent such modifications of OCT can replace invasive imaging in the diagnosis, natural history and response to treatment in uveitic white dot syndromes and other inflammatory chorioretinal interface diseases such as birdshot retinopathy, with or without choroidal neovascularization.[21]

Advances in OCT for *in vivo* imaging of the retina have allowed for improved quantitative and qualitative assessment of uveitis-related pathology. High-resolution OCT imaging has led to better understanding of distinct changes at the vitreoretinal interface, retinal layers and choroid that are specific to various inflammatory entities. The integrity of the IS/OS line has also been shown to be a valuable predictor of visual recovery, treatment response and prognosis. Consequently, SD-OCT has become a standard ancillary test for detecting and monitoring uveitic ocular disease. It remains unclear to what degree the knowledge SD-OCT has provided about these disorders will improve prognostic skills, eliminate the role for invasive procedures such as fluorescein or indocyanine angiography, or allow clinicians to distinguish more confidently those syndromes for which no treatment is necessary (e.g., MEWDS) from those in which long-term immunosuppression is typically indicated (e.g., MFC-PU, birdshot chorioretinopathy). REVIEW

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Oxidative Stress Reduction for Dry Eye

Antioxidants' effects on harmful reactive oxygen species may be helpful in the fight against dry eye.

Mark B. Abelson, MD, CM, FRCSC, FARVO, George Ousler and Linda Stein, Andover, Mass.

What does dry eye have in common with cancer, neurodegenerative disorders, normal aging and heart disease? One answer is oxidative stress. We all know what it's like to feel stressed out over deadlines or other demands of life. Similarly, our cells experience oxidative stress in response to a variety of molecular disturbances. With dry eye, the pressure might come from exposure to environmental variables such as cigarette smoke, low humidity, sun, wind or pollutants. Certain medications or medical conditions may also contribute to dry eye. Aging itself is associated with decreased tear production and dry eye. All of these variables have the capacity to impact oxidative stress levels on the ocular surface and in so doing contribute to ophthalmic conditions beyond dry eye, including macular degeneration, cataracts, uveitis, keratitis and corneal inflammation.[1]

This month, we take a look at oxidation as a root cause of ocular surface disease, examine how this occurs and consider potential steps toward an antioxidant-based approach to dry-eye treatments.

Oxidative Stress Explained

What exactly is oxidative stress? Oxidative stress occurs when the level of reactive oxygen species produced in cells and tissues exceeds normal levels. ROS are types of free radicals (an atom with one or more unpaired electrons) that play a beneficial role in cell signaling and overall cellular homeostasis. Antioxidants naturally present in tissues usually control ROS levels, but surplus ROS react with nearby proteins, lipids or other cellular components, leading to unpredictable, cumulative and often deleterious effects on normal cell function. Oxidative injury from ROS occurs in the tears and conjunctiva of Sjögren's syndrome patients, and high levels of ROS and oxidative stress have been identified in the tear film of dry-eye patients[2] and in animal models of dry eye.[3]

A primary source of cellular ROS is mitochondria, the intracellular organelles responsible for oxidation of glucose into H_20, CO_2 and the chemical energy of adenosine triphosphate; ROS are often a byproduct of this process. Antioxidants such as reduced glutathione or enzymes such as superoxide dismutase provide electrons to convert ROS into less-reactive forms, but the cellular supply of antioxidants can be overwhelmed by too much ROS. As electrons pass along the mitochondrial electron transport chain, a fraction is lost to ROS and subsequent local oxidation events. This theft of electrons by ROS can lead to a host of cellular dysfunctions including membrane disruption. ROS can also inflict damage on DNA, RNA or cell proteins, effects that can ultimately lead to cell apoptosis.

Inflammation

While high ROS levels within the mitochondria lead to oxidative stress and potential organelle damage, ROS outside the mitochondria may be involved in inflammation, a primary mechanism of dry-eye disease.[1] This inflammation can be the result of ROS exiting the mitochondria, or the generation of ROS in other cellular structures. Macrophages and other phagocytes involved in fighting infection use ROS as a weapon against foreign invaders, but control of these

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The intricate membrane structure of the mitochondria provides the architecture to generate proton concentration gradients; using oxygen as an electron acceptor, the gradient drives ATP synthesis and produces reactive oxygen-containing molecules as a byproduct.

ROS is not always adequate. In particular, pro-inflammatory cytokines, such as IL-1β, can stimulate ROS to levels that can lead to oxidative tissue injury.

A number of preclinical models have been used to explore the relationship between oxidative stress and inflammation in dry-eye disease. In one study, increased ROS activated the NLRP3 gene, a key player in immune cell recognition of microbial pathogens and stress-related signals.[4] NLRP3 activation in this dry-eye study increased secretion of the pro-inflammatory cytokine IL-1β. The same inflammatory process was confirmed in another dry-eye study using stressed human corneal epithelial cells: Increased ROS activated NLRP3, which in turn stimulated IL-1β and subsequent tissue inflammation.[5] This study also examined 20 dry-eye patients and 15 normal subjects. In the dry-eye subjects, levels of ROS, NLRP3 and IL-1β were elevated in tear samples and conjunctival epithelial cells, indicating that inflammation in dry-eye disease may occur through the ROS–NLRP3–IL-1β signaling pathway. IL-1β levels in the dry-eye patients correlated with ocular surface disease index and Schirmer's test scores and were elevated compared to control subjects. Previous studies found that NLRP3 is involved in other ocular diseases, including macular degeneration, glaucoma and corneal ulcer, as well as non-ocular diseases. In the future, it's possible that inhibiting the ROS–NLRP3–IL-1β pathway may turn out to be an effective approach for dry-eye relief.[5]

Benefits and Limitations

Most of us have heard about the purportedly miraculous qualities of antioxidants in food or nutritional supplements that allegedly can keep us healthy and help keep various diseases at bay. Antioxidant-rich foods (such as blueberries) are highly recommended by health experts, and sales of antioxidant supplements (such as vitamin C, vitamin E and Coenzyme Q) have skyrocketed. Although the evidence for a role of oxidative damage in conditions from diabetes, cancer or heart disease is undeniable, efforts to use antioxidants as therapeutics have been hit-or-miss: Antioxidant supplements have shown beneficial effects in some trials, while other studies have found little or no benefit. This is true both for overall health and for eye health specifically.

In one preclinical study, nutritional polyunsaturated fatty acid supplementation produced statistically significant changes in serum fatty acids and a dose-related inhibition of rabbit corneal infiltrates and corneal angiogenesis. This process involved modulation of eicosanoid precursors, changes in corneal neovascularization and in alkali-induced inflammation.[6] A subsequent study, however, was unable to reproduce the effect of nutritional supplementation with the same PUFAs, gamma-linolenic acid, eicosapentaenoic acid or a combination of the fatty acids used in the prior study.[7] The latter study is in line with more recent publications showing little or no effect of fish oils in reducing ocular inflammation.

For macular degeneration, a combination of antioxidant vitamins C and E, plus beta-carotene and zinc, afforded a statistically significant protection in disease onset in the Age-Related Eye Disease Study.[8] A second AREDS study showed that lutein plus zeaxanthin—which are two carotenoids—can substitute for beta-caro-

tene, which has been associated with an increased risk of some types of cancer.[9] While the effects are modest, the AREDS studies represent the most prominent examples of the benefits of antioxidants in the eye. Other studies have suggested that selenium or lactoferrin supplementation may similarly protect the corneal epithelium from oxidative stress.[1,10] Antioxidants have also been explored as potential therapy in many other conditions associated with ROS. For example, supplements of vitamin E, vitamin C and Coenzyme Q have yielded some relief from the ocular complications associated with diabetes, although overall effects are mixed.[11]

It's important to note that there are also a few other studies that have suggested an increased risk of disease associated with the use of antioxidant supplements.

Two studies showed an increase in cancer risk for people who were heavy smokers or were exposed to asbestos and were taking beta-carotene or a beta-carotene/vitamin A combination.[12] It's possible that the mixed results of antioxidant supplementation in reducing oxidative stress and disease may be due to the limited ability of natural antioxidants to reach a cell's mitochondria and accumulate there, due to the relatively poor bioavailability, pharmacokinetics or stability of these antioxidant supplements. For some degenerative diseases, for example, very large doses were necessary to show a significant treatment benefit.[13] And although antioxidant supplements have been beneficial for certain eye conditions, it's also true that, except for the retina, enzymatic antioxidant activity in the eye is limited, with few protections against ROS.[1,14]

Targeted Antioxidants

Because of the limitations of natural antioxidant supplements in reducing ROS damage, mitochondrial-targeted antioxidants have been developed that are capable of accumulating in mitochondria. These therapies have shown beneficial effects for ocular and non-ocular diseases in some animal and clinical studies, although other studies did not confirm these results.[15]

Although antioxidant supplements have been beneficial for certain eye conditions, it's also true that, except for the retina, enzymatic antioxidant activity in the eye is limited, with few protections against reactive oxygen species.

Mice lacking the enzyme superoxide dismutase displayed degenerative loss of retinal pigment epithelial cells; this defect was corrected in these superoxide dismutase knockout mice by directed RPE expression of superoxide dismutase, which is capable of reducing mitochondrial and extracellular ROS generation.[16] Using this same mouse model, another study showed that superoxide dismutase knockout resulted in abnormalities in lacrimal gland tissue, tear quantity and stability and the ocular surface.[1] This murine model may be useful for future dry-eye studies.

MitoQ's mitochondrial-targeted drug MitoQ (ubiquinone, which is identical to the antioxidant moiety in Coenzyme Q10) has been tested both in animals and in humans. In rodent studies MitoQ protected cells from pathological mitochondrial oxidative changes associated with effects such as cardiac damage, hypertension, liver damage, kidney damage and processes related to Parkinson's disease.[17] In human studies, MitoQ has had mixed but promising results. In subjects with hepatitis C it significantly reduced liver enzyme levels, suggesting a reduction in liver inflammation, although viral levels were not significantly reduced.[18] MitoQ didn't slow the progression of Parkinson's disease in an Australian/New Zealand study, possibly because it may be too late to rescue remaining dopamine neurons once the clinical signs of Parkinson's are present.[19]

Compounds with known antioxidant activity are chemically diverse. For example, another approach is the use of Szeto-Schiller peptides, short sequences of alternating aromatic and basic amino acids that are selectively taken up by mitochondria and are capable of reducing ROS at nano-molar concentrations.[20] These peptides have shown promise in treating several conditions associated with inflammation or oxidative stress, including cardiac ischemia/reperfusion injury, insulin resistance and Parkinson's.[17] This approach may also be relevant as an ocular therapeutic, although no studies have been published to date.

Other antioxidant therapeutics targeting mitochondria include plastoquinone derivatives such as SKQ1 (Mitotech, Luxembourg). This compound is an approved treatment for dry eye in Russia. At the cellular level, SKQ1 reduces cell damage caused by excessive ROS by modulating the mitochondria's membrane electrical potential, the driving force for the electron transfer chain, ATP production and ROS formation.[21] An important feature of SKQ1 is that its oxidation chemistry is such that it is recycled in the mitochondria, allowing it to serve as a renewable antioxidant. In addition to its antioxidant proper-

ties, studies in cell cultures of human conjunctival epithelial cells showed that SKQ1 reduced the production of prostaglandin E2, a pro-inflammatory signaling molecule that has been implicated in dry eye. Other SKQ1 studies of human endothelial cells indicated that mitochondria ROS are involved in regulation of the immune response.[22]

In mouse models of dry eye, SKQ1 reduced corneal staining and appeared to have a rapid onset and long duration of action. Other studies of the compound showed SKQ1 or related plastoquinones had beneficial therapeutic effects in animal models of retinopathy, glaucoma, macular degeneration and UV damage to the lens;[23,24] systemic benefits in ischemia-related diseases have also been documented.[25]

In Russian clinical trials, SKQ1-induced reductions in dry-eye signs and symptoms were significantly greater than those seen with an artificial tear control.[26] SKQ1 improved corneal cell function, increased tear-film stability and reduced dryness, burning, grittiness and blurred vision. In a subsequent U.S. clinical trial, SKQ1 reduced corneal and conjunctival staining, improved ocular discomfort scores and was generally superior to placebo control treatment.[27] Of note, this study demonstrated SKQ1 improvements in both signs and symptoms of dry eye evoked through the use of the controlled adverse environment, a model that is designed to exacerbate dry-eye instigators, including oxidative stress effects. In both clinical trials, the compound exhibited a good safety profile and was well-tolerated by subjects.

Results with the compound SKQ1 confirm the importance of the mitochondria as a target for reducing oxidative stress in the body, and also support the notion that ROS are important contributors to dry-eye disease.

Looking Ahead

Novel treatments for dry eye hold promise in the not-to-distant future; treatments that hone in on the initial damaging events of intracellular oxidation could halt dry eye signs and symptoms in their tracks. Treating dry eye from the inside out may very well de-stress the cells that are under the onslaught of oxidative stress, allowing both the patient and the ophthalmologist some much needed respite from this disease. REVIEW

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Solving the Mystery Of Rainbow Glare

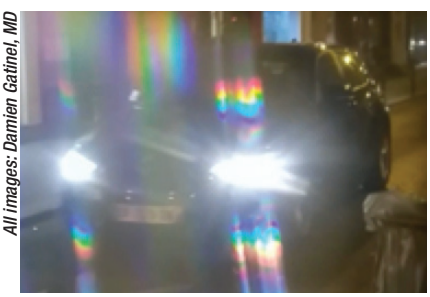
A surgeon says you may be able to treat this infrequent but aggravating complication of LASIK.

Walter Bethke, Managing Editor

Rainbow glare following LASIK is an infrequent complication that can be maddening for a patient and confounding for a surgeon. Now, however, if you encounter a patient who complains of such a complication, you have options for treatment that can resolve it. Here, a surgeon describes how his run-ins with rainbow glare prompted him to come up with a solution.

The Face of the Problem

When Damien Gatinel, MD, of Paris, France, encountered his first case of post-LASIK rainbow glare, the patient was in dire straits. "He had already spent two weeks in a psychiatric hospital because he was complaining about color fringes," Dr. Gatinel recalls. "No one took him seriously because the complication wasn't very well-known at that time. He was telling his doctors that the problems started after his refractive surgery, and when he was asked to draw what he saw—or was pretending to see—what he drew was quite scary: Bizarre bands of colors. When I finally saw him, I'll never forget what he told me: 'Dr. Gatinel,' he said, 'I'm looking at you, and if you were a bright light I would also see another you in colors 50 cm to your left, another you 50 cm to your right, and a ghost head floating above yours.' He was quite serious, and was so concerned about his vision that he could no longer drive, and what was particularly disturbing for him was the ghosting effect. He told me that when he would walk at night and would look at the pedestrian walk signals at intersections, he'd see duplicates of the signals floating in the air on all sides of the light. This is because such lights are monochromatic, as opposed to a white light that will produce a spectrum when it's viewed by someone with this complication. Fortunately, his case resolved within six months, and we now know that some cases resolve spontaneously."



All images: Damien Gatinel, MD

The effects of post-femto LASIK rainbow glare, simulated here using a treated PMMA disk, can be frightening to patients.

Studying Rainbow Glare

Rainbow glare after LASIK was first described in a retrospective study from the Cleveland Clinic's Cole Eye Institute in 2008.

In the study, investigators reviewed 215 patients (399 eyes) who had been treated using an older model IntraLase laser and 97 patients (186 eyes) who had been treated with a newer model. They found that 37 (19 percent) of the older-laser patients whom they had been able to contact had rainbow glare. However, in the new-laser patients whom they were able to contact, only two patients (2 percent) reported rainbow glare.[1] These findings seem to jibe with current surgeons' experience that newer femtosecond technology has greatly reduced, but not eliminated, rainbow glare as a complication.

To get an idea of what was behind rainbow glare, Dr. Gatinel placed a PMMA disk beneath his FS200 femtosecond laser and programmed a

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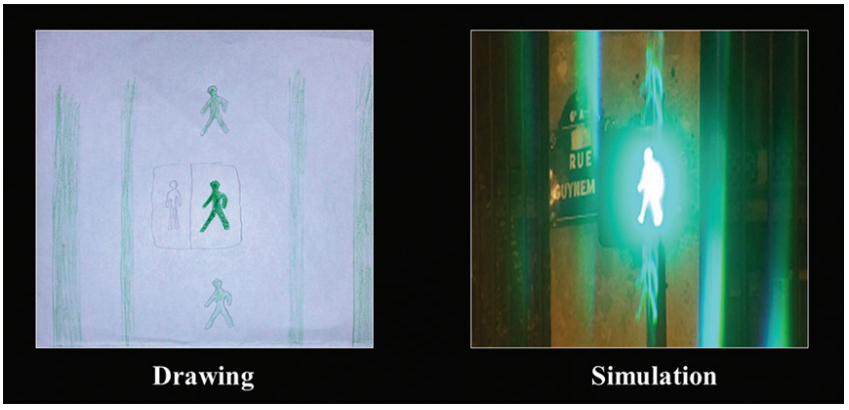
regular flap cut that placed the laser's raster pattern inside the plastic. When he went outside and looked at light sources through the disk, he was able to replicate patients' rainbow-glare complaints, right down to the duplicate images surrounding pedestrian walk signals. He says the glare is the result of a diffractive process that, ironically, stems from the perfect regularity of the spacing of the treatment. "The glare arises from a diffractive effect caused by the regularity of the pattern," he says. "If the femtosecond were randomly shooting the spots and they weren't evenly spaced, you wouldn't have much diffraction of light and rainbow glare because the diffracted light rays would cancel each other out. Rainbow glare is the price you pay for a very regular spot delivery."



When Paris surgeon Damien Gatinel used a femtosecond laser to simulate a flap cut on a PMMA disk, and then held the disk up to the light, he was able to reproduce the images patients had drawn to illustrate their rainbow glare complaints after femto LASIK.

Erasing the Rainbow

After another patient was referred to Dr. Gatinel with rainbow glare, he began to devise a strategy for treating it.

"At that time, I knew that the cause of the rainbow glare was probably the posterior surface of the flap," he says. "The mechanism is quite straightforward: Because the femtosecond laser's raster pattern imprints some spots in the stroma and the posterior surface of the flap, when you perform the LASIK ablation the excimer erases the raster pattern from the stromal bed but not from the posterior flap surface. I began thinking of doing some treatment on the back surface of the flap."

The first patient on whom he tried this treatment was one of his own who came back with complaints of rainbow glare, and who also had 0.75 D of astigmatism. "I proposed that I'd treat both conditions by ablating the back surface of the flap," he says. "I told her it could work, but wasn't sure because I hadn't done it before. She consented. So, I performed a 15-µm ablation on the back of the flap. It treated the astigmatism and completely resolved the rainbow-glare symptoms." Since then, he's treated a second rainbow-glare patient who was emmetropic. Because the patient didn't have any refractive error, Dr. Gatinel used a 10-µm PTK on the posterior of the flap. "It didn't fully resolve the rainbow glare, but it greatly minimized it," he says.

For a surgeon who'd like to treat a patient with rainbow-glare complaints, Dr. Gatinel offers some tips. "If the patient also has a refractive error, you can kill two birds with one stone by a treatment on the back surface of the flap to improve vision and erase the raster pattern," he says. "But, for an emmetropic patient, you can do a 10- to 15-µm PTK instead. To place a treatment on the back surface of the flap though, you have to deactivate the excimer's eye tracker because it looks for the center of the pupil, which will not be there because the flap will be reflected back. So, before you reflect the flap back, be sure to mark the center of the pupil with an ink dot so you can center the treatment on that. Also, if you're treating astigmatism, you have to reverse the astigmatism axis of your treatment because, when you lift the flap, the astigmatism is a mirror image of what it is normally. The formula for the treatment axis, then, is 180 degrees minus the astigmatic axis from your measurements.

"In terms of treatment limits, if the flap is thin you need to be cautious," Dr. Gatinel adds. "For a 110-µm flap, for example, if the epithelium is 50 µm, you're left with about 50 or 60 µm of stroma. That's probably not enough to treat more than 20 or 30 µm. Thirty µm is around a 2-D correction with a 6-mm zone. I don't think hyperopia is a good indication because in a hyperopic correction you don't remove the stroma in the center, but the goal of the rainbow-glare treatment is to remove the depth of the femtosecond spots, which is about 10 µm. This means a hyperopic treatment that doesn't treat the center might not be that effective. What you could do, however, is put a non-refractive PTK treatment on the back surface of the flap to treat the glare and then do a hyperopic treatment on the stromal surface."

Dr. Gatinel thinks that, even if a rainbow-glare treatment doesn't eliminate the problem, just reducing it can be enough for many. "After the rainbow-glare surgery that minimized my second patient's symptoms," he recalls, "the patient looked into the light of a smartphone and burst into tears of relief, saying, 'I've been brought back to life.' " REVIEW

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Assessing the Angle: Which Method Is Best?

Gonioscopy, optical coherence tomography and ultrasound biometry all have advantages and limitations.

Shan C. Lin, MD, San Francisco

Examining the angle is a crucial part of diagnosing angle-closure glaucoma, as well as a key part of determining its probable cause. There are several ways to evaluate the angle, including direct observation using gonioscopy and imaging the angle, the latter most commonly done using optical coherence tomography and/or ultrasound biomicroscopy. As studies have demonstrated, many ophthalmologists do not perform gonioscopy even in glaucoma patients, so imaging may be of benefit as a screening tool.[1] However, each modality has benefits and drawbacks and reveals different kinds of information, so being able to do all three—and knowing when to do them—offers your patients the best chance for an accurate diagnosis.

Here, I'd like to discuss the pros and cons of each method and share my protocol for their use when managing glaucoma.

Seeing It for Yourself

Using gonioscopy to look directly into the eye can provide many visual clues to what's going on that can't be picked up by digital imaging. Gonioscopy also allows real-time manipulation of the eye and observation of the results. Gonioscopy is direct, interactive and can easily observe 360 degrees of the angle if the surgeon desires. In fact, the first line of defense for a glaucoma specialist is usually examining the patient and then doing gonioscopy.

One advantage of performing gonioscopy is that you can do a dynamic evaluation of the angle by pushing gently on the eye, causing a narrow angle to open up. This allows you to look for areas where there is chronic angle closure, which is signified by peripheral anterior synechiae; those areas will not open up in response to the pressure. Being able to do this test gives you information you can't garner from looking at a single cross-sectional image.

Gonioscopy can also provide visual information, including color, that will allow you to rule out other conditions that can cause an angle to appear closed, such as neovascular glaucoma. Because you're looking directly at the angle, you can see any neovascular vessels. You can also identify other types of glaucoma such as angle-recession glaucoma, and you can look for pigment from pigmentary or pseudoexfoliation glaucoma, the latter of which is also often associated with angle-closure glaucoma.

Gonioscopy has some practical advantages compared to imaging. For example, if you're in the clinic with the patient in the chair, gonioscopy only takes a short amount of time to quickly assess whether the patient is occludable (180 degrees or more of grade 1 or less by the Shaffer system). In contrast, to perform anterior segment scanning using OCT you need to have the device, which can cost $50,000 or more. That makes OCT cost-prohibitive in poorer countries—and maybe even in a regular doctor's clinic. Gonioscopy also has the advantage of portability; it can be done anywhere a slit lamp is available. The instrumentation required for high-resolution imaging, of course, is far less portable.

Nevertheless, there are downsides to gonioscopy. It requires skill and experience on the part of the surgeon, and can't be done by a technician. The analysis of what is seen is subjective.

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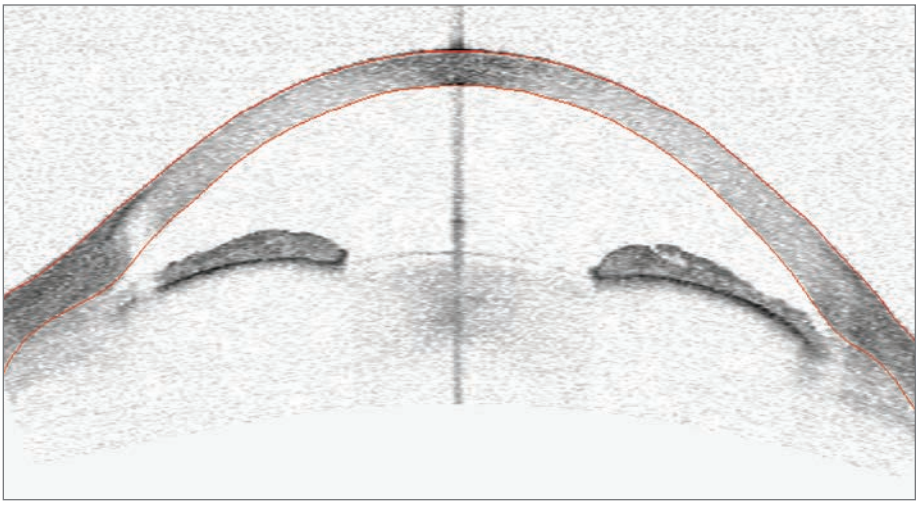
Many surgeons are simply not comfortable doing it, and it's also uncomfortable for the patient. These points may account for the findings of a 1996 study by Lars Hertzog, Paul Lee and others, which evaluated the charts of people with glaucoma seen in a large Los Angeles practice.[1] That study found that gonioscopy was only documented in patient records 50 percent of the time—a good indication that about half the time it wasn't being done.



Optical coherence tomography, ultrasound biometry and gonioscopy can each reveal things about the angle that cannot be detected using the other methods. Here, an eye judged to be occludable on gonioscopy shows narrow but open angles on OCT imaging. High lens vault and iris bowing make it difficult to see into the angle recess, resulting in the non-agreement with gonioscopy.

The fact that gonioscopy requires a skilled surgeon also makes it a less-than-ideal choice for mass screenings. Having a doctor perform gonioscopy on a large group of individuals is time-consuming and expensive, especially compared to having a technician and a machine do the screening. If individuals are screened using OCT, those with a potential problem can later be identified by someone looking over the digital scans.

Despite the downsides, I believe every patient deserves to have gonioscopy performed, especially if the patient has glaucoma. Gonioscopy can help the doctor distinguish whether the problem is angle-closure glaucoma or open-angle glaucoma. The exam might also pick up other types of glaucoma, such as pigmentary glaucoma or pseudoexfoliation glaucoma, and with some patients, it will help you rule out neovascularization in the angle. Gonioscopy provides many kinds of information that imaging can't.

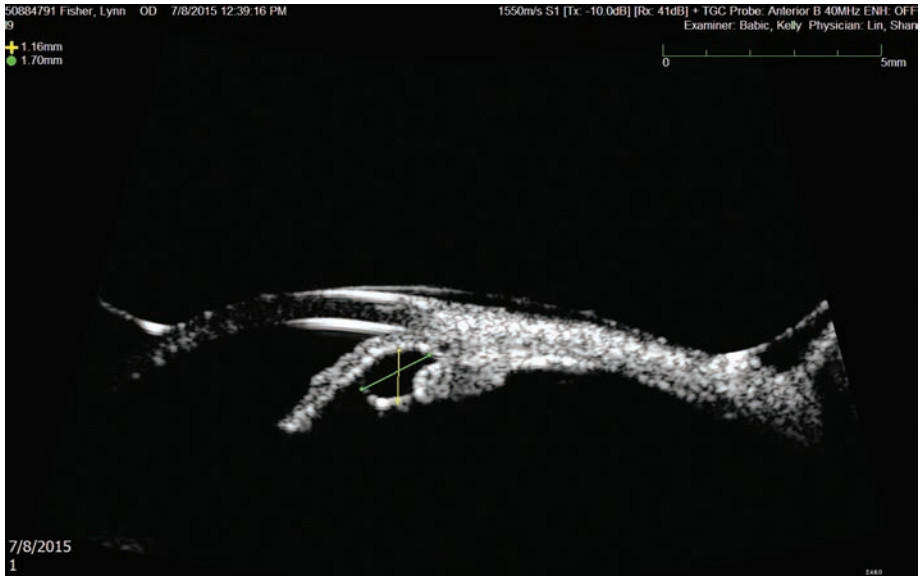
The Pros and Cons of Imaging

The best argument for imaging is that it's a true cross-section of the angle that allows you to do quantitative measures of the angle, after identification of the scleral spur. The software also automatically gives you measurements of the angle recess area and the angle-opening distance, measurements that describe how narrow or open the angle is. That's especially useful because cutoffs have been established regarding what constitutes an occludable angle that might require a laser iridotomy. Thus, imaging is quantitative in a way that gonioscopy is not.

Another argument in favor of using imaging to assess a narrow angle is that it's very reproducible, which has been demonstrated in many studies.[2] In contrast, gonioscopy is highly variable between different doctors—and even the same doctor can show some variability regarding whether the angle is grade 0, 1 or 2. Also, imaging can be performed by a technician. (And as the technology becomes more compact and portable over time, its use as a screening tool could become even easier and more common.)

One disadvantage of the kind of anterior segment imaging being done in the United States is that it only reveals one "slice" of the anterior segment at a time. While that is useful, it doesn't tell us everything we might need to know about the overall condition of the angle. This limitation may eventually disappear, however. There is now a device available outside the United States that can do 360-degree scanning of the angle: the Casia swept-source-1000 OCT from Tomey. This device quickly takes 128 scans as it rotates around the axis of the eye; then it constructs an accurate, measureable, three-dimensional model of the anterior segment. I've taken part in some studies using this device, but currently it's only available in the United States in a few locations on an experimental basis.

How much of an advantage is it to be able to scan the entire angle? Some of my colleagues in other countries are thrilled with this new technology. They say that getting a single cross-section of the angle is a little like getting a single cross-section through a tumor; it simply doesn't give you enough information, because the "slice" you see may not be representative of the rest of the tumor. The Casia will reveal areas of closure all the way around the angle. (However, as already noted, that still won't tell you whether the closed areas are complicated by PAS.)



An iris cyst is revealed by ultrasound biomicroscopy. Such a cyst might not be observed on clinical exam and cannot be delineated using anterior segment OCT.

Imaging with Ultrasound

The other type of imaging that's useful when assessing the angle is ultrasound biomicroscopy. UBM imaging can reveal some things that anterior segment OCT can't. For one thing, it can often help determine the mechanism of the glaucoma because it can penetrate through the iris and look at things behind it that may be causing the angle closure. It can be especially helpful when the problem is plateau iris, where the ciliary body is pressed up against the iris and pushing it forward. Anterior segment OCT can't capture that information because it can't penetrate through the iris. (Obviously, gonioscopy also can't reveal what's happening behind the iris.) This is important because plateau iris has been shown to be a major cause of angle-closure glaucoma; close to 20 percent of angle-closure glaucoma may be attributable to plateau iris.[3]

The major downside of UBM is the contact nature of it; it's more cumbersome because it requires touching the eye. It's true that the new UBM instruments are much less challenging for the patient than the old technology that used an eye cup filled with Goniosol jelly. But the probe still needs to touch the patient's eye and the procedure still requires the use of an anesthetic; and of course you have to have well-trained technicians, because there's a potential danger of scratching or injuring the cornea. In contrast, anterior segment OCT is noncontact and very quick.

Whether OCT or UBM provides better digital information is another question that remains unanswered.

Is One Approach Better?

As already noted, each of these methods for assessing the angle has benefits and drawbacks. Interestingly, they don't always agree in their assessment. Studies have found that the agreement between gonioscopy and imaging is fairly poor. From an overall statistical viewpoint they correlate reasonably well; that is, if the doctor performs gonioscopy and says a patient is at risk of angle closure, the imaging will often agree. But when you look at specifics such as the grading of the angle, the correlation is poor. (The explanation for this poor correlation seems to depend on which method you favor. For example, people who really believe that scanning the angle gives the best representation of its condition would say that gonioscopy is the source of the problem because it's so subjective.)

One issue that is always raised with any approach to assessment is sensitivity and specificity. When quantifying an angle and comparing the result to a benchmark, for example, we run the risk of missing eyes that really are in danger, or choosing to treat eyes that are not. Studies of this in OCT angle analysis are currently under way. But so far, no one has published a prospective study comparing the effectiveness of assessments made with gonioscopy versus imaging. Similarly, whether OCT or UBM provides better digital information is another question that remains unanswered. UBM gives you plenty of information, and it can provide quantitative measures. Whether those are more accurate or useful than the information provided by OCT may depend on the situation.

My Protocol

So, what does a glaucoma specialist with experience in this area do? I believe my protocol is similar to that of most glaucoma specialists. I begin by examining the patient and then performing gonioscopy. Once I suspect that a patient may have a

narrow angle, based on exam and gonioscopy, I do anterior segment OCT to confirm that diagnosis and decide whether the patient might meet the criteria for doing further treatment such as an iridotomy.

In most cases, I only resort to imaging with UBM if the patient still has a narrow angle after I've performed an iridotomy. That indicates a greater likelihood that the patient has plateau iris or another problem that only UBM would be able to detect, such as iris cysts. *(For example, see facing page.)* Many ophthalmologists think of iris cysts as being rare, but one study found that among younger angle-closure glaucoma patients, iris cysts were the number-two cause of angle-closure.[4] My experience has confirmed that. For example, UBM revealed iris cysts in one of my younger patients; because she had a family history of glaucoma, I asked the first-degree family members to come in. All of the family members scanned had iris cysts that were causing angle closure.

It's worth noting that not all ophthalmologists reserve UBM for special cases. Some of my colleagues in China don't bother with gonioscopy at all; if a patient appears to be narrow based on the examination, they go straight to UBM. Many of them don't have OCT because of the cost of the equipment. UBM is far less expensive.

Given the nature of gonioscopy and today's imaging technology, I believe it's important to have all of these options available. If you're comfortable performing gonioscopy, it's an excellent first option after examining a glaucoma patient or suspect. If you're not comfortable with it, anterior segment OCT will provide you with useful information; just bear in mind that it has limitations that may impact the accuracy of a diagnosis without additional information. REVIEW

Dr. Lin is a professor of clinical ophthalmology and director of glaucoma at the University of California, San Francisco. He has no financial interest in any of the products mentioned.

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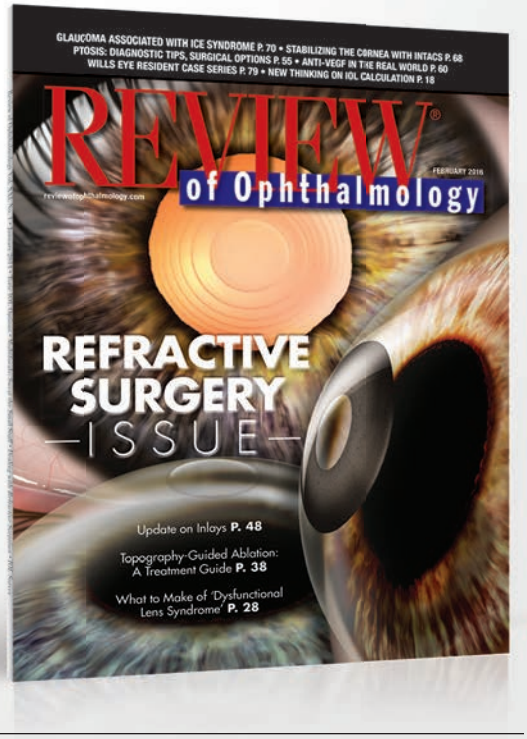

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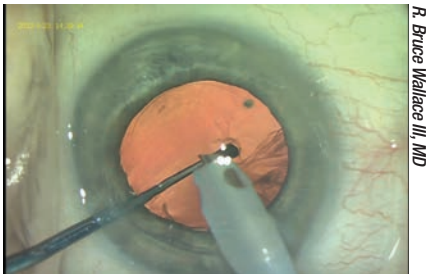
(continued from page 28)

with sutureless incisions is to make an incision that's as square as possible," he says. "When creating the incision, try to stay in stroma as long as possible. This usually creates what appears to be a square incision rather than a longitudinal incision. I also recommend using a 2.8-mm diamond knife, because I've found that you can direct a diamond knife more easily; it will stay in stroma longer. That allows for stronger incision closure after stromal hydration."

21. Stop and reevaluate if the capsule ruptures. "One of the most important things to do when you unintentionally rupture the capsule is to immediately stop the procedure," says Dr. Kershner. "Do not proceed until you have reassessed the situation and determined how to move forward in a safe way that will ensure a successful outcome. Make sure that you'll maintain the integrity of the remaining capsule while you remove vitreous and remaining lens material; then complete the procedure, and be sure to implant the IOL in a way that ensures it will remain stable. If you have any uncertainty about any of this, seek help immediately."

Dr. Wallace notes that a surgeon can take precautions to avoid posterior capsule tears. "I designed an instrument called the Wallace Guardian, made by Storz, in which I have no financial interest," he says. "It's a blunt chopper that can be used to manipulate the nucleus, but also is helpful for protecting the posterior capsule from the phaco energy. I place it posterior to the phaco tip when I'm almost done removing the nucleus; it acts as a barrier, making it very hard to engage the posterior capsule with the phaco tip."

22. Reposition the IOL if it ends up misplaced. "A misplaced IOL is one that is not centrally placed, is tilted or is more posterior or anterior than you expected," explains Dr. Kershner. "This problem is much more common than many would think. Surgeons often miss this diagnosis because they don't assess the actual intraocular location of the IOL after placement." (He notes that a misplaced IOL is not the same as a dislocated IOL, which is the result of preexisting or intraoperative trauma.)



R. Bruce Wallace III, MD

A tool such as the Wallace Guardian (Storz), designed to be a blunt chopper, can help protect the posterior capsule by keeping the phaco tip from contacting the capsule during phacoemulsification. The tool can be placed behind the phaco tip near the end of nucleus removal.

"Once this inadvertent outcome is determined, the only treatment is surgical repositioning of the IOL," he says. "The surgeon needs to externally fixate the IOL with transscleral suture fixation."

23. Look out for elevated intraocular pressure following surgery. "There are a variety of reasons IOP may go up following cataract surgery," notes Dr. Trattler. "A pressure rise can be caused by inflammation, lens particles that are liberated during the surgery or retained viscoelastic. The key to preventing a serious problem is prompt diagnosis. One option is to see patients the same day instead of waiting for them to come back the next day. I have many of my patients, especially those that live more than an hour away from our office, return the same day—anywhere from one or two hours postop to four or six hours. Fortunately, my surgery center and office are in the same building.

"If elevated eye pressure is a major issue," he adds, "additional steps can include providing pressure-lowering eye drops at the conclusion of cataract surgery. Also, certain viscoelastics can raise the pressure more than others, so switching to a viscoelastic that is less likely to raise IOP is an option to consider."

24. Be aware of the possibility of cystoid macular edema. As noted earlier, the best treatment for CME is prevention, starting with a careful preoperative retinal exam to detect retinal problems such as lattice degeneration, maculopathy, vitreoretinal degeneration, an epiretinal membrane or a retinal tear or hole. "The risk also goes up if your patient has vitreous loss during cataract surgery," notes Dr. Trattler. "If CME occurs despite your precautions, either restart or increase your anti-inflammatory therapy. Referring the patient to a retina specialist for further treatment may also be helpful."

25. If something does go wrong, admit it and be straightforward about it. "If you want to end up with a happy patient, you have to recognize when things don't go according to plan and immediately address it," notes Dr. Kershner. "If you can't figure out what happened, seek out someone else who can. A patient will not fault you if you make every effort to help him; but if you fail to recognize a problem, ignore the patient's complaints or fail to seek out the help the patient needs, it will come back to haunt you. No doctor is perfect and neither is any procedure. If you make that clear to the patient before surgery, you won't have any backpedaling to do." REVIEW

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One-Year Results from The TREX-AMD Trial

One-year study results from the treat-and-extend neovascular age-related macular degeneration (TREX-AMD) strategy resulted in visual and anatomic gains comparable with gains obtained with monthly dosing of intravitreal ranibizumab.

In this Phase IIIb multicenter, randomized clinical trial, 60 patients with treatment-naïve neovascular AMD and Early Treatment Diabetic Retinopathy Study best-corrected visual acuity from 20/32 to 20/500 (Snellen equivalent) were randomized 1:2 to receive intravitreal 0.5-mg ranibizumab monthly or treat-and-extend (TREX) management. The TREX patients were treated monthly for at least three doses, until resolution of clinical and spectral-domain optical coherence tomography evidence of exudative disease activity; the interval between visits then was individualized according to strict prospective protocol. Outcomes were measured via mean ETDRS BCVA change from baseline.

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

Ophthalmology 2015;122:2514-2522.

Wykoff C, Croft D, Brown D, Wang R.

Baseline VA and CRT After One Year of Anti-VEGF for DME

Comparisons of the relative effect of three anti-vascular endothelial growth factor drugs in treating diabetic macular edema suggests that for eyes with better initial visual acuity and thicker central subfield thickness, some VA outcomes may be worse in the bevacizumab group. Given small sample sizes and the exploratory nature of the analyses, the members of the Diabetic Retinopathy Clinical Research Network suggest caution is warranted when using data to guide treatment considerations for patients.

Researchers performed post hoc exploratory analyses of randomized trial data evaluating three anti-VEGF agents on 660 adults with diabetic macular edema and decreased VA (Snellen equivalent, approximately 20/32 to 20/320). The original study was conducted between August 2012 and August 2013. Treatment subgroups were based on baseline VA and CST as evaluated by OCT, with repeated 0.05 mL intravitreous injections of 2-mg aflibercept (224 eyes), 1.25 mg of bevaciumab (218 eyes) or 0.3 mg of ranibizumab (218 eyes) as needed per protocol. Outcomes were measured at one year within the prespecified subgroups based on both baseline VA and CST thresholds, defined as worse (20/50 or worse) or better (20/32 to 20/40) VA and thicker (≥400 µm) or thinner (250 to 399 µm) CST.

In the subgroup with the worse baseline VA (n=305), irrespective of baseline CST, aflibercept showed greater improvement than bevacizumab or ranibizumab for several VA outcomes. In the subgroup with better VA and thinner CST at baseline (61 to 73 eyes across three treatment groups), VA outcomes

(continued on page 81)



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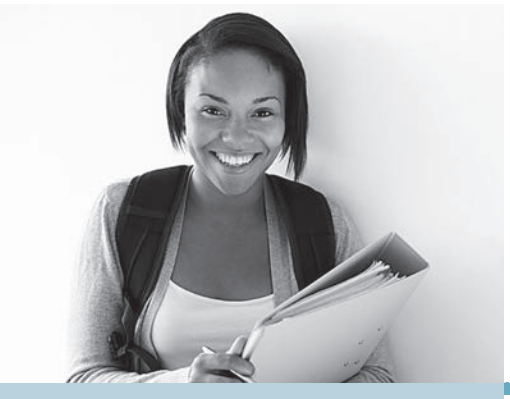

About Rick

Rick Bay served as the publisher of The *Review* Group since 1991.

To those who worked for him, he was a leader whose essence was based in a fierce and boundless loyalty.

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FDA Clearance for Oculus Pentacam AXL

The new Oculus Pentacam AXL has received 510(k) clearance from the Food and Drug Administration. Oculus says the Pentacam AXL represents the systematic further development of the successful and time-proven Pentacam HR, providing anterior segment tomography and optical biometry—all in one device and with a single measuring operation.

The intuitive and network-compatible IOL calculation software offers standard formulas, ray-tracing formulas and formulas for treated corneas already integrated into the IOL calculator. The calculation of toric intraocular lenses is based on the total corneal refractive power, thus taking the influence of the posterior corneal surface into account. A comprehensive IOL database with IOL constants for the Pentacam AXL is also integrated.

Also the Pentacam AXL offers a well-targeted screening process, Fast Screening Report, Belin/Ambrósio Enhanced Ectasia Display (early detection of corneal ectasia) and densitometric evaluation (Corneal Optical Densitometry & PNS) for every cataract patient. Whether aspherical, toric or multifocal, with the Cataract Pre-OP display, the premium IOL can be selected in four steps.

The IOL Constants Optimization from Prof. Wolfgang Haigis permits a continuous enhancement of the results. Surgical data and post-refractive examination findings are secured with just a few clicks. For information, visit pentacamaxl.com.

Eye Eco Dry-Eye Mask

If your meibomian gland dysfunction dry-eye patients have trouble complying with home remedies such as warm washcloths, Eye Eco may have a solution.

The company has developed the Dry Eye Relief Mask, or DERM, a compress mask that can be used to apply moist heat or cold to help relieve symptoms. To use the DERM to apply heat, the patient heats the mask in the microwave for 20 seconds to provide four to six minutes of moist-heat treatment. The company says the treatment time can be extended by three minutes by placing a moistened cotton liner over the mask before heating. Once applied, the mask helps melt the meibum in the glands while hydrating and relaxing the skin of the lids. Eye Eco notes that the use of liners also means that doctors can use the DERM in their offices to complement their in-office dry-eye treatments. For information, call 1 (888) 730-7999 or visit eyeeco.com.

Eye Check Adds Oculoplastics

For the oculoplastics surgeon who wants a more efficient way to make preop measurements in the exam room, the oculoplastics module add-on to the Volk Eye Check device may be useful.

The Eye Check is a handheld digital imager that records external ocular measurements to speed record keeping and diagnosis, and now it can take measurements germane to the world of oculoplastics, as well. The module can analyze 26 data points in under a minute, including margin reflex distance 1 and 2, the palpebral aperture, the aperture at the limbus, pupil diameter and eccentricity and iris diameter.

The company says a grid scale provides a convenient way to measure and compare landmarks such as brow

This article has no commercial sponsorship.

position, and says the touch-screen interface is easy to navigate. It adds that objective documentation of such characteristics is useful for securing insurance reimbursement, as well as providing "before and after" evidence for patients and clinicians. The device's real-time, accurate, objective results eliminate interclinician variability and enable quick decision making, Volk says. When an exam is complete, the system can generate a single-page report on the patient which includes a side-by-side diagram and a list of measured values. The report can also be exported over a Wi-Fi connection to attach it to a medical record. For information, call 1 (800) 345-8655 or visit volk.com.

Rhein's New Incision Dissector

Rhein Medical announces the new Friedman Double-Ended Femto Incision Dissector, developed in coordination with Neil Friedman, MD.

The dissector has:

- an angled, tapered end that is thin, with a smooth tip to enable easy and gentle dissection of all corneal incisions without the risk of creating false planes or damaging intact tissue. It is used vertically to open plane one of corneal incisions and then used horizontally to open planes two and three of incisions.
- a 90-degree paddle end, designed to accurately find and gently open plane two of clear corneal cataract incisions by placing the paddle parallel to the incision plane one (i.e., hold the handle of instrument vertically so paddle is parallel to incision), pushing the paddle down into the incision to the base of plane one and then rotating the paddle 90 degrees into plane two of the incision by twirling the handle of the instrument between the fingers. It can also be used vertically to open plane one of corneal incisions. For information, contact Rhein Medical at (727) 209-2244.

Study Supports NovaTears for Evaporative Dry Eye

NovaTears, the first commercially available topical eye drop from Novaliq GmbH for the treatment of evaporative dry-eye disease, was found to significantly improve four of five measures associated with evaporative DED, new research shows. The findings were published recently in the *Journal of Ocular Pharmacology and Therapeutics*.

Thirty patients with evaporative DED received NovaTears (perfluorohexyloctane F6H8) during a prospective, multicenter, observational, six-week study. Subjects applied one drop of NovaTears to both eyes four times daily and returned six weeks later for follow-up. Parameters assessed included best-corrected visual acuity, intraocular pressure, Schirmer I test, tear fluid, tear-film breakup time, corneal staining, meibum secretion and OSDI. Twenty-five subjects completed the study per protocol, of which 24 were female, and one was male. After six weeks of use, NovaTears treatment led to a significant reduction of corneal staining, and a significant increase of Schirmer I and TFBUT. In addition, OSDI score dropped significantly from a mean of 55 (±23) to 34 (±22.4). Visual acuity and IOP did not change.

The significant decrease in corneal staining can be seen in the shift of the number of patients diagnosed with Grade 1 or Grade 2 at baseline toward Grade 0 at follow up. At baseline, 11 eyes were Grade 0, 29 were Grade 1, and eight were Grade 2. At the end of the study, 37 eyes were Grade 0, 10 were Grade 1, and one eye was Grade 2. Tear secretion and tear-film stability improved significantly over the study period as can be seen in the increase in Schirmer I and the TFBUT. Schirmer I test showed increases from 10.5 ±4.1 mm/five minutes in the right eye to 16.6 ±9.8 mm/five minutes (p=0.0040), and in the left eye from 10.2 ±4.2 mm/five minutes to 15.9 ±9.7 mm/five minutes (p=0.0013). TFBUT increased from 6.0 ±2.5s in the right eye to 8.8 ±4.9s (p=0.0026), and in the left eye from 5.8 ±2.6s to 9.6 ±5.9s (p=0.0006).

Patient meibum was examined at both baseline and follow up visit, and improved in some cases. In seven cases, no expressible meibum was reported at study conclusion. Overall safety and tolerability was good; five adverse events were reported in the study, all of mild to moderate intensity. The study was supported by Novaliq GmbH.To view the study: https://www.researchgate.net/publication/281167218_Semi-fluorinated_Alkane_Eye_Drops_for_Treatment_of _Dry_Eye_DiseaseA_Prospective_Multicenter_Non-interventional_Study.

For information, visit novaliq.com, or call (813) 323-1438. REVIEW

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Equipment and Supplies

A middle-aged woman seeks a LASIK consult, but unilateral disc edema leads the examination on a new course.

Brett M. Weinstock, MD, and Jerry Shields, MD

Presentation

A 44-year-old woman with a medical history of depression and ocular history of mild myopia presented for LASIK evaluation. Her best-corrected visual acuity was 20/20 in both eyes, but examination revealed a swollen optic disc in the left eye. LASIK surgery was deferred and she was referred for evaluation of the unilateral optic nerve head swelling. She recalled minor head trauma three months earlier. Systemic review of symptoms was negative except for a subjective sensation of tingling of left side of her head and earlobe. She denied pain and decreased vision.

Medical History

The patient had a history of depression and mild myopia. As mentioned above, she did note a minor trauma to her head three months earlier for which she did not receive any treatment. She denied any history of vision loss, eye pain or systemic neurologic symptoms (weakness, numbness, paralysis). She smoked one pack of cigarettes per day for 30 years, described minor social alcohol use and no other drug use. Medications included only Escitalopram (Lexapro) 10 mg daily. She had no family history of systemic problems.

Examination

Examination showed a best corrected visual acuity of 20/20 in each eye. Pupil examination noted 1 mm of anisocoria that was the same in light and dark with no afferent pupillary defect. Applanation intraocular pressures were 18 mmHg and 15 mmHg. She had full ocular motility, full confrontational fields and color plate testing was full. Hertel measurements were 15 mm OD and 16 mm OS with a base of 105 mm. She denied red desaturation. Anterior segment examination revealed normal findings. Fundus examination of the right eye revealed 1+ hyperemia without disc elevation. The left eye was noted to have 3+ disc elevation and 3+ hyperemia without visible drusen, but both eyes were otherwise within normal limits *(See Figure 1)*. Her blood pressure was 122/66.

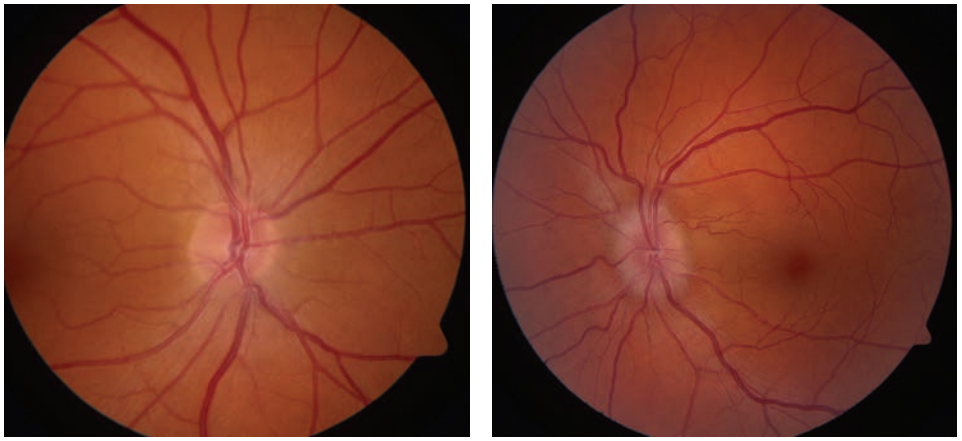

Figure 1. The right eye showed 1+ hyperemia without disc elevation. The left eye was noted to have 3+ disc elevation and 3+ hyperemia without visible drusen. Both eyes were otherwise within normal limits.

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

Diagnosis, Workup and Treatment

A broad differential diagnosis can be generated for unilateral optic disc edema. Common diagnoses can be broadly categorized as traumatic, demyelinating/autoimmune (multiple sclerosis, neuromyelitis optica, lupus erythematosis, thyroid eye disease), infectious conditions (tuberculosis, lyme disease, syphilis, herpetic, bartonella), infiltrative/inflammatory (neoplasm, sarcoidosis, drusen), congestive (asymmetric pseudotumor, orbital pseudotumor/cellulitis) or vascular (diabetic papillopathy, giant cell arteritis, nonarteritic anterior ischemic optic neuropathy).

B-scan ultrasonography revealed no optic disc drusen. Humphrey visual field testing showed peripheral relative and absolute scotomas *(See Figure 2)*.

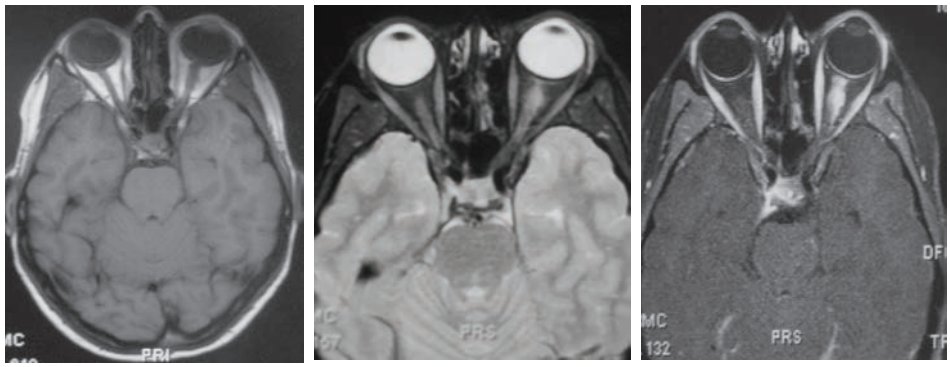

Figure 3. After gadolinium, there was significant enhancement of the left optic nerve. Cavernous sinus and pituitary was unremarkable.

The patient was sent for MRI. Initial magnetic resonance imaging of the brain demonstrated a left optic nerve with diffusely increased diameter, with a mildly infiltrative appearance of the intraconal and retro-orbital fat without extraocular muscle enlargement. Mild proptosis was also noted. After gadolinium, there was significant enhancement of the left optic nerve as seen above. The remainder of the scan including cavernous sinus and pituitary was unremarkable. *(See Figure 3)*.

Based on her clinical findings, her differential diagnosis was narrowed to optic nerve meningioma, optic nerve drusen, resolving optic neuritis or an optic nerve glioma. Her imaging was thought to be most consistent with an optic nerve sheath meningioma involving the orbital portion without extension into the canal. She was seen again six weeks after initial evaluation and the findings were unchanged. Given the stability of her examination, visual fields, her good vision and lack of color abnormalities, it was recommended that she have no active treatment. She was referred for consultation with neurosurgery, and advised to return if she noticed any change in vision. Serial MRI images have shown stability of the optic nerve meningioma and the patient has remained asymptomatic.

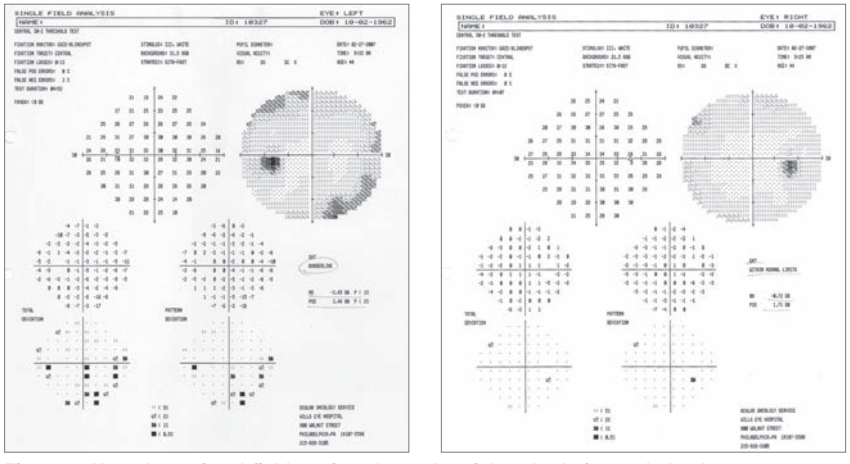

Figure 2. Humphrey visual field testing showed peripheral relative and absolute scotomas.

Discussion

Optic nerve sheath meningiomas are benign neoplasms of the optic nerve sheath.[1] In contrast to the intracranial portion of the optic nerve, the intracanalicular and intraorbital optic nerve segments are surrounded by all three layers of meninges (dura, arachnoid and pia mater). The subarachnoid and subdural spaces created by these sheathes are continuous with the brain. The central retinal artery runs along the optic nerve and pierces this dural sheath approximately 1.25 cm behind the globe.

Meningiomas represent 20 to 30 percent of primary brain tumors of which optic nerve sheath meningiomas represent 1 to 2 percent.[2] The optic nerve sheath meninges are composed of meningothelial cells, which are the cells responsible for neoplastic transformation. Pathologically the tumors have many variable and mixed subtypes, with the meningothelial variant

characterized by classic whorls of syncytial cells with indistinct cell membranes and typically show positive immunoreactivity for vimentin and may contain psammoma bodies.[2] Malignant transformation is exceedingly rare. For unknown reasons, there is a higher incidence of optic nerve sheath meningiomas in middle-aged women. While these meningiomas are usually slow growing, they may rapidly increase in size during pregnancy, so increased testing in this period is encouraged. There is also an association with neurofibromatosis type 2.[2,3] Rarely, these neoplasms can occur in children.

The tumor typically tracks along the optic nerve sheath and can grow to surround and compress the optic nerve, central retinal artery or the central retinal vein.[3,4] Vision loss is usually caused by a compressive optic neuropathy, but patients may live without symptoms for decades. The mass can also grow back towards the chiasm and cause contralateral field deficits.[4]

Clinical signs and symptoms include painless monocular vision loss, optic atrophy and opticociliary shunt vessels.[3,5] Axial proptosis, optic disc edema, color vision abnormalities and extraocular muscle movement abnormalities may also be noted.[5] Unlike many other brain tumors, associated mortality is very low.[6]

Imaging studies classically show an enlarged optic nerve complex that can either be round or fusiform. There is also often enhancement of the arachnoid and a negative shadow of the optic nerve.[3,6,7] Calcification around the optic nerve is also noted in 20 to 50 percent of cases.[4]

Management depends on symptoms and progression. In asymptomatic patients, observation with exams every six to 12 months including vision, pupils, color vision, visual fields as well as periodic MRI imaging is indicated.[1,3,8,9] With quality imaging, biopsy is rarely indicated. Many patients do have progressive visual loss over time, but there are currently no tests available that can predict the aggressiveness of these benign neoplasms. If there is progression of a patient's symptoms, the optic nerve can be approached with radiotherapy or gamma knife surgery. Historically, surgical removal is rarely indicated, except for very advanced cases with a blind eye. REVIEW

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(continued from page 72)

showed little difference between groups; mean change was +7.2, +8.4 and +7.6 letters in the aflibercept, bevacizumab and ranibizumab groups, respectively. However, in the subgroup with better VA and thicker CST at baseline (31 to 42 eyes), there was a suggestion of worse VA outcomes in the bevacizumab group; mean change from baseline to one year was +9.5 letters for the aflibercept group, +5.4 letters for the bevacizumab group and +9.5 letters for the ranibizumab groups, and the VA letter score was greater than 84 (approximately 20/20) in 21 of 33 aflibercept eyes (64 percent), seven of 31 bevacizumab eyes (23 percent), and 21 of 43 ranibizumab eyes (49 percent). The adjusted differences and 95 percent confidence intervals were 39 percent (17 to 60 percent) for aflibercept vs. bevacizumab, 25 percent (5 to 46 percent) for ranibizumab vs. bevacizumab and 13 percent (-8 to 35 percent) for aflibercept vs. ranibizumab.

JAMA Ophthalmol 2016;134:2:127-134.
Wells J, Glassman A, Jampol L, Aiello L, Antoszyk A, et al.

A Cochrane Systematic Review of Avastin vs. Lucentis for Treatment of Neovascular AMD

Using results from a Cochrane Eyes and Vision Group systematic review, researchers found no important differences in effectiveness or safety between bevacizumab (Avastin) and ranibizumab (Lucentis) for neovascular age-related macular degeneration treatment, but did find a large difference in cost.

Utilizing Cochrane methods for trial selection, data extraction and data analyses, researchers included only randomized controlled trials in which the two anti-vascular endothelial growth factor agents had been compared directly; six eligible trials with 2,809 participants were identified. The primary outcome was one-year gain in best-corrected visual acuity of ≥15 letters.

The proportion of eyes that gained ≥15 letters of BCVA by one year was similar for the two agents when the same regimens were compared (risk ratio: 0.90; 95 percent confidence interval, 0.73 to 1.11). The mean change in BCVA from baseline also was similar (mean difference: -0.5 letter; 95 percent CI, -1.6 to +0.6). Other BCVA and quality of life outcomes were similar for the two agents. One-year treatment cost with ranibizumab was 5.1 and 25.5 times the cost of bevacizumab in the two largest trials. Ocular adverse events were uncommon (<1 percent), and rates were similar for the two agents.

Ophthalmology 2016;123:70-77.
Solomon S, Lindsley K, Krzystolik M, Vedula S, et al.

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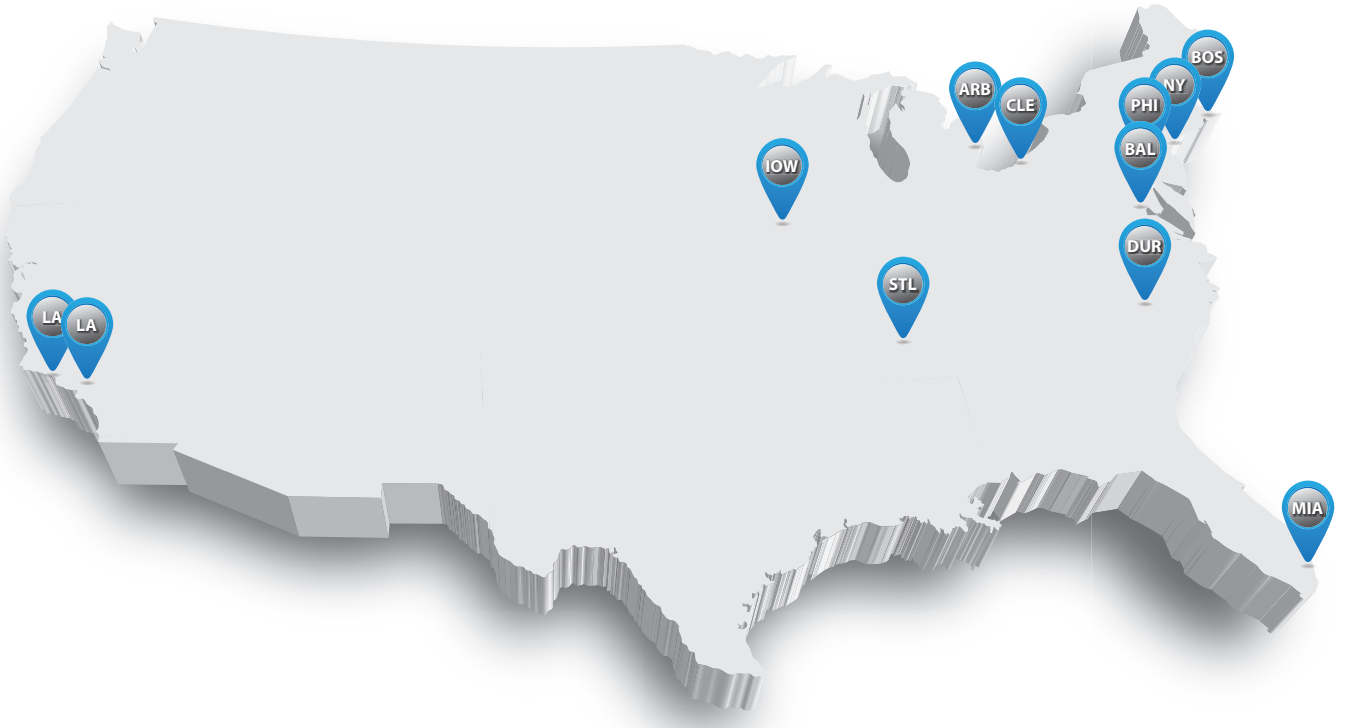

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