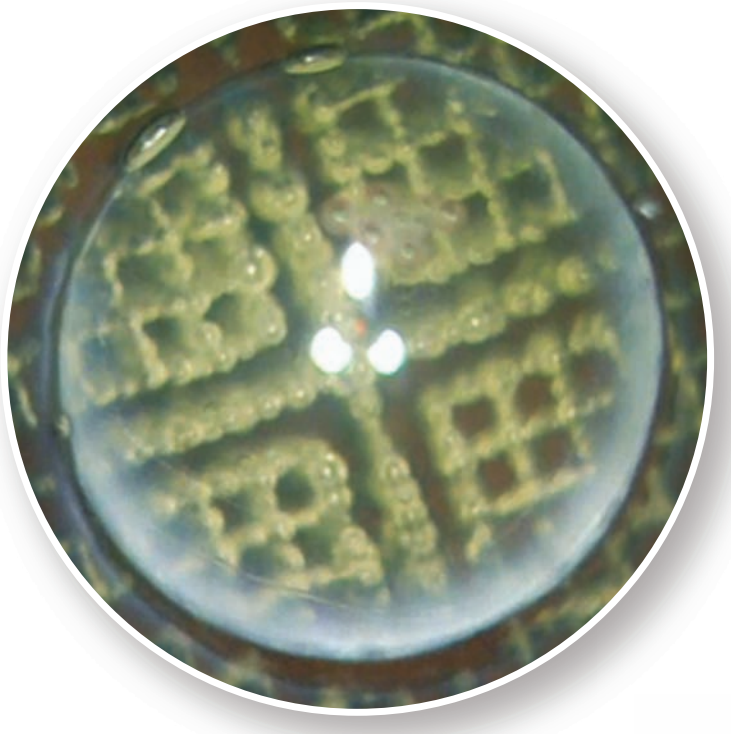
REVIEW® of Ophthalmology

July 2014 • revophth.com

Managing FEMTO CATARACT Complications

P. 26

Innovative Technologies. Excellent Outcomes.



Experience Laser Cataract Surgery with the **CATALYS**® Precision Laser System

Visit **www.amo-inc.com** or call **877-AMO-4-LIFE**

IMPORTANT SAFETY INFORMATION

INDICATION The CATALYS® Precision Laser System is indicated for use in patients undergoing cataract surgery for removal of the crystalline lens. Intended uses in cataract surgery include anterior capsulotomy, phacofragmentation, and the creation of single plane and multi-plane arc cuts/incisions in the cornea, each of which may be performed either individually or consecutively during the same procedure. **CONTRAINDICATIONS** Patients with corneal ring and/or inlay implants, severe corneal opacities, corneal abnormalities, significant corneal edema or diminished aqueous clarity that obscures OCT imaging of the anterior lens capsule, patients younger than 22 years of age, descemetocele with impending corneal rupture, and any contraindications to cataract surgery. **ADVERSE EFFECTS** Complications associated with the CATALYS® System include mild Petechiae and subconjunctival hemorrhage due to vacuum pressure of the LIQUID OPTICS Interface suction ring. Potential complications and adverse events include those generally associated with the performance of capsulotomy and lens fragmentation, or creation of a partial-thickness or full-thickness cut or incision of the cornea. **CAUTION** Federal law (USA) restricts this device to sale by or on the order of a physician. The system should be used only by qualified physicians who have extensive knowledge of the use of this device and who have been trained and certified in its use.

CATALYS® Precision Laser System

Abbott Medical Optics

Clinical image courtesy of Jason Jones, MD.

REVIEW NEWS
Volume XXI • No. 7 • July 2014

Projections Grim for Costs and Prevalence of Visual Problems

As the U.S. population ages, the number of Americans with eye disease and vision problems will continue to spiral upward. A new report released by Prevent Blindness, "The Future of Vision: Forecasting the Prevalence and Costs of Vision Problems," predicts more than $384 billion in 2032 and $717 billion in 2050 in nominal costs related to eye disease and vision problems.

Statistics from the report, commissioned from researchers at the University of Chicago, point to some alarming projections, including:

- Costs related to eye disease, including government, insurance and patient costs, are projected to increase 376 percent by 2050.
- Hispanics are projected to exhibit extremely high growth in diabetic retinopathy, glaucoma and cataract cases.
- As the baby-boomer generation ages into the Medicare program, costs will further shift from patients and private insurance to government. By 2050, government will pay more than 41 percent of costs, while patients will pay 44 percent, and private insurers, 16 percent.
- Women will continue to outnumber men in prevalence of all eye disease and vision loss categories except for diabetic retinopathy.
- Those aged 90 and older project to be by far the fastest growing population segment. This will have a significant effect on those living with eye disease, as many of these conditions are age-related.

The estimated average age of AMD patients is 80 years old, the oldest of any of the included eye diseases. Diabetic retinopathy patients have an average age of 66 years, the youngest of any of the included eye diseases.

"We cannot stand by and passively accept vision loss as an inevitable condition of growing old," said Hugh R. Parry, president and CEO of Prevent Blindness. "The sheer numbers of those who are and will be personally and financially impacted by vision impairment and blindness is far too great to ignore. The time to plan and develop a national strategy for saving sight is now."

For more information, visit preventblindness.org.

Study Uncovers The Brain's Role in Glaucoma

Findings from a new study published in *Translational Vision Science & Technology* show the brain, not the eye, controls the cellular process that leads to glaucoma. The results may help develop treatments for glaucoma and contribute to the development of future therapies for preserving brain function in other age-related disorders like Alzheimer's.

The researchers performed a data and symmetry analysis of 47 patients with moderate to severe glaucoma in both eyes. In glaucoma, the loss of vision in each eye appears to be haphazard. Conversely, neural damage within the brain caused by strokes or tumors produces visual field loss that is almost identical for each eye, supporting the idea that the entire degenerative process in glaucoma must occur at random in the individual eye—without brain involvement.

However, the team's analysis revealed that as previously disabled optic nerve axons—that can lead to vision loss—recover, the remaining areas of permanent visual loss in one eye coincide with the areas that can still see in the other eye. The team found that the visual field of the two eyes fit together like a jigsaw puzzle, resulting in much better vision with both eyes open than could possibly arise by chance.

"As age and other insults to ocular health take their toll on each eye, discrete bundles of the small axons within the larger optic nerve are sacrificed so the rest of the axons can continue to carry sight information to the brain," said author William Eric Sponsel, MD, of the University of Texas at San Antonio, Department of Biomedical Engineering. "This quite intentional sacrifice of some wires to save the rest, when there are decreasing resources to support them all (called apoptosis), is analogous to pruning some of the limbs on a stressed fruit tree so the other branches can continue to bear healthy fruit."

The researchers say the cellular process used for pruning small optic nerve axons in glaucoma is "remarkably similar to the apoptotic mechanism that operates in the brains of people afflicted with Alzheimer's disease."

"The extent and statistical strength

of the jigsaw effect in conserving the binocular visual field among the clinical population turned out to be remarkably strong," said Dr. Sponsel. "The entire phenomenon appears to be under the meticulous control of the brain."

The TVST paper is the first evidence in humans that the brain plays a part in pruning optic nerve axon cells. In a previous study, a mouse model suggested the possibility that following injury to the optic nerve cells in the eye, the brain controlled a pruning of those cells at its end of the nerve. This ultimately caused the injured cells to die.

"Our basic science work has demonstrated that axons undergo functional deficits in transport at central brain sites well before any structural loss of axons," said David J. Calkins, PhD, of the Vanderbilt Eye Institute and author of the previous study. "Indeed, we found no evidence of actual pruning of axon synapses until much, much later. Similarly, projection neurons in the brain persisted much longer, as well.

"This is consistent with the partial recovery of more diffuse overlapping visual field defects observed by Dr. Sponsel that helped unmask the more permanent interlocking jigsaw patterns once the eyes of his severely affected patients had been surgically stabilized," said Dr. Calkins.

Dr. Sponsel has already seen how these findings have positively affected surgically stabilized patients who were previously worried about going blind. "When shown the complementarity of their isolated right and left eye visual fields, they become far less perplexed and more reassured," he said. "It would be relatively straightforward to modify existing equipment to allow for the performance of simultaneous binocular visual fields in addition to standard right eye and left eye testing."

The authors suggest their findings can assist in future research with cellular processes similar to the one used for pruning small optic nerve axons in glaucoma, such as occurs in the brains of individuals affected by Alzheimer's.

From Stem Cells, Light-Sensitive Photoreceptors

Using a type of human stem cell, Johns Hopkins researchers say they have created a three-dimensional complement of human retinal tissue in the laboratory, which notably includes functioning photoreceptor cells capable of responding to light.

"We have basically created a miniature human retina in a dish that not only has the architectural organization of the retina but also has the ability to sense light," said study leader M. Valeria Canto-Soler, PhD, an assistant professor of ophthalmology at the Johns Hopkins University School of Medicine. She said the work, reported online June 10 in *Nature Communications*, "advances opportunities for vision-saving research and may ultimately lead to technologies that restore vision in people with retinal diseases."

Dr. Canto-Soler cautions that photoreceptors are only part of the story in the complex eye-brain process of vision, and her lab hasn't yet recreated all of the functions of the human eye and its links to the visual cortex of the brain. "Is our lab retina capable of producing a visual signal that the brain can interpret into an image? Probably not, but this is a good start," she said.

The achievement emerged from experiments with human induced pluripotent stem cells and could eventually enable genetically engineered retinal cell transplants that halt or even reverse a patient's march toward blindness, the researchers say. They turned iPS cells into retinal progenitor cells destined to form light-sensitive retinal tissue. Using a simple, straightforward

Sensor in Eye Could Track Intraocular Pressure

University of Washington engineers have designed a low-power sensor that could be placed permanently in a person's eye to track changes in eye pressure. The sensor would be embedded with an artificial lens during cataract surgery and would detect pressure changes instantaneously, then transmit the data wirelessly using radio frequency waves.

"No one has ever put electronics inside the lens of the eye, so this is a little more radical," said Karl Böhringer, PhD, a UW professor of electrical engineering and of bioengineering. "We have shown this is possible in principle. If you can fit this sensor device into an intraocular lens implant during cataract surgery, it won't require any further surgery for patients."

The research team wanted to find an easy way to measure eye pressure for management of glaucoma. "The implementation of the monitoring device has to be well-suited clinically and must be designed to be simple and reliable," said Tueng Shen, MD, PhD, a collaborator and UW professor of ophthalmology. "We want every surgeon who does cataract surgeries to be able to use this." The UW engineering team built a prototype that uses radio frequency for wireless power and data transfer. A thin, circular antenna spans the perimeter of the device—roughly tracing a person's iris—and harnesses enough energy from the surrounding field to power a small pressure sensor chip. The chip communicates with a close-by receiver about any shifts in frequency, which signify a change in pressure. Actual pressure is then calculated and those changes are tracked and recorded in real-time.

The team is working on downscaling the prototype to be tested in an actual artificial lens. Designing a final product that's affordable for patients is the ultimate goal, researchers said. "I think if the cost is reasonable and if the new device offers information that's not measureable by current technology, patients and surgeons would be really eager to adopt it," Dr. Shen said.

The researchers published their results in the *Journal of Micromechanics and Microengineering.*

technique they developed to foster the growth of the retinal progenitors, Dr. Canto-Soler and her team saw retinal cells and then tissue grow in their petri dishes. The growth corresponded in timing and duration to retinal development in a human fetus in the womb. Moreover, the photoreceptors were mature enough to develop outer segments, a structure essential for photoreceptors to function.

The lab-grown retinas recreate the three-dimensional architecture of the human retina. "We knew that a 3-D cellular structure was necessary if we wanted to reproduce functional characteristics of the retina," said Dr. Canto-Soler, "but when we began this work, we didn't think stem cells would be able to build up a retina almost on their own. In our system, somehow the cells knew what to do."

When the retinal tissue was at a stage equivalent to 28 weeks of development in the womb, with fairly mature photoreceptors, the researchers tested these mini-retinas to see if the photoreceptors could in fact sense and transform light into visual signals.

They did so by placing an electrode into a single photoreceptor cell and then giving a pulse of light to the cell, which reacted in a biochemical pattern similar to the behavior of photoreceptors in people exposed to light.

Dr. Canto-Soler said the new system gives them the ability to generate hundreds of mini-retinas at a time directly from a person affected by a particular retinal disease such as retinitis pigmentosa. This provides a unique biological system to study the cause of retinal diseases directly in human tissue, instead of relying on animal models.

The system opens an array of possibilities for personalized medicine such as testing drugs to treat these diseases in a patient-specific way. In the long term, the potential is also there to replace diseased or dead retinal tissue with lab-grown material to restore vision. REVIEW

REVIEW Editorial Board

Contributors

CHIEF MEDICAL EDITOR
Mark H. Blecher, MD

BOTTOM LINE
Dennis D. Sheppard, MD

CONTACT LENSES
Penny Asbell, MD

CORNEA / ANTERIOR SEGMENT
Thomas John, MD

GLAUCOMA MANAGEMENT
Peter Netland, MD, PHD
Kuldev Singh, MD

PEDIATRIC PATIENT
Christopher M. Fecarotta, MD

PLASTIC POINTERS
Ann P. Murchison, MD, MPH

REFRACTIVE SURGERY
Arturo S. Chayet, MD

RETINAL INSIDER
Carl Regillo, MD, FACS
Emmett T. Cunningham Jr., MD, PHD, MPH

TECHNOLOGY UPDATE
Steven T. Charles, MD
Michael Colvard, MD

THERAPEUTIC TOPICS
Mark Abelson, MD

WILLS RESIDENT CASE SERIES
David Perlmutter, MD

Advisory Board

PENNY A. ASBELL, MD, NEW YORK CITY
WILLIAM I. BOND, MD, PEKIN, ILL.
ALAN N. CARLSON, MD, DURHAM, N.C.
Y. RALPH CHU, MD, EDINA, MINN.
ADAM J. COHEN, MD, DOWNERS GROVE, ILL.
UDAY DEVGAN, MD, FACS, LOS ANGELES
ERIC DONNENFELD, MD, ROCKVILLE CENTRE, N.Y.
DANIEL S. DURRIE, MD, KANSAS CITY, MO.
ROBERT EPSTEIN, MD, MCHENRY, ILL.
ROBERT D. FECHTNER, MD, NEWARK, N.J.
WILLIAM J. FISHKIND, MD, TUCSON, ARIZ.
JAMES P. GILLS, MD, TARPON SPRINGS, FLA.
HARRY GRABOW, MD, SARASOTA, FLA.
DOUGLAS K. GRAYSON, MD, NEW YORK CITY
R. BRUCE GRENE, MD, WICHITA, KAN.
THOMAS S. HARBIN, MD, MBA, ATLANTA
DAVID R. HARDTEN, MD, MINNEAPOLIS
KENNETH J. HOFFER, MD, SANTA MONICA, CALIF.
JACK T. HOLLADAY, MD, MSEE, HOUSTON
JOHN D. HUNKELER, MD, KANSAS CITY, MO.
THOMAS JOHN, MD, TINLEY PARK, ILL.
ROBERT M. KERSHNER, MD, MS, FACS, BOSTON
GUY M. KEZIRIAN, MD, PARADISE VALLEY, ARIZ.
TERRY KIM, MD, DURHAM, N.C.
TOMMY KORN, MD, SAN DIEGO
DAVID A. LEE, MD, HOUSTON
FRANCIS S. MAH, MD, PITTSBURGH
NICK MAMALIS, MD, SALT LAKE CITY
WILLIAM G. MARTIN, MD, OREGON, OHIO
MIKE S. MCFARLAND, MD, PINE BLUFF, ARK.
JEFFREY B. MORRIS, MD, MPH, ENCINITAS, CALIF.
MARLENE R. MOSTER, MD, PHILADELPHIA
ROBERT J. NOECKER, MD, FAIRFIELD, CONN.
ROBERT OSHER, MD, CINCINNATI
MARK PACKER, MD, EUGENE, ORE.
STEPHEN PASCUCCI, MD, BONITA SPRINGS, FLA.
PAUL PENDER, MD, BEDFORD, N.H.
CHRISTOPHER J. RAPUANO, MD, PHILADELPHIA
AUGUST READER III, MD, SAN FRANCISCO
TONY REALINI, MD, MORGANTOWN, W.V.
KENNETH J. ROSENTHAL, MD, GREAT NECK, N.Y.
ERIC ROTHCHILD, MD, DELRAY BEACH, FLA.
SHERI ROWEN, MD, BALTIMORE
JAMES J. SALZ, MD, LOS ANGELES
INGRID U. SCOTT, MD, MPH, HERSHEY, PA.
JOEL SCHUMAN, MD, PITTSBURGH
GAURAV SHAH, MD, ST. LOUIS
DAVID R. STAGER JR., MD, DALLAS
KARL STONECIPHER, MD, GREENSBORO, N.C.
JAMES C. TSAI, MD, NEW HAVEN, CONN.
VANCE THOMPSON, MD, SIOUX FALLS, S.D.
FARRELL C. TYSON, MD, CAPE CORAL, FLA.
R. BRUCE WALLACE III, MD, ALEXANDRIA, LA.
ROBERT G. WILEY, MD, CLEVELAND
FRANK WEINSTOCK, MD, CANTON, OHIO
JACQUELINE M.S. WINTERKORN, MD, PHD, NEW YORK CITY

Jobson Professional Publications Group

BUSINESS OFFICES
11 CAMPUS BOULEVARD, SUITE 100
NEWTOWN SQUARE, PA 19073
SUBSCRIPTION INQUIRIES (877) 529-1746
(USA ONLY); OUTSIDE USA, CALL (847) 763-9630

BUSINESS STAFF
SALES MANAGER, NORTHEAST,
MID ATLANTIC, OHIO
JAMES HENNE
(610) 492-1017 JHENNE@JOBSON.COM

SALES MANAGER, SOUTHEAST, WEST
MICHELE BARRETT
(610) 492-1014 MBARRETT@JOBSON.COM

CLASSIFIED ADVERTISING
(888)-498-1460

VICE PRESIDENT OF OPERATIONS
CASEY FOSTER
(610) 492-1007 CFOSTER@JOBSON.COM

PRODUCTION MANAGER
SCOTT TOBIN
(610) 492-1011 STOBIN@JOBSON.COM

SUBSCRIPTIONS
$63 A YEAR, $99 (U.S.) IN CANADA,
$158 (U.S.) IN ALL OTHER COUNTRIES.
SUBSCRIPTIONS E-MAIL: **RHSUBS@HALLDATA.COM**
CIRCULATION E-MAIL: **RHSUBS@HALLDATA.COM**

CIRCULATION
PO BOX 2026, SKOKIE, IL 60076
(877) 529-1746
OUTSIDE USA: (847)763-9630
FAX: (847)763-9631

SENIOR CIRCULATION MANAGER
HAMILTON MAHER
(212) 219-7870 hmaher@jhihealth.com

CHIEF OPERATING OFFICER
JEFF MACDONALD

CEO, INFORMATION GROUP SERVICES
MARC FERRARA

SENIOR VICE PRESIDENT, HUMAN RESOURCES
LORRAINE ORLANDO

VICE PRESIDENT, CREATIVE SERVICES & PRODUCTION
MONICA TETTAMANZI

VICE PRESIDENT, CIRCULATION
EMELDA BAREA

jmi
100 Avenue of the Americas
New York, NY 10013

REVIEW OF OPHTHALMOLOGY (ISSN 1081-0226; USPS No. 0012-345) is published monthly, 12 times per year by Jobson Medical Information. 100 Avenue of the Americas, New York, NY 10013-1678. Periodicals postage paid at New York, NY and additional mailing offices. Postmaster: Send address changes to Review of Ophthalmology, PO Box 2026, Skokie, IL 60076, USA. Subscription Prices: US One Year $63.00, US Two Year $112.00, Canada One Year $99.00, Canada Two Year $181.00, Int'l One Year $158.00, Int'l Two Year $274.00. For subscription information call (877) 529-1746 (USA only); outside USA, call (847) 763-9631. Canada Post: Publications Mail Agreement #40612608. Canada Returns to be sent to Bleuchip International, P.O. Box 25542, London, ON N6C 6B2.V

OMIDRIA™

(phenylephrine and ketorolac injection) 1%/0.3%

— FDA APPROVED —

INDICATIONS AND USAGE

OMIDRIA™ is an alpha 1-adrenergic receptor agonist and nonselective cyclooxygenase inhibitor indicated for:

- Maintaining pupil size by preventing intraoperative miosis
- Reducing postoperative pain

OMIDRIA™ is added to an irrigation solution used during cataract surgery or intraocular lens replacement.

IMPORTANT RISK INFORMATION

Systemic exposure of phenylephrine may cause elevations in blood pressure. The most common reported ocular adverse reactions at 2-24% are eye irritation, posterior capsule opacification, increased intraocular pressure, and anterior chamber inflammation. OMIDRIA™ must be diluted prior to use. Use of OMIDRIA™ in children has not been established.

Please see full prescribing information for OMIDRIA™ at www.omidria.com/prescribinginformation

For more information on OMIDRIA™, please visit www.omidria.com

OMEROS®

Trade Up To Keeler

Trade-in your hand-held slit lamp & get $600 towards Keeler's Advanced PSL Classic!

Powerful & Portable!

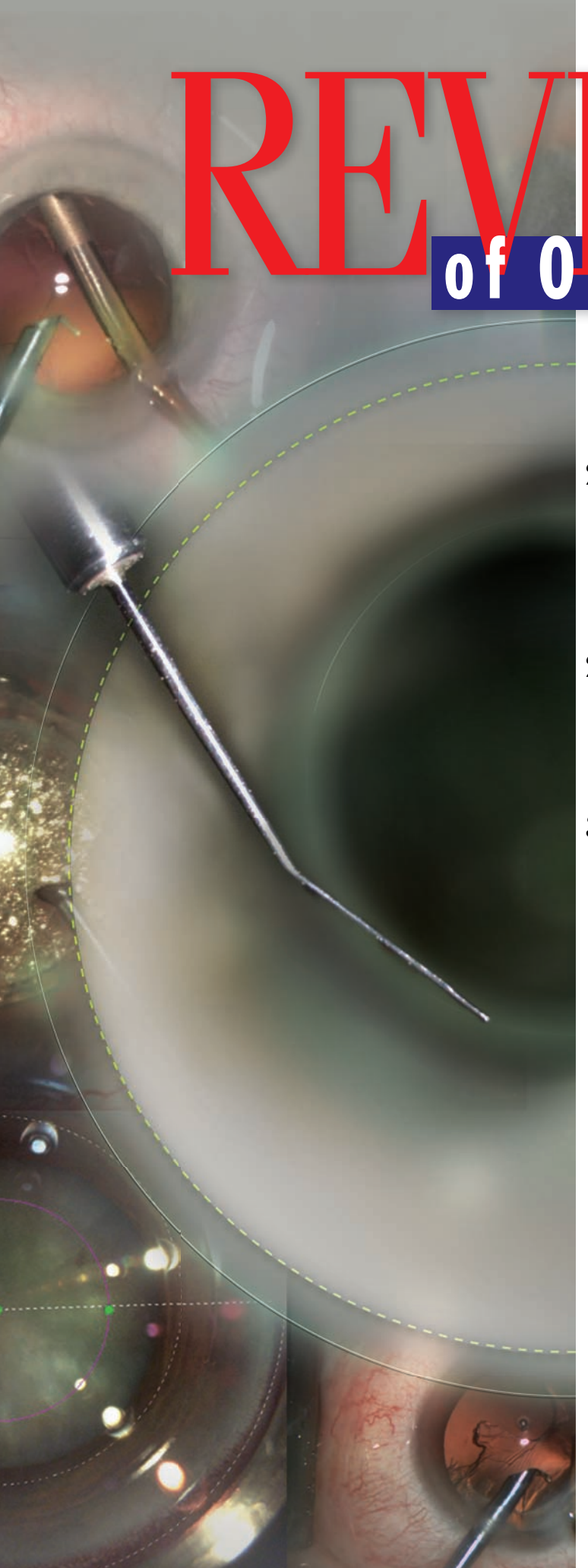
- Precision machined aluminum chassis
- Advanced optics, x10 & x16 magnification
- Controllable illumination from maximum to zero
- Most Apertures and filters along with 1.mm square light patch for assessing a/c flare

Trade-in & Special Bonus
FREE iPhone 4 Adapter and Carrying Case. Only Portable Slitlamps that have a binocular microscope allowed as trade-in. Offer expires July 31, 2014

Buy Online!
keelerusa.com

Keeler
OPTICS

Keeler Instruments, Inc. • 456 Parkway • Broomall, PA 19008 • Tel: (800) 523-5620 • Fax: (610) 353-7814 • email: keeler@keelerusa.com

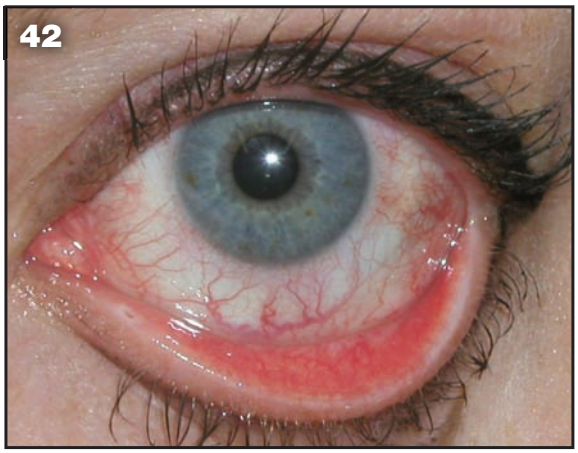


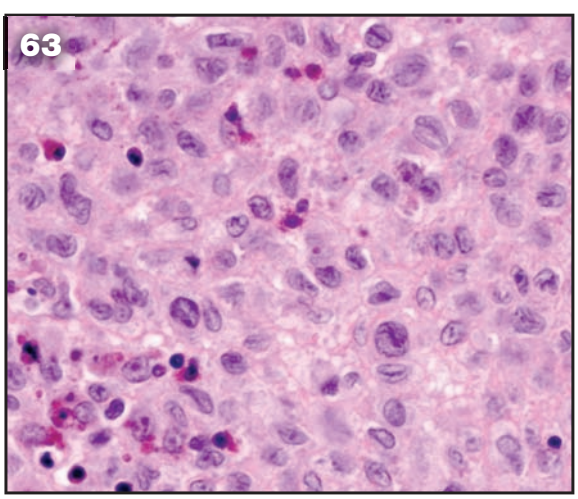
REVIEW® of Ophthalmology

July 2014 • Volume XXI No. 7 | revophth.com

Feature Articles

Departments





The Quintessential

Antibiotic™

BACITRACIN OPHTHALMIC OINTMENT USP

Proven therapeutic utility in blepharitis, conjunctivitis, and other superficial ocular infections

- **Profound bactericidal effect against gram-positive pathogens**[1]
- **Excellent, continued resistance profile**—maintains susceptibility,[2,3] even against methicillin-resistant *Staphylococcus aureus*[4]
- Ointment provides **long-lasting ocular surface contact time** and **greater bioavailability**[5]
- **Anti-infective efficacy** in a lubricating base[6]
- **Unsurpassed safety profile**—low incidence of adverse events[6]
- **Convenient dosing**—1 to 3 times daily[6]
- **Tier 1 pharmacy benefit status**—on most insurance plans[7]

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

The low incidence of allergenicity exhibited by Bacitracin means that adverse events are practically non-existent. If such reactions do occur, therapy should be discontinued.

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

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

www.perrigobacitracin.com

Please see adjacent page for full prescribing information.

References: 1. Kempe CH. The use of antibacterial agents: summary of round table discussion. *Pediatrics*. 1955;15(2):221-230. **2.** Kowalski RP. Is antibiotic resistance a problem in the treatment of ophthalmic infections? *Expert Rev Ophthalmol*. 2013;8(2):119-126. **3.** Recchia FM, Busbee BG, Pearlman RB, Carvalho-Recchia CA, Ho AC. Changing trends in the microbiologic aspects of postcataract endophthalmitis. *Arch Ophthalmol*. 2005;123(3):341-346. **4.** Freidlin J, Acharya N, Lietman TM, Cevallos V, Whitcher JP, Margolis TP. Spectrum of eye disease caused by methicillin-resistant *Staphylococcus aureus*. *Am J Ophthalmol*. 2007;144(2):313-315. **5.** Hecht G. Ophthalmic preparations. In: Gennaro AR, ed. *Remington: the Science and Practice of Pharmacy*. 20th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2000. **6.** Bacitracin Ophthalmic Ointment [package insert]. Minneapolis, MN: Perrigo Company; August 2013. **7.** Data on file. Perrigo Company.

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

REVIEW® of Ophthalmology

REVIEW Editor's Page

Christopher Glenn, Editor in Chief

New Thinking Needed About the Oldest of Us

For most of us, the Sicilian toast, "Cent'anni" came to our attention through *"The Godfather"* where it ironically wished 100 years of happiness to characters who would often be dead within hours.

For most of our history, only the very rare few enjoyed anything near such longevity. Recent, well-documented trends show that is changing, and quickly.

Census data cited in a much-publicized 2011 report showed that from 1980 to 2010 the 90-and-older population has steadily increased and this trend is expected to continue into the middle of the century. Two age groups are leading the way. "Between 2020 and 2030," the authors report, "the population aged 65–89 ... is projected to increase by 32 percent and the 90 and over by 21 percent. However, in the following decade (2030s) the 90-and-older population is projected to experience a 71 percent jump."

This week, Prevent Blindness further refined projections on the issue, focusing on the impact of vision-related diseases and their cost in the very elderly population *(See p. 3).*

The report projects that "By the year 2032, the baby-boomer population will have almost fully moved into the Medicare ranks and the rapid growth of the population from ages 65 to the mid 80s will cause dramatic increases in the prevalence and costs of vision problems. In the following decades, the confluence of the aging baby-boomers' numbers and increased longevity will drive spectacular growth in the elderly population, which will lead to the age group of persons 90 and older exhibiting by far the highest rates of growth in the prevalence of vision loss and eye disease of any age group."

The leading edge of the trend is, indeed, already here. Even *60 Minutes* got in on the story with a recent extended report.

Obviously, the treatment options and decisions ophthalmologists need to make in managing a rapidly growing population of patients with long-term, vision-threatening diseases are becoming more complex.

We're fortunate this month to feature the highly practical and timely advice of Dr. Carla J. Siegfried, who describes her approach to these "Super Seniors." In this case, the condition is glaucoma, but the approaches and tips are useful for almost anyone interacting with members of this population. Our thanks to Dr. Siegfried, and Cent'anni!

1. 90+ in the United States: 2006–2008. ACS-17. American Community Survey Reports. Wan He and Mark N. Muenchrath. Issued November 2011.


Intraoperative OCT Coming into Focus

Manufacturers are finding ways to make this technology available during surgery, giving surgeons a whole new view.

Christopher Kent, Senior Editor

One way to make manual ocular surgery safer is to improve the surgeon's ability to see what's happening. With current microscope optics at an impressive level, the next step forward may be adding another, completely different way to see, such as optical coherence tomography.

A number of companies have been working on that premise, and while some of the products are not yet approved for sale in the United States (and others are still in development), the technology appears to be useful and promising. Here, surgeons familiar with several current options talk about their experience using them during surgery.

OCT in the Microscope

Carl Zeiss Meditec launched its Rescan 700 OCT system this spring. The Rescan 700, which is not approved for sale in the United States, is a real-time intraoperative SD-OCT that can be fully integrated into the OPMI Lumera 700 microscope; the surgeon doesn't need to look up from the microscope to see the OCT data. Key functions of the OCT system can be controlled from the microscope's foot pedal, so the surgeon can take videos, snapshots and 3-D OCT images without looking up or stopping the surgery. The Rescan allows the surgeon to see the surgical field in both a planar view and a cross-sectional view simultaneously, in real time.

Justis P. Ehlers, MD, an assistant professor of ophthalmology at the Cole Eye Institute of the Cleveland Clinic in Ohio, is currently using Zeiss's Rescan system under a research protocol. "The Rescan 700 can be used for any ophthalmic surgical procedure that requires the microscope, such as anterior segment surgeries like lamellar keratoplasty or vitreoretinal procedures such as epiretinal membrane peeling," he says. "The OCT can be used for either live action monitoring or stop-action scans, and you can display the scans alongside the live microscope view with a heads-up display. The Lumera 700 has the Callisto video display system on the side; that can also display both images, so that anybody in the OR can see the surgical video and the OCT signal. Typically, while you're in the eye operating you'll be using the live OCT via the heads-up display; when you're not operating, you can use it for static images. The OCT also has different capture modes like those you might find in a clinical OCT system, that allow you to capture a still volume cube or a five-line raster."

Carl Zeiss Meditec's Rescan 700 integrates OCT images of the area being observed into the surgeon's view in the oculars. Key OCT functions can be controlled via the footpedal.

Dr. Ehlers says the biggest difference between this type of system design and previous intraoperative OCT systems is that a microscope-integrated system allows for real-time OCT

This article has no commercial sponsorship.

AS YOUR PATIENT'S DAY CHANGES, SO WILL THEIR IOP.

For your patients in need of a PGA,

LOWER IOP | SUSTAIN IOP[1,2]

Choose BAK-free TRAVATAN Z® Solution

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

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

IMPORTANT SAFETY INFORMATION
Warnings and Precautions

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

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

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

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

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

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

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

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

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

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

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

Alcon®
a Novartis company

TRAVATAN Z®
(travoprost ophthalmic solution) 0.004%

TRAVATAN Z®

(travoprost ophthalmic solution) 0.004%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

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

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

CONTRAINDICATIONS
None

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Alcon®

ALCON LABORATORIES, INC.
Fort Worth, Texas 76134 USA

5/13 TRV13049JAD

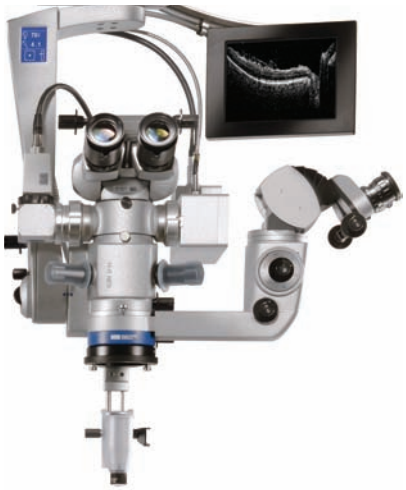
without pausing the surgery to look away from the microscope. "There have been a few microscope-integrated systems developed, including one of the first systems designed at Duke University by Drs. Cynthia Toth and Joseph Izatt," he notes. "Other systems include our prototype at the Cleveland Clinic. To my knowledge the only two systems that currently have a heads-up display system are the Cleveland Clinic prototype and Zeiss' Rescan 700."

A Touchscreen Display

Haag-Streit's intraoperative iOCT system, developed by OptoMedical Technologies in Lübeck, Germany (also not approved for sale in the United States), attaches to the camera port of the microscope; data is displayed on a screen mounted on the microscope. The screen is also used to operate the system (to switch from anterior to posterior views, for example). The device follows the zoom and focus of the microscope so the scanned area matches the area being viewed, and scans and images can be saved for future review. Surgeons report that the device can reveal structure to a depth of about 4.2 mm in air and 3.1 mm in water, with a resolution of about 10 µm.

Prof. Claus Cursiefen, FEBO, managing medical director of the Center of Ophthalmology at the University of Cologne in Germany, has been using this system for several months. "Online intraoperative OCT is easy and convenient to use since it does not disturb normal operative flow," says Professor Cursiefen. "One can see surgical details via the microscope and OCT details by looking onto the screen next to the oculars. It's a new and fascinating experience since it adds a new dimension of visibility, showing things one cannot see through the operating microscope."

Professor Cursiefen says this technology helps in difficult surgeries and in certain steps of standard surgeries. "For example, when performing DMEK on a very opaque cornea, it helps the surgeon determine whether the orientation of Descemet's membrane is correct," he says. "It helps with Boston keratoprosthesis surgery in terms of orientation, correct assembly and positioning of the device. In DALK it helps with monitoring the depth of the preparation, the interface fluid, the status of Descemet's membrane and so forth. The only downside I see is the cost."



Haag-Streit's intraoperative OCT system can be attached to the camera port of the microscope; scans are displayed on a screen mounted on the microscope.

Professor Cursiefen recently began using the Zeiss Rescan as well. "The resolution and image quality do not seem to vary much between the two systems," he notes. "The main differences are that the Zeiss system projects the OCT image into the microscope axis, so you don't have to move your head to the side to see it, and the projector on the side shows the standard view and OCT images at same time, which is good for teaching and for assisting personnel."

Available in the United States

One intraoperative OCT system is currently available in the United States: Bioptigen's Envisu C2300 Spectral Domain Ophthalmic Imaging System, designed for handheld or microscope-mounted use. *(See picture, p. 18.)* (In April, Bioptigen unveiled the Envisu IntraSurgical OCT, designed for real-time imaging during ophthalmic surgical procedures, compatible with most operating microscopes. The new system, which features independent focus and zoom control, is not approved.)

Cynthia Toth, MD, professor of ophthalmology at Duke University Medical Center and professor of biomedical engineering at Duke University's Pratt School of Engineering in Durham, N.C., was one of the early pioneers of using OCT during surgery. "Surgeons are used to using OCT before and after their surgical cases to evaluate their work—particularly in macular surgery," Dr. Toth says. "Using OCT in the operating room seems like a natural progression, both to identify endpoints and to see whether we've reached our surgical goals."

Dr. Toth initially used the handheld OCT system from Bioptigen. "The Bioptigen device is approved for commercial use in supine imaging of adults and infants in the OR, but it's not built into the microscope," she notes. "The handheld portable OCT can go to the OR and be held over the patient's eye, and there's an attachment that hooks it on to the microscope. Of course, you still have to pause in order to look at it. But I've found that the more you see, the more you want to stop surgery and check things. I've peeled this internal limiting membrane, but is the hole still open? Should I use a gas bubble? How much of a gas bubble do I need?"

Clinical Impact

"There are a lot of questions out there regarding where intraopera-

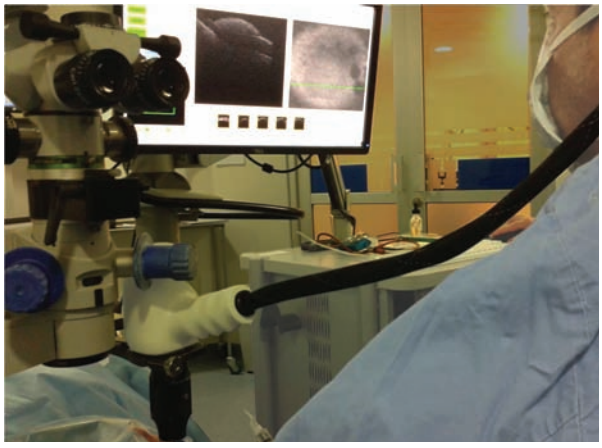
tive OCT is useful and how it can make a difference," notes Dr. Ehlers. "Many of the surgeons at Cleveland Clinic use this technology in almost every macular case. Most of our corneal surgeons at Cleveland Clinic do almost all of their lamellar keratoplasties with intraoperative OCT guidance. They believe it's a valuable tool in those procedures.

"To better assess the impact this technology is having on surgical decision-making, we've been prospectively assessing intraoperative OCT over the past three years," he continues. "We've enrolled more than 800 patients in prospective studies. We've found that in a large number of cases intraoperative OCT appears to inform surgical decision-making. In fact, in 10 percent or more of cases, the OCT data actually causes surgeons to change their mind. For example, if the surgeons think they've peeled all of the membrane, they may look at the OCT and realize there's residual membrane that requires peeling. Or the opposite: They think there's more they need to peel, but when they look at the OCT the membranes are entirely removed and they're able to finish the procedure.

"We're still investigating how much difference this technology makes in terms of surgical efficiency and outcomes," he says. "If it's simply used to find out whether you accomplished what you set out to accomplish, it can be done very quickly, whether you're using a microscope-integrated system or a portable system mounted to the microscope."

In terms of potential downsides, one issue is whether the added information might become a distraction. "We don't yet know for sure what to make of all the information this technology provides," admits Dr. Ehlers. "One concern is information overload. When does this become too much information? I believe the answer will sort itself out as we learn the best ways to display the information. With that in mind we've been experimenting in our lab on different formats to show the data to the surgeon through a heads-up display feedback system. You want to be sure you're providing information that's helpful and not distracting. (The Zeiss system also provides some flexibility in its heads-up display options.)

"The other issue, of course, is cost, which currently is a major disadvantage," he notes. "In the current climate, the price points of these systems may dictate to some degree how rapidly the technology is adopted. Certainly, the development of a paradigm-shifting procedure that requires this technology would also dramatically impact the adoption and need for these systems."



Bioptigen's Envisu C2300 (the white device seen here nested in the microscope mount) is designed for handheld or intraoperative use. Images are displayed on a separate screen.

Down the Line

"Using OCT to guide you in real time as you're reaching and performing maneuvers is the way I think OCT will be used in the long run," says Dr. Toth. "Right now, the speed of SD-OCT is probably not ideal for truly guiding the surgeon while performing maneuvers, but different technologies that will increase the speed are being developed. Swept-source OCT is coming down the pike; image-guided surgery is further down the line. But even at current speeds having SD-OCT in the microscope does make it much easier to capture images so you can stop and view the structure of the tissues."

Dr. Toth is currently helping to develop a swept-source OCT system with a heads-up display at Duke University. "With our generation-one system, you had to look up at a screen; our generation-two system is inside the microscope," she explains. "We're trying different display options, including Google Glass. The current version of Google Glass probably wouldn't be my favorite viewing option choice, but we've just begun exploring the alternatives."

Professor Cursiefen says he's looking forward to future advances in this technology, such as precise intraoperative measurement of tissue thickness for surgeries such as DALK, and high-resolution imaging of the angle during glaucoma surgery. "In fact, that's one of the most exciting things about this technology: where it may lead in the future," says Dr. Ehlers. "It could potentially open the door to procedures we haven't been able to do without this type of information, such as intratissue-targeted delivery of pharmacotherapy." REVIEW

Dr. Ehlers' research includes equipment provided by Zeiss, and he owns intellectual property licensed to Bioptigen and Synergetics related to intraoperative OCT technology. One of Dr. Toth's co-investigators has a financial interest in Bioptigen. Professor Cursiefen has no financial ties to any product mentioned.

Dear Third Year Residency Program Director,

We would like to invite you to review the upcoming 3rd Year Residency Programs for 2014. Each program offers a unique educational opportunity for third-year residents by providing the chance to meet and exchange ideas with some of the most respected thought leaders in ophthalmology. The programs are designed to provide your residents with a state-of-the-art didactic and wet lab experience. The programs also serve as an opportunity for your residents to network with residents from other programs.

After reviewing the material, it is our hope that you will select and encourage your residents to attend these educational programs.

Best regards,
Postgraduate Healthcare Education

Third-Year Residency Programs 2014:

August 1-2
Fort Worth, TX
Program Chair:
James Katz, MD

August 8-9
Fort Worth, TX
Program Chair:
Tommy Korn, MD

September 12-13
Fort Worth, TX
Program Chair:
Anthony Arnold, MD

www.revophth.com/ResFellowEdu2014

For more information:
Visit the registration site above or
Email: dholmes@postgradhealthed.com
Call: Denette Holmes 866-627-0714

There is no registration fee for these activities. Air, ground transportation in Fort Worth, hotel accommodations and modest meals will be provided through an educational scholarship for qualified participants.
These meetings are approved for *AMA PRA Category 1 Credits*™.

Endorsed by
Review Of Ophthalmology

Jointly Provided by
PHE ONRI

Partially supported by an independent medical educational grant from
Alcon

Uncover a potential systemic cause of dry eye **before it takes hold**

What appear to be symptoms of routine dry eye may be rooted in something deeper.

As many as 1 in 10 dry eye patients also have Sjögren's syndrome, a common but serious autoimmune disease.[1,2]
Sjö™ is an advanced diagnostic test that allows you to detect Sjögren's syndrome early and improve patient management.[2-4]

Introducing

Sjö™

Early detection of Sjögren's syndrome
for patients with dry eye

Novel biomarkers for early detection

nicox
Ophthalmic Diagnostics

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

For more information about Sjö™, please call a *my*Nicox concierge professional at **1.855.MY.NICOX** (1.855.696.4269), email **concierge@mynicox.com**, or visit **mynicox.com/Sjo**.

Femtosecond Cataract: Getting Up to Speed

Walter Bethke, Managing Editor

Expert advice on minimizing the time femtosecond cataract surgery adds to your procedures.

Picture this: You've just spent $400,000 on a femtosecond laser for cataract surgery, and then one morning you walk into the operating room to find it broken and shoved against the wall. Though it sounds like a fictional worst-case scenario, it actually happened to Denver ophthalmologist Michael Taravella. "We thought, OK, we have to find a separate room for this laser," recalls Dr. Taravella, who had placed the laser in an OR he shared with surgeons and staff from other specialties who had made it a habit of bumping it out of their way. He says that this dark episode illustrates just one potential issue that can crop up when a surgeon invests in this new technology and then has to address the logistics of making it work in his surgery center. In this article, surgeons and surgery-center experts share their tips on how you can incorporate the femtosecond without slowing down.

Scheduling Cases

Surgeons say your cases will take longer when you first begin using the laser, but you'll speed up with experience. However, they note that even then it will usually take more time than a non-laser case. Moran Eye Center surgeon Alan Crandall, whose practice was the second to purchase a femto-cataract laser in the United States, says everyone who works with the laser needs to get comfortable. "Initially, your techs aren't super comfortable with it and so on," he says. "So I'd say it adds eight to 10 minutes to your case until techs get comfortable with the steps involved." You'll eventually shave this time down, though.

"When the doctor gets familiar with docking and the staff gets comfortable with the laser programming, they can bring the added time down to maybe three or four minutes," says Carlos Bravo, lead OR tech and materials manager for Specialty Surgical Center in Beverly Hills, Calif. Mr. Bravo makes sure the center's flow isn't impeded by the addition of femtosecond cataract cases. "When a surgeon begins using the femtosecond for cataract surgery, we block out about 10 to 15 extra minutes so there's enough time for the learning process. Then, as he gets more efficient we take time off that. Now, some are even ahead of schedule because we've gotten that efficient. Part of this is because the intraoperative time is a little shorter due to the steps that were done with the femtosecond, such as fragmenting the cataract."

Mr. Bravo says scheduling multiple surgeons is another aspect that a cen-

ter needs to address. "Here at the center, one of the biggest initial hurdles when femtosecond was introduced was the fact that we have several surgeons using it on any given day," Mr. Bravo explains. "In the beginning, we used to spread them out and try to give a little time in between each femto case so we could turn over the room. But now we schedule them concurrently since all the doctors are familiar with the technology. A femto laser shouldn't take longer than four or five minutes now. As soon as one patient is wheeled out, the next one comes right in. Initially, though, it takes time getting the staff trained. They also have to be efficient at getting the paperwork and other postop data that comes out of the femto case to the doctor so the next patient can come in.

"When multiple surgeons have femto cataracts on the same day, we have a first-come, first-served process," Mr. Bravo adds. "There are times when we have three cases lined up one after the other. In those instances, we'll come out to the preop area and say, 'The laser room is open and whoever gets ready first gets to go in.' In the beginning, though, these situations were an issue, since a doctor would point out that he was next on the schedule, but it would turn out his team wasn't ready to move into the laser room. We had to get the doctors to communicate with each other. Let's say that two doctors finish at the same time and each of their next cases is a femto. We'll go up to them and say, "Both of you are finished, who would like to go first?" In many cases, one of them will say that he or she doesn't mind waiting, and will let the other go ahead, since he knows that he can make up for any lost time in the OR."

Sometimes, however, Mr. Bravo says femto cataract throws everyone a curveball, and the center has to be ready for it. "It just takes one patient who is uncooperative or maybe scared and uncomfortable with the laser process to disrupt the system," he says. "If this happens we make sure that the nurse in the room lets the next surgeon know that we're having issues so that he knows what's going on and doesn't get antsy. During our clinical training with the laser's clinical application experts, they taught us how to recognize the danger signs, such as when a patient is moving his head a lot or is being uncooperative. At some point, you have to know when to stop. The surgeon will say, "We tried docking you and it didn't work out, so we'll do your case the traditional way—it's not a problem.' This is rare, though, and happens only 1 to 2 percent of the time at most." Mr. Bravo says you can keep the patient flow going by recognizing potentially difficult patients before they're under the laser. "Sometimes a doctor may come and tell us ahead of time that a patient may need a little extra sedation or a little extra time because he's anxious," he says. "Sometimes, a surgeon will schedule a potentially difficult patient, such as a patient with a small fissure, first or last in the lineup to keep him out of the way."

Robert Rivera, MD

Your practice will need at least one person to be trained in the programming of the laser in order to assist the surgeon.

Surgeons' Experiences

Surgeons say it's one thing to draw up a patient flow schedule on paper and another to put it into practice. Here's what they've learned.

Sandy, Utah, surgeon Robert Rivera, who uses the AMO Catalys laser, has gone through a couple of ways of managing patient flow. "It does require the oversight of an ASC manager or charge nurse who can help you decide which system would work best," he says. "For example, when I started, I thought I'd actually be more efficient doing two femtos at a time and always staying one femto ahead. That is to say I wouldn't go into the actual operating room until I'd done two patients on the femto laser. Then, when I was done with the OR part of my first case, I'd go do another femto—this would be the third—and I'd then bring the second femto into the OR while the third was waiting. But, it turns out that, after the director of nursing helped us with a little time/efficiency study, we found out that in fact the easiest way for a single surgeon to do surgeries was to just do the femto on a patient and then bring that patient into the OR." Dr. Rivera schedules all his femto cataract cases for the beginning of his surgery day.

Some surgeons, however, have had success with a patient-flow design in which non-femto cases are interspersed among the femto ones. "We tried a bunch of different ways at first," recalls Dr. Crandall. "We tried to do them all at once but that wasn't really efficient; the problem was you'd have to go back to the laser in between. It's true that, once you got going, you could do this, but we found it was easier if you had a break in between because it was quicker for the team to have them all ready to go.

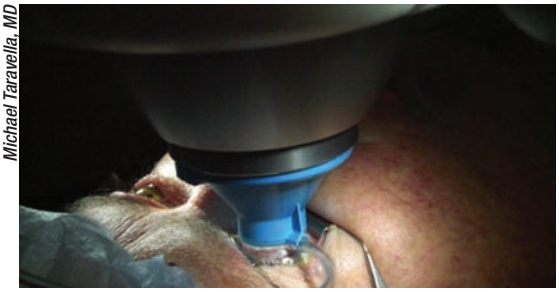
"For instance, in the way we do it now, I go into OR-1, and while I start a non-femto cataract there, my staff moves a femto patient into the LenSx room," Dr. Crandall continues. "As soon as I've finished the non-femto cataract, I walk in to the LenSx room and they've got the laser ready to go and the patient situated. I do the LenSx, which now takes us about two to

three minutes and, while that's being done, the staff has already moved another non-femto patient into OR-2 for me. So I can go into OR-2, and they'll take the LenSx patient I just completed into OR-1, and so on."

Surgeons say that such approaches work for mild to moderate volumes of femto cataract patients, such as up to 40 percent or so. If the day ever came when a practice derived most of its volume from femto cataract, however, they say a two-surgeon approach might be best. "I believe the best system, if you have a sufficient volume of femto cataract cases, will be to have a dedicated surgeon doing the femtosecond part of the case," says Dr. Rivera. "This will allow the anterior segment surgeon to stay in the OR." Surgeons point out, however, that this ties up two surgeons, so the volume has to be there to support it.

Even without a high volume, having someone such as a subspecialty fellow around can help alleviate slowdowns. "In our center, the patients are assigned their surgical times before they even know whether they're getting femto or not, and then we work it out," explains Baylor College of Medicine Chair of Ophthalmology and Catalys user Doug Koch. "That may not be optimal, but it's certainly convenient and saves a lot of headaches such as, 'We should move Mary Smith over here because Peter Thomas is having that done, etc.' It seems to make things simpler. On the day of surgery, as those femtosecond patients transition from one room to the next, I'll step out and do the femto while my staff is either rolling the patient into the operating room or while my fellow is prepping and getting everything ready, and maybe making incisions and the capsulorhexis, in the other operating room. The time lost is quite minimal."

Beverly Hills, Calif., surgeon Uday Devgan, whose practice has both an AMO Catalys and an Alcon LenSx, says that since the laser needs particular data before it can perform astigmatic incisions, it's best to come prepared. "Write your exact LRI nomogram on the paperwork ahead of time so you can input it in the laser as soon as you get to the center," he says. "It makes life much easier. Just get to the surgery center a half-hour early in the morning and program all your eyes for the day."



Michael Taravella, MD

To ensure an efficient docking process, make sure the patient's cheek and brow are level, surgeons say.

Logistical Concerns

Experts say that, in order to make the big idea of femtosecond cataract surgery work, you have to consider several little ideas first.

• ***The laser's location.*** Though surgeons have the option of putting the laser in the OR or in a separate room, it seems like the consensus among experts is the latter is preferable. The main advantage of having it in the sterile OR is minimizing the transition time between the laser and the phaco machine. The disadvantages, however, are many. "If it's in the OR, it's paramount to make sure that whoever's operating in that room is out by a certain time for the next surgeon," says Richard Ferdon, a femtosecond applications expert for Alcon who trains practices on making the transition to femtosecond cataract. "So, for multiple physicians with multiple ORs and a high volume of cases, it's best to position a laser outside the OR and put it in a procedure room. If there is a problem with a patient at the laser or a laser issue that needs repair, the entire operating room goes down and no one can use it. Having the laser in another room also becomes an extra location for patients to flow to."

Dr. Taravella says putting his LenSx laser in the OR just caused it to be in the way of other surgeons and staff. "It was in a room that was used by non-eye surgeons," he says. "The problem with that was it has a cooling fan or something that people didn't like, so they'd try to move it or bump it. In fact, one morning we came in and found that a small arm connected to a light had been broken and was just dangling from the machine. Also, we had a lot of issues with having to re-calibrate it multiple times when it was in the OR because of someone bumping it. We found a home for it near the primary ORs. We're currently remodeling the Eye Institute and it will eventually be in a room adjacent to the ORs and can feed the ones I'm working in."

• ***Prep the space.*** If you're going to place the laser in its own room, the space it will require will depend on the model you purchase, but experts say to plan on a minimum of around 11 ft. x 12 ft, though some lasers may be able to squeeze into a smaller space. You may also have to do some renovations. "Prepping the space was a challenge," says Mr. Bravo. "We had to install a cooling system and thermostat for the room to keep it between 65 and 78 degrees or so, and it had to be close to our wireless infrastructure so it could communicate with our printer and phone ports so it would have remote access." Some lasers also need a 220 VAC power supply.

• ***Mark the patients.*** Mr. Ferdon says everything in the femto cataract process should be managed in a writ-

ten or symbol format. "The entire staff, from admitting to postop, has to be aware of which patients are which without interrupting or bothering the patients," he says. "For instance, maybe change the color of the sticker on the operative eye to make the femtosecond patients' a different color, and use different colored clips on their charts." He says training the whole staff to be prepared for femtosecond patients avoids such situations as the anesthesia professional instilling a nerve block when the patient arrives that prevents the patient from moving the eye or fixating on the femtosecond's fixation light. (Femto patients must be aware and able to participate for the femto portion of the procedure.)

• ***Bed issues.*** An integrated patient bed may or may not be an issue for you, but it's something to be aware of, surgeons say. "In terms of logistics, the LenSx is somewhat easier because with it the patient stays on the same gurney from preop to the LenSx laser, to the OR and then to recovery," says Dr. Devgan. His Catalys has its own bed that the patient must be transferred to and from. The LensAR laser doesn't have an integrated bed while the Bausch + Lomb Victus does.

The gurney used by the LenSx, though, may not work for all facilities, says Dr. Taravella. "LenSx touts its moveable bed as being able to be used in the OR," he says. "But the problem for us is the laser isn't sitting close enough to the ORs in our current situation so that we can use that bed. Our techs didn't like it in terms of being able to roll patients any significant distance; it's not really suitable for rolling more than 30 or 40 feet. Transferring patients back and forth between the conventional gurney and the LenSx laser gurney is probably the longest part of the procedure, actually." He says in the pending renovation of his surgical center, the laser room will be close enough to the ORs that the patient can stay on the same gurney throughout.

Though adopting femtosecond cataract surgery technology may have its logistical logjams, surgeons say that you can make the process much easier if you can get your staff as motivated for it as you are. "The biggest advantage of the laser that the staff can readily see is how much easier it makes the removal of the cataract," says Dr. Rivera. "When they see it takes less phaco energy and infusion fluid and so forth, and the surgery team reports back to the rest of the staff about the patient outcomes, that's where the enthusiasm really comes in." REVIEW

Femto Laser Cataract: Avoiding Complications

Christopher Kent, Senior Editor

Like every new surgery, this one is associated with unique potential problems. Here's how to keep things going smoothly.

As more surgeons explore the possibility of femtosecond laser cataract surgery (in which the incision, capsulotomy and nucleus fragmentation are accomplished by the laser), the focus on the details of the surgery's advantages and pitfalls has become more intense. And as with any surgery, one of the most important details is potential complications.

"Any new surgical technique involves a learning curve, and complications will occur," notes Ronald Yeoh, MD, medical director, founding partner and senior consulting ophthalmic surgeon at Eye & Retina Surgeons, Camden Medical Centre in Singapore. "The increasing trend towards femto-laser-assisted cataract surgery, or FLACS, means that we are encountering complications peculiar to this surgery. The transitioning surgeon needs to recognize these and modify surgical technique to manage them appropriately."

Here, Dr. Yeoh and three other surgeons with extensive experience using femtosecond laser technology as part of cataract surgery share pearls taken from their experience with complications: what those potential complications are, how to manage them if they occur, and how to minimize the likelihood of them occurring in the first place.

Preoperative Precautions

For any surgery to succeed, appropriate patients must be chosen, and the patients must be made aware of possible postop concerns.

• ***Make sure the patient can lie flat and remain still.*** "There are some challenges that are unique to femtosecond cataract surgery—things that would not be a challenge in conventional surgery," says Sonia H. Yoo, MD, professor of ophthalmology at the Bascom Palmer Eye Institute, University of Miami School of Medicine. "One is that the patient must have the ability to lie down flat in the right position and remain still. During manual surgery we can give the patient IV sedation that can help if he has a tremor or neck pain, but during laser surgery the patient has to be alert and awake.

"That's true for several reasons," she continues. "For one thing, most surgeons have the laser in a different room from the operating arena, so the patient has to get up and be transferred to the other room after the laser part of the procedure. Also, we need to have the patient's cooperation during the laser, so that he can look at the light or adjust his position. With IV sedation on board, that might not be possible—the patient might fall

This article has no commercial sponsorship.

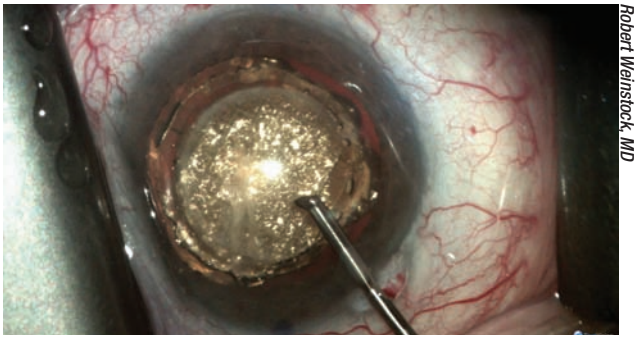
asleep; his head might bob; he's more likely to move at an inopportune time. As a result, we don't sedate patients before the femtosecond laser part. So when you evaluate patients you need to make sure they'll be able to lie flat and remain still."

• ***Select cooperative patients with wide palpebral apertures.*** "As any LASIK surgeon knows, suction loss will create problems with flap creation," says Dr. Yeoh. "When performing FLACS, suction loss can lead to incomplete capsulorhexes, incomplete nuclear division or incomplete incisions. Prevention is the best cure for this, so it is best to select patients with wide palpebral apertures who are cooperative."

Dr. Yoo agrees. "If an individual has a very deep orbit or high brow, it can be difficult to dock the laser to the eye just because of the anatomy," she says.

• ***Alert patients of the possibility of conjunctival redness.*** "This can result from the suction applied by the patient interface," explains Zoltan Z. Nagy, MD, PhD, clinical professor of ophthalmology at Semmelweis University in Budapest, Hungary. (In 2008, Dr. Nagy performed the first-ever femtosecond-laser-assisted cataract surgery.) "This is more of an issue when the patient is on anticoagulant therapy, as many elderly patients are, so we need to ask patients about this before starting the procedure. It may be possible for them to stop the medication for a few days before the surgery, but if they cannot stop it because of cardiovascular problems, they should be informed of the possibility of postop conjunctival redness before the surgery. Usually, patients accept this as part of the surgery, so it's not a problem.

"In most cases the redness goes away by the next day, or within a couple of days," he adds. "Once in a while the redness lasts for a longer period, but only in patients who are on anticoagulant therapy. Fortunately, conjunctival redness is not as big a problem as it used to be [in our practice] because the new SoftFit patient interface on our LenSx machine allows us to use lower pressure."



Robert Weinstock, MD

Surgeons need to be aware that when the laser is used to make a cube fragmentation pattern, the red reflex and view of the capsulotomy can be obscured, making it difficult to find and grasp the capsule. If the capsulotomy is incomplete, the surgeon can have difficulty seeing the adhesion points and might inadvertently tear the anterior capsule.

• ***During the preop examination, make sure the pupil dilates well with drops.*** "During conventional cataract surgery we've gotten pretty good at dealing with small pupils, using hooks and rings and intraocular mydriatics," says Dr. Yoo. "A small pupil is also an issue with femtosecond laser cataract surgery, because if the pupil is too small we might not be able to use the laser. However, the usual aids may not be advisable in this situation. The problem isn't so much having a drug or hooks or rings inside the eye; it's that you have to make a wound to get them into the eye. When you use the laser you pressurize the eye, so if you've made any wounds you could lose the anterior chamber, putting the patient at risk. Admittedly, there have been some reports of surgeons placing hooks or rings or drugs in the eye and then cutting with the laser, but those are special cases.

"On the other hand, it's pretty common to use drugs once the femtosecond laser part of the procedure is completed, because after you make your capsulotomy and do the lens softening the pupil will often come down," she continues. "In that case, at the beginning of your manual surgery you might have to place some mydriatic into the eye to get the pupil to enlarge. Some surgeons use viscoelastic to expand the pupil, or in really severe cases use hooks or a ring.

"If you're surprised on the day of the surgery by a pupil that you thought would dilate but for some reason doesn't," she adds, "one option is to simply not use the femtosecond laser. Another option would be to go ahead and make a wound and inject drugs or use hooks or rings prior to applying the laser, but you'd have to weigh the risks and benefits of doing so, because doing so may increase the patient's risk of a complication."

• ***An NSAID can help prevent femtosecond-laser-induced miosis.*** "Prostaglandins are released in the anterior chamber during the femtosecond laser step, causing pupillary constriction," explains Dr. Yeoh. "Small pupils can cause the rest of the surgery to be more difficult. My publication in the latest issue of the *Journal of Cataract and Refractive Surgery*[1] shows that a single application of a non-steroidal anti-inflammatory agent, used with the dilating drops an hour before surgery, is very useful in preventing femtosecond-laser-induced miosis."

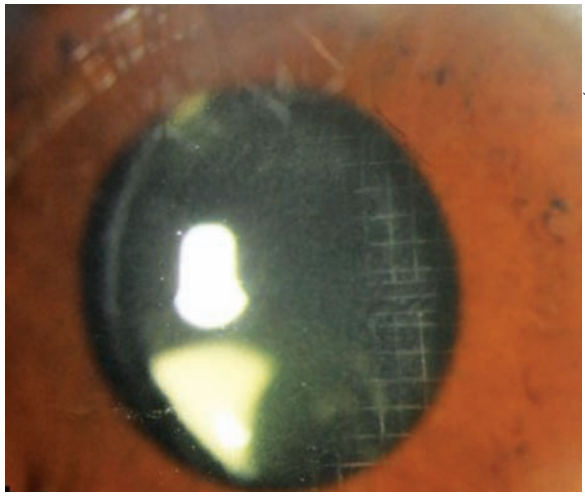
Working with the Laser

Surgeons offer these strategies for minimizing problems during the laser part of the procedure:

• ***When docking the patient, make sure the eye is flat to the plane of the patient interface and properly centered.*** "Making sure the

eye is flat to the plane of the patient interface will minimize the relative tilt of the lens," says Dr. Yoo. "If you have significant lens tilt, you may end up with an incomplete capsulotomy."

"If you put the patient interface on correctly and in a centered manner, lots of complications can be avoided," agrees Dr. Nagy. "If the patient interface of our LenSx machine is well-centered, for example, the information collected by the OCT is accurate, so it can define the lowest and highest points of the anterior capsule and avoid any piercing of the crystalline lens or incomplete capsulotomies. This has helped us achieve a free-floating capsulotomy 97 to 98 percent of the time.



Sonia H. Yoo, MD

In this patient suction loss occured during lens segmentation, causing the segmentation pattern to be briefly applied to the cornea. The resulting grid pattern left on the cornea was outside the line of sight, and the patient has done well.

"Good centration is especially important for creating the corneal wound," he adds. "If the patient moves his eye and the interface is decentered, then the corneal wounds may be more central than expected, creating surgically induced astigmatism. The other possibility is that the wound could become too peripheral. It's good to make the corneal incision as peripheral as possible, but if it's too peripheral because of a decentered interface, it may hit the conjunctival vessels, which could lead to bleeding and an incomplete corneal incision. So centering the patient interface is very important."

• ***If bubbles are present, undock and redock.*** "Imperforate incisions can result from poor docking, with air bubbles obstructing the incision site and poor positioning of the incisions," notes Dr. Yeoh. "Good docking technique will help avoid trapped air bubbles."

• ***Do everything possible to prevent suction loss during femtosecond application.*** Dr. Nagy notes that factors which can cause suction loss include loose conjunctiva and the patient moving or blinking while the laser is working. "If loose conjunctiva gets into the visual area, then the suction may not be secure, which could allow the interface to move during the treatment," he says. "The surgeon should also remind the patient not to move or blink while the laser is working. If the patient moves his eye, it could break the suction. It's rare for this to happen, but it is possible."

Dr. Yoo notes that suction loss isn't always a big deal because you can often reapply or switch to manual surgery. However, suction loss can sometimes lead to trouble. "I did have one case where suction loss occurred during the lens segmentation and the segmentation pattern was briefly applied to the cornea because the laser is so fast," she says. *(See picture, above.)* "There's a safety mechanism on our laser that cuts it off once suction is lost, but I guess there's a brief time during which you haven't completely lost suction, and during that instant the laser energy was directed in the wrong plane. Fortunately, there were no visual consequences; the patient has done really well. You can see a waffle grid pattern in a section of the cornea—the same grid pattern the laser was making in the lens—but that area was not over the pupil, and the cornea was not cut or seriously damaged. I've been following the patient for about 18 months, and you can still see that pattern on the cornea. Other similar cases have been reported in the literature.

"The best way to prevent something like this," she notes, "is to pay close attention when applying the interface, and coach the patient verbally during the laser application, reminding her to remain still and focus on the light."

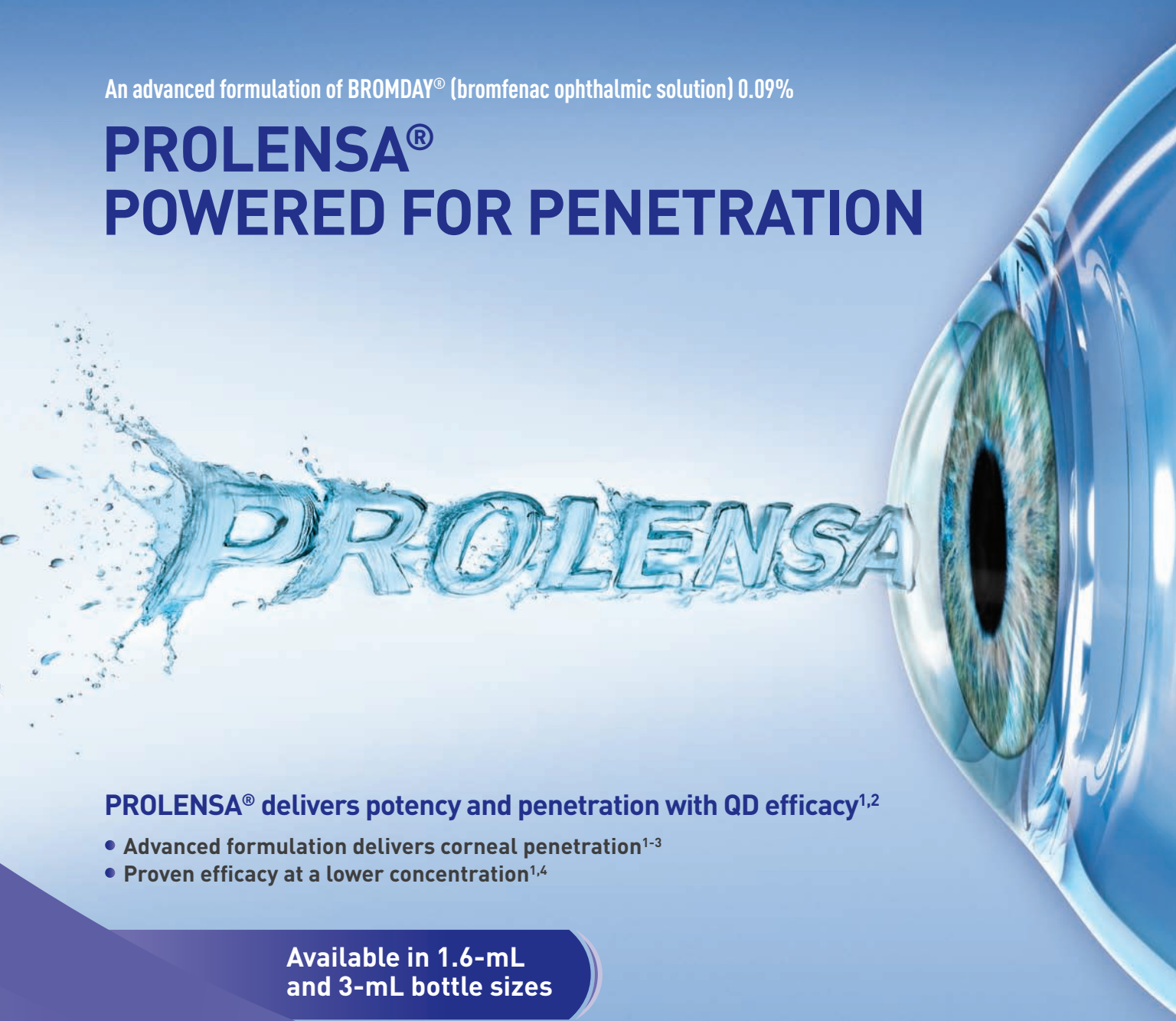
• ***If you lose suction, stop and proceed with manual surgery.*** Dr. Yoo notes that if the laser procedure is interrupted because of suction loss, most surgeons will just stop using the laser and complete the surgery by hand. "The only exception might be when the suction loss occurs while docking the laser prior to administering the laser," she says. "In that case, surgeons typically try again. But once you're depressing the foot pedal and the laser has started, if you lose suction you're basically done with the laser part."

• ***Be careful when dealing with a liquefied cortex.*** "Generally, using the laser reduces complications when you're dealing with a very dense lens," says Dr. Yoo. "However, if you have a very dense lens and a liquefied cortex, such as a white cataract where the cortex is very liquid, you may get a plume of lens material once you open the capsule. That may actually block the lens segmentation.

"In those cases, you may want to increase the energy a bit on your laser when you're doing the capsulotomy to make sure you cut through the fibrotic capsule and make sure the laser energy penetrates through small amounts of liquefied cortex that may escape during that capsulotomy," she says.

An advanced formulation of BROMDAY® (bromfenac ophthalmic solution) 0.09%

PROLENSA®
POWERED FOR PENETRATION



PROLENSA® delivers potency and penetration with QD efficacy[1,2]

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

Available in 1.6-mL and 3-mL bottle sizes

IMPORTANT RISK INFORMATION ABOUT PROLENSA®

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

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

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

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

BAUSCH + LOMB

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

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

PROLENSA®
(bromfenac ophthalmic solution) 0.07%

Brief Summary

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Recommended Dosing

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

Use with Other Topical Ophthalmic Medications

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

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Sulfite Allergic Reactions

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

Slow or Delayed Healing

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

Potential for Cross-Sensitivity

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

Increased Bleeding Time

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

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

Keratitis and Corneal Reactions

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

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

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

Contact Lens Wear

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

ADVERSE REACTIONS

Clinical Trial Experience

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

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

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

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis and Impairment of Fertility

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

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

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

PATIENT COUNSELING INFORMATION

Slowed or Delayed Healing

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

Sterility of Dropper Tip

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

Concomitant Use of Contact Lenses

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

Concomitant Topical Ocular Therapy

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

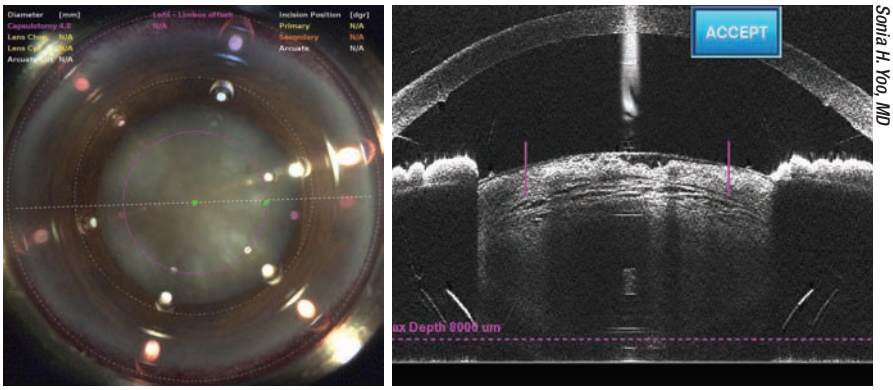
Rx Only

Manufactured by: Bausch & Lomb Incorporated, Tampa, FL 33637
Under license from:
Senju Pharmaceuticals Co., Ltd.
Osaka, Japan 541-0046

 9317600

"Once you switch to manual surgery the viscoelastic will clear your view.

"Interestingly, because these lasers generate images of the lens once the patient is docked—most platforms use OCT imaging—sometimes you can actually see that the lens is dense but the surrounding cortex is liquefied," she adds. *(See example, right.)* "In that case you should be prepared to take your foot off the pedal if you see liquid coming out during the capsulotomy."



Sonia H. Yoo, MD

Femtosecond laser technology often manages advanced cataracts more easily than manual surgery can. Here, the built-in OCT scan (right) reveals there is some liquefied cortex surrounding the dense inner nucleus of this advanced cataract. The microscopic view (left) is shown for comparison.

Managing the Capsulotomy

Once the laser portion of the operation is done, several potential problems unique to laser-assisted surgery need to be anticipated and addressed to ensure complication-free completion of the cataract surgery.

• ***Use a specially designed spatula to open the femtosecond-laser-created incision.*** "You can use any small instrument to open the femtosecond laser incisions," notes Dr. Yeoh. "However, this is less than ideal, as size and shape are not optimized. Indeed, in the early days of FLACS, we used Sinskey hooks or cyclodialysis spatulae to open the incisions, but they were found wanting. The Slade Femtosecond Spatula works well; another option is the Yeoh Femto-incision Double Ended Spatula, which I designed but have no financial interest in. The latter is optimized in shape and angulation for use with these incisions." *(See picture, p. 34.)*

• ***Use viscoelastic to avoid missing an incomplete capsulotomy.*** "When using a femtosecond laser to create the capsulotomy, some areas can remain incompletely cut," notes Robert Weinstock, MD, director of cataract and refractive surgery at the Eye Institute of West Florida in Largo, Fla. "By itself, an incomplete capsulotomy is not really a complication, because 99 percent of the time you can just grab the capsule with a forceps or microforceps and complete the capsulotomy without any problem. The problem occurs when you don't realize that there's an adhesion. If you grab the capsule quickly without paying attention and pull it out of the eye, it can rip at the point of adhesion and cause an anterior tear in the capsule, which then has a risk of running around posteriorly. So the way to prevent this complication is to pay close attention when removing the capsulotomy tissue.

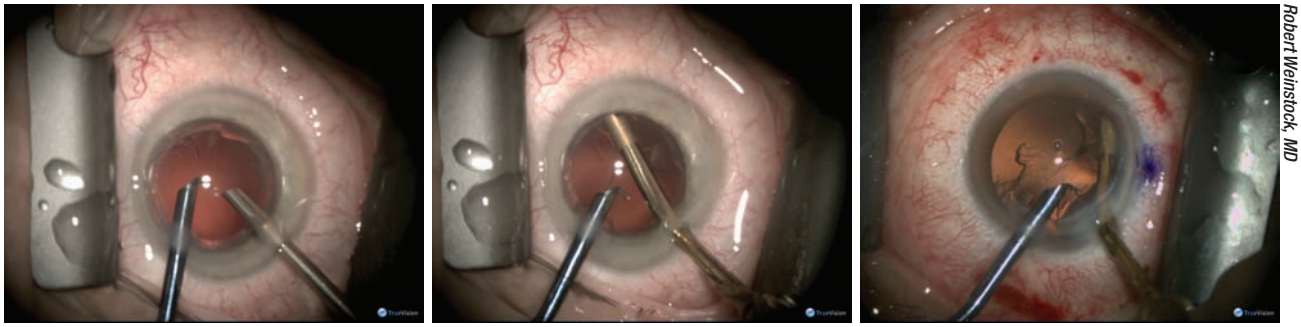
"I find it helpful to put viscoelastic inside the eye before I attempt to remove a femtosecond-laser-created capsulotomy," he continues. "That does two things. First, in many cases the process of making the capsulorhexis and breaking up the lens releases gas; those gas bubbles rise into the anterior chamber to the underside of the cornea where they interfere with the surgeon's view. Putting in the viscoelastic pushes the gas bubbles out of the way so you can see what you're doing.

"Second, it can be difficult to visualize what's happening with the capsulotomy tissue," he says. "If the flap folds over itself or rolls up like a taco, you can't see what's going on where it's near the capsule edge; it might not be completely separated. Instilling viscoelastic flattens the anterior capsule, even if it's trying to come off and be free-floating, so you have a better view of what's going on. Once I've done that I can use my microcapsulorhexis forceps to tease all of the flap tissue to the center to make sure there are no adhesions. If I find that there's an adhesion, I just finish the capsulorhexis manually. Also, pushing down gently in the middle of the capsule can help visualize where an adhesion may be."

• ***Watch for an oval bubble under the anterior capsule.*** "If the capsulotomy is not free-floating, there are some telltale signs you can see through the microscope," says Dr. Nagy. "One is an oval bubble under the anterior capsule. If the bubble is oval you can be nearly certain there's an incomplete cut in that area. The oval bubble will not appear every time you encounter an incomplete cut, but if it does appear, it's a telltale sign that the capsulotomy may be incomplete. If the capsulotomy is incomplete, use your capsulotomy forceps to lift the tissue following the circular contour created by the laser. If you follow the contour you should avoid tearing the capsule 100 percent of the time."

Removing the Nucleus

The way the laser creates the capsulotomy and fragments the nucleus



Robert Weinstock, MD

Above, left: One difference between a laser capsulotomy and manual capsulorhexis is that the laser not only cuts the capsule but also cuts into the cortex. This creates a flush edge of cortex fused to the capsule, making it difficult to find the plane between the tissues into which you can stick the cannula to hydrodissect between them—sort of a "manhole cover" effect. (After nucleus removal, it often appears that there is no cortex at all, when in fact there is a complete layer present. The clue is that a white ring is present at the anterior capsule.) Center and right: During irrigation and aspiration following use of the femtosecond laser, the aspiration tip has to be placed up under the edge of the anterior capsule in order to grasp the cortex. This is in contrast to non-laser-treated eyes, where there is usually a tongue of cortex protruding centrally that's easier to grasp.

is very different from a manual approach, resulting in some unique problems (and solutions) when it's time to remove the crystalline lens from the bag.

• ***Pupil constriction.*** As already noted, one issue during femtosecond laser cataract surgery is that the pupil can come down. "The laser puts energy into the eye and—in my opinion—sets off a little inflammatory response," explains Dr. Weinstock. "If you have a widely dilated pupil that's away from the capsulotomy, usually you're fine. But if you have a Flomax case, where the pupil is already predisposed to constriction during surgery, you're at risk of the pupil coming down pretty quickly right after the laser treatment. For example, if you're making a 6-mm capsulotomy and the pupil's only at 7 or 7.5 mm, you will have enough room to do the capsulotomy, but the laser energy will be close to the pupil margin. That can trigger pupil constriction.

"To minimize the chances of pupil constriction in this situation, you want to do two things," he continues. "First, get the patient under the microscope pretty quickly after performing the capsulotomy, probably within 15 minutes. Second, put a drop of a strong dilating agent such as 10% neosynephrine in the eye right after the laser treatment. You should get good penetration with the drops, in part because you've pressed on the eye during the laser treatment, causing a tiny bit of epithelium breakdown.

"Because of the possibility of extra pupil constriction, we now routinely put in a strong dilating drop right after using the laser, before the patient goes under the microscope and is prepped and draped," he adds. "We do this for all eyes, not just Flomax cases. Of course, there is a small risk that the drops will have a systemic effect, but patients are under monitored anesthesia, so if their blood pressure goes up they're in a controlled environment. In any case, we haven't seen any adverse complications from that addition to our protocol."

• ***Be cautious when hydrodissecting and doing the cortical cleanup.*** Dr. Weinstock notes that hydrodissection and hydrolineation are a little harder to do during femtosecond laser cataract surgery. "We're used to seeing a very good fluid wave when we do hydrodissection during manual cataract surgery, because when we peel off the capsule, usually the cortex is intact underneath," he explains. "It's very easy just to slip the irrigation tip into that space between the underside of the anterior capsule and the first layer of cortex. But when you do femtosecond laser surgery, the laser not only cuts the capsule, it goes down and cuts a rim of cortex too, the exact same size and shape as the capsulorhexis.

"The result is a kind of manhole cover effect," he continues. "It makes a flush edge where you're trying to hydrodissect. That makes it very hard to find the little space where you need to stick the cannula to get a true fluid wave between the capsule and the peripheral cortex. So instead of just doing this through one incision I find myself going in through my second incision and trying a different orientation. I find myself trying to puncture through the cortex and elevate it a little bit to get into that space. It doesn't leave you a lot of room to grab cortex, and you have to go up underneath the iris. Because of this, when using femtosecond laser capsulotomy we're not typically hydrodissecting as well as we have in the past."

• ***Problems with gas buildup.*** Another potential complication with a femtosecond laser using a fragmentation pattern is that one of the byproducts is gas buildup. "If gas is being created during the fragmentation, gas bubbles will accumulate inside

REVIEW of Ophthalmology online

EVERY MONDAY

E-News You Can Use

Have you been receiving and reading custom e-blasts from *Review of Ophthalmology*? If not, you're missing out on valuable information!

You're a busy practitioner and not surprisingly, your e-mail inbox is often full. Fortunately, when you scan through the sender list, determining which messages to delete and which to save or read, you can feel confident knowing that e-blasts from *Review of Ophthalmology*, a Jobson Medical Information, LLC publication, contain the most current and comprehensive information available in the field to keep you on the cutting edge.

Review of Ophthalmology's online stable of products includes editorial newsletters and promotional information about new products, treatments and surgical techniques, as well as alerts on continuing education courses for ophthalmologists.

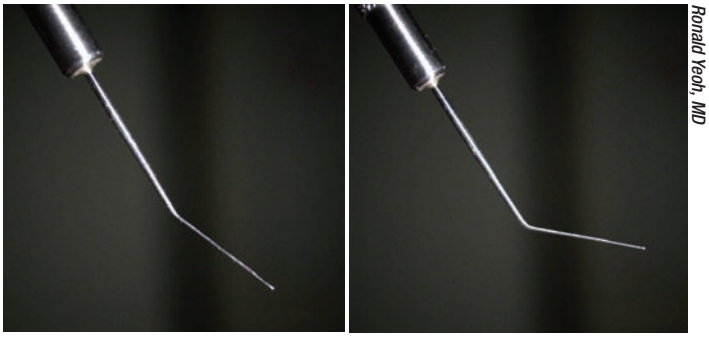
- Our FREE weekly e-newsletter, *Review of Ophthalmology Online*, brings you the latest in ophthalmic research, as well as industry news. In an effort to keep eyecare professionals informed, this resource is waiting in your inbox every Monday morning.
- *Retina Online*, our free monthly e-newsletter, is for retina specialists and general ophthalmologists interested in enhancing their knowledge on the topics of retina and related disease diagnosis and treatment, as well as the latest in surgical procedures.

Your time is valuable — and so is your practice. These e-products are the most effective way for you to receive updates on breaking news and research — all just a click away. Don't miss out!

Unfamiliar with our products? Visit www.revophth.com and check out our newsletter archives.

Go to www.jobson.com/globalEmail/default.aspx to sign up for the e-newsletters that interest you.

jmi



Ronald Yeoh, MD

Opening the wounds created by the laser is more easily done with a tool specially designed for that purpose, such as the Slade Femtosecond Spatula or Yeoh Femto-Incision Double-Ended Spatula (pictured above). The latter has ends that are optimized for the main port (160-degree angle) and side port (130-degree angle).

the lens or behind the lens—and the greater the density of the lens, and the more fragmentation patterns you lay down in the lens, the greater the gas buildup," notes Dr. Weinstock. "In theory, this will create increased tension inside the capsular bag.

"Early on, when people first started using femtosecond lasers for this purpose, there were several reports of nuclei dropping into the posterior segment," he continues. "Many people believe these were caused by overly aggressive hydrodissection. Essentially, you've created pent-up pressure in the bag from the gas and then you're adding fluid. In theory, you can blow the capsule open just from the pressure. For this reason it makes sense to titrate your hydrodissection when you perform femtosecond laser cataract surgery, and do it a little more slowly."

"How much gas is formed depends on the energy we use and the spot size and spot separation parameters during the femtosecond pretreatment," Dr. Nagy points out. "If a gas bubble forms within the crystalline lens, the surgeon should allow the gas to leave the eye through the anterior chamber and the corneal wound. I recommend the so-called "rock-and-roll" technique. This means that we perform a gentle hydrodissection and then move around the lens, pushing it down and back a little to allow the gas bubble to escape. If the surgeon does not do this and the hydrodissection is abrupt with a high-speed water jet, then there's no chance for the gas bubble to escape. This can result in a rupture of the posterior capsule, the so-called capsular block syndrome."

Dr. Weinstock also favors the rock-and-roll technique. "It helps to decompress the eye a little by rocking the lens a bit as you're hydrodissecting," he says. "Sometimes the gas will release and pop forward, relieving some of the pressure inside the capsular bag. For the same reason, I depress the wound and burp a little viscoelastic out of the eye before I hydrodissect to make sure the eye is a little soft as I'm doing it. Fortunately, I have not had any posterior rips from hydrodissection or hydrodelineation."

Dr. Yoo notes that in her experience, capsular block syndrome is rare. Dr. Yeoh agrees. "With gentler hydrodissection after burping the gas out from the capsular bag," he says, "there have been no more reports of dropped nuclei after FLACS."

• ***Use a paddle prechopper to complete the nuclear division before emulsifying the nucleus.*** "FLACS can divide a nucleus up in many ways: cross; cylinder; grid; and so forth," says Dr. Yeoh. "However, surgeons don't always realize that femtosecond nuclear fragmentation leads to incompletely divided nuclei, which can be difficult to remove. There's a 500- to 700-µm offset from the posterior capsule during nucleus fragmentation, so the posterior part of any nucleus is invariably going to be untreated and hence unseparated. Surgeons therefore need to adapt their technique to complete the nucleus separation.

"I recommend the use of a paddle prechopper to complete this nuclear division," he says. "The paddle prechopper from ASICO (designed by me with no financial interest) is helpful in most cases. It's simple to insert into the lasered grooves; then opening the prechopper completes the separation. After that, emulsification of the nucleus is straightforward."

• ***Beware of unnoticed capsular tags when during irrigation/aspiration of cortex.*** "Current femtolasers have reduced the risk of incomplete capsulotomies to well under 5 percent," says Dr. Yeoh. "Among the current instruments, AMO's Catalys makes the capsulotomy the quickest, taking only about 1.5 seconds, which may further reduce the risk of incomplete capsulotomies. Nevertheless, the surgeon needs to make sure the femto-created capsulotomy is complete without tags, and he needs to take special care when doing irrigation/aspiration of cortex around the edge of the capsulotomy to make sure that a hidden capsular tag is not inadvertently aspirated, leading to a radial tear."

Dr. Weinstock agrees. "It's possible to engage the capsule by accident during cortical cleanup and damage it," he notes. "Sometimes it's easier to leave cortex behind, and that means potential complications down the road."

• ***Do a careful sweep of the angle underneath the wound with your irrigation/aspiration tool.*** When a surgeon uses the laser to chop a lens into very small pieces, some pieces may be out of sight and difficult to find at the end of the removal process, causing them to be left behind. "Of course, this can also happen in manual surgery after emulsification of the lens," Dr. Yoo notes. "You simply need

to be aware that this could happen. To make sure it doesn't, use irrigating fluid through your paracentesis to generate some high-velocity flow inside the bag. If there's a little chip hiding somewhere, it's more likely to emerge so you can see it prior to finishing the case."

Experience Counts

Perhaps the most important pearl for surgeons considering performing femtosecond laser cataract surgery is to expect a significant learning curve. "Capsular block syndrome was first described by an Australian group," says Dr. Nagy. "They were early users of the femtosecond laser for this purpose, and they didn't realize how much of a learning curve was involved. I think it takes 30 to 50 cases to become comfortable with this procedure and avoid most mistakes. Until reaching this point, the surgeon should be very cautious."

Dr. Nagy believe that despite being associated with a few possible complications, femtosecond laser cataract surgery has many real advantages. "I think this technology helps to create consistent results, with a customized capsulotomy, customized corneal wounds and prefragmentation of the crystalline lens," he says. "Now we're using this technology up to Grade +4 cataracts. If a lens is white with a lot of water content, femtosecond laser capsulotomy is especially useful, reducing the risk of a peripheral tear and helping to avoid the so-called "Argentinean flag" sign—the spontaneous rupture of the anterior capsule due to high pressure within the crystalline lens. This technology is very good for trauma cases where there's damage to the anterior capsule because of an injury, and also in pediatric cases because the pediatric anterior capsule is very elastic; a manual capsulotomy tends to end up much larger than you intended it to be. The laser also has great promise for other related surgeries, such as posterior capsulotomy."

One thing is clear: While many surgeons remain skeptical of the value of femtosecond laser cataract surgery—especially given its price tag—it does appear to be here to stay. REVIEW

Dr. Nagy is a consultant to LenSx/Alcon. Dr. Yeoh is on Alcon and AMO's speaker panels. Dr. Yoo is a consultant for Alcon and AMO. Dr. Weinstock has no financial interest in any product mentioned.

1. Yeoh R. Intraoperative miosis in femtosecond laser-assisted cataract surgery. J Cataract Refract Surg 2014;40:5:852-3. doi: 10.1016/j.jcrs.2014.02.026.

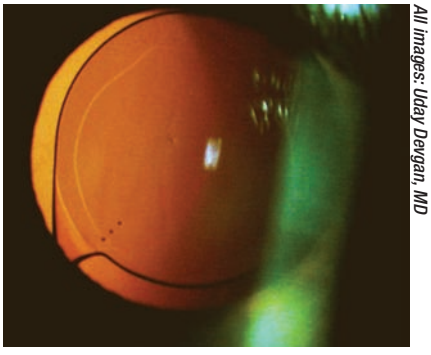
Toric IOLs: Nailing The Target Axis

Michelle Stephenson, Contributing Editor

Success with torics comes down to measuring and marking the corneal astigmatism axis and accurately placing the lens at that position.

As toric intraocular lenses continue to gain popularity, accurate alignment of the lenses inside the eye remains a challenge. According to Uday Devgan, MD, a surgeon from Los Angeles, the key to success with toric lenses is lining them up accurately with the pre-existing corneal astigmatism axis. "This consists of three steps: measuring the corneal astigmatism axis; marking that axis; and placing a lens at that position. Errors can occur during any of these three steps," he says. And even small errors can significantly impact patients' vision.

It is important to be extremely accurate because, for every degree that the lens is off, the patient loses 3.3 percent of astigmatism correction. In other words, if the toric lens is off by 30 degrees, it has no effect. "One minute on a clock is 6 degrees. If you are off that much, 20 percent of the astigmatic correction of the lens is lost," Dr. Devgan notes.



All images: Uday Devgan, MD

Figure 1. This is a toric IOL in the eye with the capsulorhexis overlapping the edge of the IOL to hold it in position. The three dots on the IOL indicate the axis of astigmatism correction on the optic.

Measure

There are several ways to measure the axis of astigmatism. "Most ophthalmologists use a corneal topographer to measure the corneal axis, but what if the patient's head is not straight during the measurement? If the patient's head has a slight tilt to it, everything is going to be off because the measurement will be off. When measuring, the patient's head must be absolutely perpendicular to the floor," Dr. Devgan says.

To measure the axis of astigmatism, Daniel H. Chang, MD, in private practice in Bakersfield, Calif., first performs IOLMaster biometry on all of his IOL patients followed by Atlas corneal topography. "I do at least two different IOLMaster measurements on separate days," he says. "That way, I can see if there is significant variability in the keratometry readings. Typically, I determine the amount or power of cylinder from the IOLMaster, and I

determine the axis from topography. I then print out the pupil image from my topographer, and I use the iris and limbal structures as a reference point for finding the axis on the eye."

Mark

There are several methods for marking the axis of astigmatism, and they vary in accuracy. Since the approval of the first toric IOL, the standard of care for marking the axis has been ink. However, because of the precision required for both measuring and marking the target axis, ink pens are not ideal. "This is the least accurate method because it is a guesstimation," says Robert H. Osher, MD, in practice at the Cincinnati Eye Institute. "The ink diffuses and may even completely disappear. Surgeons who rely on ink cannot have a very high degree of confidence that they have nailed the target meridian with the lens."

He notes that surgeons are always aiming for precise toric lens alignment. "We have all of this sophisticated technology for removing the cataract and wonderfully sophisticated intraocular lenses to replace the cataractous crystalline lens. So, how can the international standard of care for aligning the toric lens be a $1 ink pen?" Dr. Osher asks.

Dr. Chang agrees that marking pens are not ideal. "They are okay, but the ink mark itself is wide," he says. "These ink marking pens don't have a microscopically fine tip. It's more like a Sharpie. It makes a thick mark instead of a tiny pinpoint mark. Additionally, the marks bleed and can smear out after a while."

Dr. Osher notes that there are basically four methods of alignment. The first method is to place a mark at the limbus or on the cornea prior to surgery. "The mark can be used during surgery for a protracting device to find the target meridian," he says. "Yet, this can be inaccurate because the surgeon is dependent on an estimate."

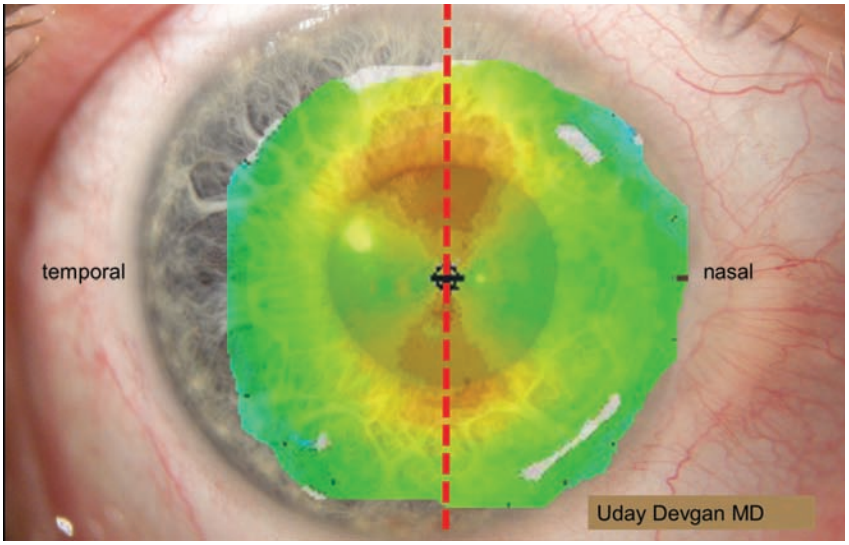


Figure 2. Here is the corneal astigmatism map of with-the-rule cylinder overlaid onto a photo of the front of the eye. The red line shows the steep axis of astigmatism, and this is the meridian at which the toric IOL should be aligned.

Another method is using imaging or fingerprinting. "A picture is taken of the iris when the pupil is dilated during the original examination, and then software superimposes a protractor so every landmark on the iris or the limbus has the exact degree associated with it," says Dr. Osher. "The surgeon can easily identify crypts, pigment, the vessels and the unique stromal patterns of the iris. A detailed photograph of the iris when the pupil is dilated, just like it is going to be in surgery, allows the surgeon to be confident about finding the target meridian. This is an accurate method that I introduced during the Kelman Innovator's Lecture in 2009."

To avoid the smearing or disappearance of an ink dot, Dr. Osher has developed Thermodot with BVI. "A probe leaves a tiny cautery dot that is placed at the limbus, signifying either the major meridia or where the target meridian is located," he says. "The intraoperative version is available today, and BVI is planning to introduce a portable unit for marking in the preoperative area at ASCRS next year."

The next method is limbal registration. "Basically, you take a picture of the limbus, and the technology memorizes it," says Dr. Osher. "In surgery, you can use a thumb drive to re-create the image on a monitor or through the microscope and then overlay the digital degree marker. You can see the target meridian based on the captured registered image, and then it's very easy to know exactly where to orient the toric lens. SMI (Germany) pioneered this technology, and Zeiss has developed its own registration software. Alcon bought SMI and is pioneering this approach in the United States with the Verion Guidance System."

The last method is wavefront intraoperative aberrometry, and there are currently two of these systems: WaveTec's ORA System with VerifEye and Clarity's Holos. "An intraoperative refraction using wavefront aberrometry will identify where the cornea is steepest," Dr. Osher says. "It takes into account both the anterior and posterior cornea and does not depend upon preoperative diagnostics. This technology provides a surgeon with information that allows rotation of the toric

lens until it is precisely aligned. In addition, this sophisticated technology not only confirms the toric axis, but also confirms emmetropia. Intraoperative wavefront has the potential to confirm that both the sphere and the cylinder are corrected. Confirming emmetropia on the table is every ophthalmologist's holy grail."

Dr. Devgan notes that the ORA and Holos devices work well, but he says they will be even better after a few generations. "With aberrometry, after the toric IOL is placed in the eye, the machine indicates whether the lens needs to be rotated and how much," he says. "If the lens needs to be rotated, that is done, and then placement is checked again. These systems work better in patients with larger amounts of astigmatism. The more astigmatism, the easier it is to measure. For mild degrees of astigmatism, these machines are less accurate. For more than 3 D of astigmatism, they are super accurate."

Dr. Chang notes that it is not unusual for one side of the implant to match the axis mark while the other side does not. "If one set of marks on the implant matches the axis mark on the cornea and the other one does not, it is not immediately obvious which one is misaligned. The answer lies in the centration of the toric lens. I would prefer my toric lens to be centered, with the lens marks parallel to my limbal marks rather than to have my toric lens decentered and both sets of marks aligned. Therefore, I am actually trying to line up the two limbal corneal marks, the two marks on the implant and the center of the implant. Rotational accuracy is important because if there is malrotation, not only are you losing astigmatic effect, but you are also inducing astigmatism in another meridian," he says.

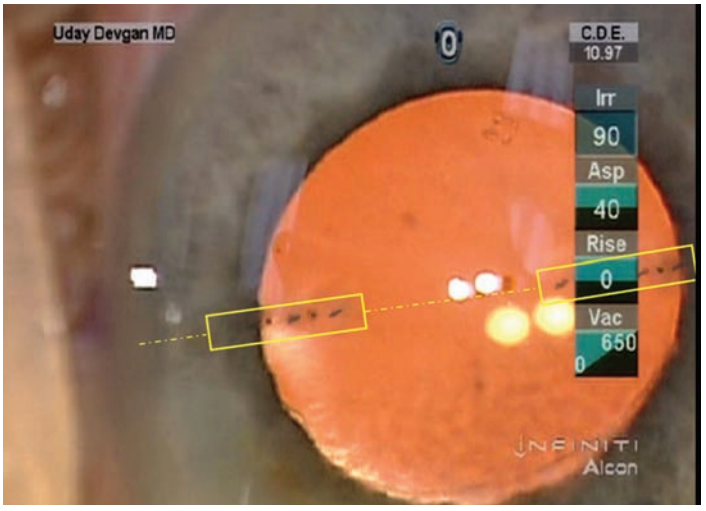


Figure 3. This shows the three dots of the toric IOL aligned with three hash marks made in the cornea at the steep astigmatism axis. The yellow line/box shows that this toric IOL is very well aligned.

Lens Placement

The last step is to keep the toric IOL in place after it has been implanted. According to Dr. Devgan, there are several pearls for achieving lens stability. First is to make the capsulorhexis so that it overlaps the edge of the optic. "If the optic is 6 mm wide, even if the capsulorhexis is 5 mm, it will shrink wrap down and really hold that lens very well. The second pearl is to remove all of the viscoelastic. After you put the lens in the eye, you've got to go behind the IOL with your I/A probe and suck out all of the viscoelastic because you want that lens to directly touch the capsular bag. If you leave viscoelastic in there, it acts as a lubricant and allows the lens to slip," he explains.

It is also imperative to ensure that the incision is completely watertight. "If there is even a microscopic leak there, it may leak slowly over the next few hours. When the eye deflates because of a leak, the lens can rotate a little," Dr. Devgan says.

Additionally, certain lens designs are better than others at maintaining stability inside the eye. Lenses like the Alcon AcrySof are made of acrylic, which tends to be tacky. "Lenses that are slightly tacky end up staying exactly where you put them because they hold on to the capsular bag," Dr. Devgan says. "Another advantage of the AcrySof is that the haptics have bulbous tips at the end. When the capsule shrink-wraps down to hold the new lens in place, that bulbous tip prevents the lens from rotating. In fact, after the capsule shrink-wraps down, you can't even surgically rotate this lens."

Bausch + Lomb's Trulign toric IOL has the advantage of four haptics. "That lens ends up being exquisitely stable in the eye. The haptics are made of polyamide, which is a material that glues itself to the capsular bag. That lens will not shift," Dr. Devgan says.

According to Dr. Devgan, there are currently four FDA-approved toric IOLs: Staar toric, AcrySof, Trulign, and Tecnis. "Staar was the first one to enter the marketplace," he says. "It is a single-piece plate haptic design made of silicone. It has two steps of correction. Next was the AcrySof lens, which is available in the most sizes and has seven steps of correction. B&L's Trulign and AMO's Tecnis toric are the newest lenses, and they each have three steps of correction available. More toric lenses will be coming out in the future, and these lenses are among my very favorites, because they absolutely deliver on their promise. There is very high patient satisfaction. The only caveat with toric lenses is that the lenses must be stable in the eye and the corneal astigmatism should be regular and symmetric." REVIEW


CSCR: Diagnosis And Treatment

Central serous chorioretinoapthy afflicts working-age patients. While many can be observed, some will require intervention.

John D. Pitcher, III, MD and Jason Hsu, MD, Philadelphia

Central serous chorioretinopathy (CSCR) is a relatively common cause of visual impairment in the Western world, and is characterized by the accumulation of subretinal fluid in the macula.[1,2] The disease classically affects men between the ages of 20 and 50 and has been associated with corticosteroid exposure, phosphodiesterase inhibitor use, obstructive sleep apnea and "type A" personality traits. Patients can present with a variety of visual symptoms including relative central scotoma, metamorphopsia, dyschromatopsia and micropsia.[3,4] On examination, the characteristic finding is a posterior neurosensory retinal detachment caused by leakage of fluid from the level of the retinal pigment epithelium.

Multimodal imaging is useful in making the diagnosis of CSCR. Classically, fluorescein angiography demonstrates an expanding point of fluorescein leakage with late pooling into a serous detachment *(See Figure 1)*. Multiple points of leakage can be seen in some patients.[5,6] Indocyanine green angiography may show focal delays and hyperpermeability in the choroidal circulation in many patients with CSCR.[7,8] Optical coherence tomography demonstrates subretinal fluid, often associated with a focal pigment epithelial detachment *(See Figure 2)*.[9] More recently, enhanced-depth imaging spectral domain OCT has shown increased subfoveal choroidal thickness in some patients with CSCR as compared to normal eyes *(See Figure 3)*.[10]

The typical natural history of CSCR is complete spontaneous resolution of subretinal fluid with restoration of visual acuity by three months after onset of symptoms. However, up to 20 percent of patients may have persistent serous macular detachment and vision loss past six months, and may be left with some degree of subjective visual impairment such as micropsia or reduced color perception.[11-13] If subretinal fluid has not resolved by three months, the patient is defined as having chronic CSCR, and treatment is often considered.

Treatment Options

There is no gold standard for treatment of persistent CSCR, and a number of therapies have been tried with varying success. Focal laser photocoagulation to pinpoint areas of leakage on FA was the first treatment shown to be of some benefit for CSCR.[14] However, photocoagulation is destructive, can lead to symptomatic scotomas, and occasionally formation of secondary choroidal neovascularization. Therefore, this treatment is reserved for focal extrafoveal areas of dye leakage.

Photodynamic therapy more directly targets the choroidal circulation and may be used in patients with subfoveal and/or multifocal points of leakage. PDT has been used for persistent CSCR with some success. However, it is not approved by the Food and Drug Administration for the treatment of CSCR and has a number of side effects, including photosensitivity to intravenous dye and choroidal hypoperfusion following treatment.[15,16] Several recent studies have demonstrated the use of half-fluence and half-dose PDT in acute and chronic CSCR, with the goal of maintaining efficacy while minimizing risk.[17-20]

Anti-VEGF medications have a number of effects that are theoretically beneficial in CSCR, such as the upregulation of tight junctions between

This article has no commercial sponsorship.

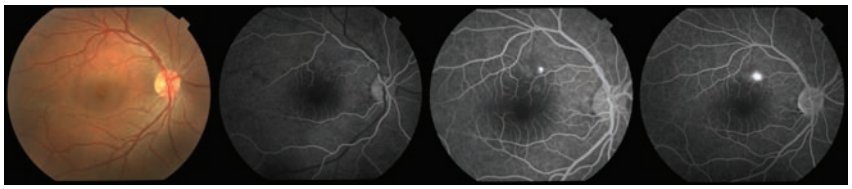


Figure 1. Color fundus photo in a patient with acute central serous chorioretinopathy demonstrating a serous detachment of the neurosensory retina in the macula. Fluorescein angiography revealed early pinpoint hyperfluorescence expanding over the course of the angiogram to pool into the subretinal space.

endothelial cells and reduction of vascular fenestrations.[21-23] A study by Ji Won Lim, MD, and colleagues suggested that VEGF levels in the aqueous humor of patients with chronic CSCR may be elevated compared to normal eyes.[24] Case studies and anecdotal reports of intravitreal anti-VEGF medications in patients with persistent or chronic CSCR have shown improvements in visual acuity, resolution of neurosensory detachments and decreased RPE leakage on FA.[25-28] Prospective studies using anti-VEGF medications have shown inconsistent results.[29,30] So far, however, the cumulative weight of evidence has failed to show sustained, clinically significant benefits.[31] Controlled clinical trials are necessary to determine the tolerability and efficacy of anti-VEGF therapies in CSCR.

Several small studies have shown mixed results from a variety of systemic medications for CSCR, including carbonic anhydrase inhibitors (acetazolamide),[32] adrenergic receptor antagonists (metoprolol, propranolol),[33,34] and steroid hormone antagonists (ketoconazole, mifeprestone, finasteride, eplerenone).[35-38]

Eplerenone, a selective aldosterone-receptor antagonist and potassium-sparing diuretic that was originally approved in 2002 by the FDA for treatment of hypertension, was recently shown in a small series of patients with chronic CSCR to improve visual acuity and significantly decrease central macular thickness.[39] The medication is generally well-tolerated but drug interactions must be ruled out prior to initiation and serum potassium and blood pressure must be monitored during treatment. Larger, prospective, placebo-controlled studies are under way to further investigate the efficacy of this treatment option.[40] Currently, pharmacologic treatments for CSCR remain investigational and are not considered standard of care. If medically appropriate, systemic corticosteroids should be discontinued in patients with active CSCR. A sleep study may be considered in patients with suspected obstructive sleep apnea.[41]

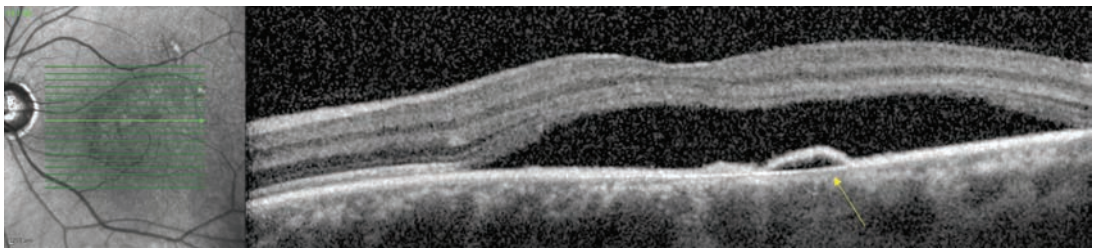


Figure 2. SD-OCT showing subretinal fluid associated with a focal pigment epithelial defect (yellow arrow).

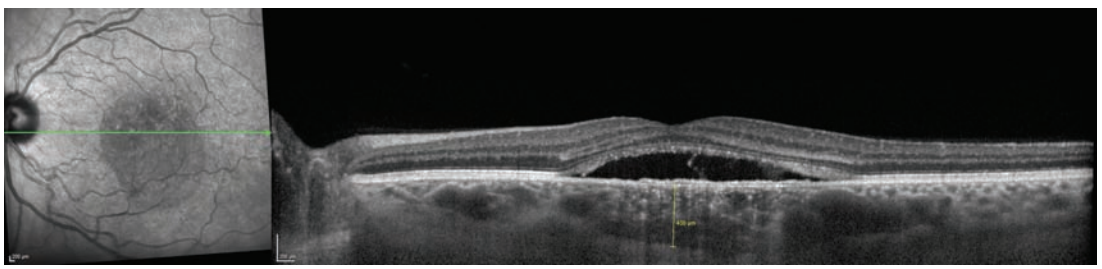


Figure 3. Enhanced depth imaging SD-OCT in a patient with CSCR demonstrating a thickened choroid (yellow bracket).

Central serous chorioretinopathy is a disease of working-aged patients, many of whom have occupations that demand high levels of visual acuity. Characteristic angiographic and OCT findings are helpful in confirming the diagnosis. While the majority of patients will return to baseline with observation, a subset of patients may be considered for intervention. No therapeutic options are approved by the FDA, but local modalities, both pharmacologic and photic, and systemic medical treatments are under ongoing investigation and may hold promise for future patients diagnosed with CSCR. REVIEW

Dr. Pitcher is a second year fellow in vitreoretinal surgery at Wills Eye Hospital and a clinical instructor of

(continued on page 65)

ARVO Comes to The City of Magic

Highlights from the posters and papers presented at the 2014 ARVO meeting in Orlando.

Mark B. Abelson, MD, CM, FRCSC, FARVO, and Ora Staff, Andover, Mass.

The annual meeting of the Association for Research in Vision and Ophthalmology returned to Florida this year after spending 2013 on the West Coast. As in previous years, ARVO 2014 featured a range of topics, with special attention given to new imaging methods, ocular genomics and some exciting reports on the latest gene-therapy efforts. Even as it adopts a changing venue every year, ARVO remains the singular location where basic and clinical ophthalmic research converge. Here's a sampling of the presentations that caught our eye this year. (Unless otherwise specified, all of the abstract citations are from this year: IOVS 2014;55)

Gene Therapy Pushes Forward

One of the most exciting areas of current ophthalmic research is gene therapy. Scientists and clinicians are taking advantage of the unique features of the visual system to make the first efforts at correcting genetic ophthalmic disorders. A prime target for these efforts is choroideremia, a single-locus, x-linked condition that results in a progressive loss of vision over several decades; affected individuals have significant loss of night vision by the second decade and are legally blind by 40 to 50 years of age.[1,2] The disease is due to the absence of the REP1 gene product, a choroid protein involved in post-translational prenylation. The slow rate of visual decay and small size of the affected gene make this condition an ideal test case for gene therapy. A research group headed by Dr. Robert MacLaren (Oxford Eye Hospital; Oxford, U.K.) recently published results from six patients treated with a functional copy of the REP1 gene packaged in an adeno-associated viral vector designed for choroidal expression. All six patients showed significant increases in VA.[3]

At ARVO, experimental details and obstacles to effective therapy were discussed in a series of presentations. *(Fischer M, et al. ARVO E-Abstract 6001; MacLaren R, et al. ARVO E-Abstract 832)* A study aimed at screening for immune responses to the vector or the rescue gene product was also presented, *(Barnard A, et al. ARVO E-Abstract 3296)* while another presentation focused on the two subjects out of six from Dr. MacLaren's study who had more advanced impairment, including retinal detachment. *(Groppe M, et al. ARVO E-Abstract 3295)* Despite these potential limitations, both subjects tolerated the viral injections without adverse effects and showed significant increases in visual acuity.

Another test case for gene therapy in the eye is Leber's congenital amaurosis (type II), a condition resulting from mutations in retinal proteins leading to premature retinal atrophy. LCA is a much more complex disease than choroideremia, so significant effort is also focused on details of the gene-function defects and how these might impact therapeutic strategies. One presentation *(Stasheff S, et al. ARVO E-Abstract 357)* showed that in two different mutations linked to the disease, ganglion cell degeneration progressed at different time courses, suggesting some difference in mechanism. Another LCA presentation demonstrated effective use of dual AAV vectors to overcome the need to introduce larger gene constructs into affected retinas *(Carvalho L, et al. ARVO E-Abstract 6002)*, one of the major obstacles to treating other forms of LCA.

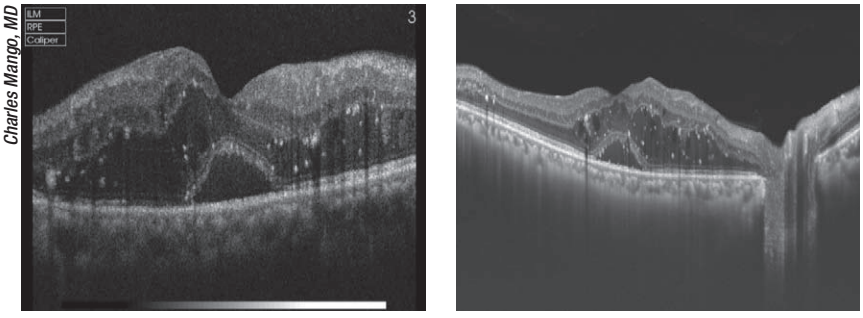
Stepping back from the clinic for

a more long-term view, we were excited by a number of presentations on progress that's being made with induced pluripotent stem cells. The logic behind this approach, at least in part, is that a patient's own cells are the best targets for reprogramming with a corrected gene. These cells are then induced to develop into the tissue of choice. Introduction of the genetic correction involves one of several DNA editing schemes followed by transplantation of repaired cells.[5] Examples of this approach were described for a therapy to treat Knoblach's syndrome *(Nguyen H, et al. ARVO E-Abstract 2982)*, as well as a test treatment to correct the male germ cell-associated kinase mutation that causes retinitis pigmentosa in patients of Ashkenazi Jewish ancestry. *(Stone E, et al. ARVO E-Abstract 2676)* Edwin Stone, MD, of the University of Iowa, showed that a corrected MAK was functionally expressed in iPSCs, a key step in bringing this technology to the clinic.

Swept-Source OCT

ARVO is a particularly opportune time to explore the latest in imaging technology. This year the biggest buzz seemed to focus on comparisons between spectral-domain and swept-source optical coherence tomography.[6] As these technologies evolve, there seems to be a progression of applications as well, as OCT use for imaging anterior structures expands as it has for the retina.

Several reports provided comparisons of retinal nerve fiber layer thickness measurement using SD and SS OCT. *(Ha A, et al. ARVO E-Abstract 4741; Lee B, et al. ARVO E-Abstract 3347)* In most of these studies, comparison of measures from SS and SD showed significant differences, suggesting values from the two methods are not readily comparable without further standardization. Another study compared retinal imaging by SD and SS in control eyes and in eyes with various opacities, including those with cataracts, vitreous opacity or corneal opacity. *(Shin Y, et al. ARVO E-Abstract 3359)* The captured images were subjectively graded by two retina specialists using a standardized OCT grading system. While images from normal eyes obtained by either method weren't significantly different, SS provided a significant improvement over SD in all eyes with reduced opacity.



Charles Mango, MD

A spectral-domain optical coherence tomograph of a patient with diabetic macular edema (left) and the same patient imaged with a new swept-source OCT (right). Researchers say standardization will be necessary before they will be able to make meaningful comparisons of the two technologies' measurements.

Another area of considerable interest was highlighted by studies that added a time component to SS-OCT to generate 4-dimensional images. One such study *(Migacz J, et al. ARVO E-Abstract 5019)* employed a technique termed phase variance OCT to image chorioretinal vascular flow. This study showed that the technique may provide greater depth resolution than traditional fluorescein angiography. Other presentations that added a time component to SS-OCT were aimed at integrating this imaging modality into the operating theater to track surgical maneuvers in real time. *(Carrasco-Zevallos O, et al. ARVO E-Abstract 1633; Keller B, et al. ARVO E-Abstract 1631)* These studies suggest that such high-resolution, high-speed imaging devices may be part of the operating rooms of the future.

Two reports used SS-OCT in assessments of angle dimensions and lamina cribrosa insertion in open-angle glaucoma. *(Rigi M, et al. ARVO E-Abstract 930; Lee K, et al. ARVO E-Abstract 904)* The resolution of the swept-source devices allows for precise morphometric analysis and provides support for the growing emphasis of these imaging metrics in the diagnosis of glaucoma. In a related study, defects in the lamina cribrosa were compared in myopes with or without glaucoma along with normal controls. *(Miki A, et al. ARVO E-Abstract 908)* This pilot study confirmed reports that such defects may be associated with development of the disease. The number of eyes with at least one focal defect in the LC were significantly different between groups: 1/20 in normal eyes; 6/32 in myopes; and 27/66 in the eyes with both myopia and glaucoma.

SS-OCT is also being employed for anterior-segment imaging, as described in a study comparing corneal thickness measurements determined by ultrasonic pachymetry and anterior segment tomography with those obtained by SS-OCT. *(Haines L, et al. ARVO E-Abstract 2464)* Although the sample size was small (n=16 eyes), the study showed all devices provided comparable measures. The authors point out that "in addition to high resolution morphological imaging of the cornea, SS-OCT can provide precise morphometric analysis of the human cornea."

Several head-to-head comparisons of devices from different manufacturers also provided a key perspec-

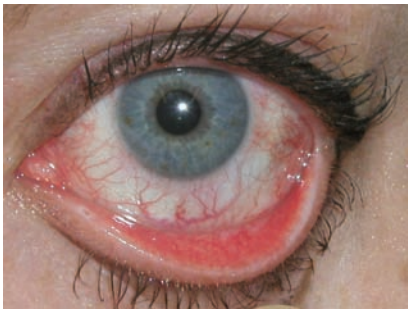
tive. Heidelberg Spectralis SD-OCT and Topcon Deep Range Imaging SS-OCT for macular imaging were used on the same subjects, providing a concise depiction of relative strengths and limitations of each device. *(Barteselli G, et al. ARVO E-Abstract 360)* Authors summarized their results by concluding that while "details of the pre-retinal vitreous are better imaged using the shorter wavelength of the spectral domain OCT, the sharpness of the choroidal structures is better using the higher scanning speed of the SS-OCT." They also point out that the two devices are comparable for visualizing the choroidal border, and that these are the images that are used to generate choroidal thickness measurements.

OCT has been used in published studies for measurement of tear meniscus height, but the higher speed and resolution of SS-OCT allow for unique studies of meniscus dynamics. *(Fukuda IOVS 2014 55: ARVO E-abstract 1981)* In a trial of 23 subjects, all with normal values for tear-film breakup, Schirmer's test and corneal fluorescein staining, a time course of tear meniscus height and volume was generated following instillation of saline, sodium hyaluronate or rebamipide. Time points ranged from 30 seconds to 20 minutes after instillation. Significant increases in meniscus measures were observed until one minute post-instillation for saline, three minutes post-instillation for 0.1% sodium hyaluronate, 10 minutes post-instillation for 0.3% sodium hyaluronate, and five minutes post-instillation for rebamipide. The authors suggest that SS-OCT could provide a new metric in studies of eye-drop efficacy.

Tear dynamics are always a topic of interest. One study examined expression of Muc16, an important mucin component of the tear film. Muc16 is expressed by conjunctival and corneal apical epithelium cells, which shed the extracellular domain of the protein into the surrounding tear layer. In a methodical series of experiments, Ilene Gipson and colleagues showed that goblet cells also produce a variant of Muc16 and contribute this to the tear film in both mouse and human eyes. *(Gipson IOVS 2014 55: ARVO E-Abstract 2760)* This finding is noteworthy for a number of reasons, but particularly because it suggests a greater than previously appreciated role for goblet cells in tear-film homeostasis.

Therapeutic Highlights

For us, the bread and butter of ARVO are the presentations on new therapeutics, both pre-clinical and clinical. Among the preclinical studies was a description of a new type of antihistamine with mixed receptor specificity. *(Chapin M, et al. ARVO E-Abstract 2482)* These new compounds, GD135 and GD136 (Griffin Discoveries; Amsterdam, Netherlands), antagonize both H1 histamine receptors (the target of traditional antihistamines) and the H4 receptor, which is thought to be important in various signal-processing pathways, including those involving pruritis.[7] In a mouse model of allergic conjunctivitis, researchers from Ora and Griffin Discoveries BV found that these compounds outperformed both olopatadine and prednisolone for reduction of hyperemia and squinting, while a pure H4 receptor was ineffective, suggesting the H1/H4 combination may provide some therapeutic synergy.



Researchers theorize that antagonizing H1 and H4 receptors in combination may be effective in treating allergic conjunctivitis.

Several presentations described clinical studies of topical antihistamines for allergic conjunctivitis. Aciex Therapeutics presented a study of its topical formulation of cetirizine, AC-170, an antihistamine commonly used in oral formulations but not yet available for topical use. The formulation was shown to significantly and rapidly reduce ocular itch, lid swelling and other signs of ocular allergy. *(Gomes P, et al. ARVO E-Abstract 2490)* Alcon presented Phase III results for olopatadine 0.77%, a new higher-strength formulation of the topical antihistamine currently available as Pataday or Patanol, that confirmed that this new formulation is superior to placebo at both 16 and 24 hours, providing unqualified q.d. dosing for ocular itching. *(McLaurin E, et al. ARVO E-Abstract 2488)*

The anti-proliferative agent PRI-321 (Prism Pharma; King of Prussia, Pa.) holds promise as an anti-fibrotic treatment for conditions such as choroidal neovascularization or proliferative vitreoretinopathy. *(Whitlock A, et al. ARVO E-Abstract 1203)* In a laser-induced model of CNV, Prism Pharma researchers and others found PRI-321 to be as good as an anti-VEGF comparator. A retinal detachment model of PVR showed similar results, with PRI-321 significantly reducing Müller cell proliferation and scar formation. Data on another new compound of interest came from Amakem's (Diepenbeek, Belgium) successful first-in-human Phase I/Phase II trial of AMA0076, a Rho kinase inhibitor with properties that minimize adverse effects without impacting efficacy. *(Hall J, et al. ARVO E-Abstract 565)* Another report of a successful Phase I/Phase II trial came from Aerpio, whose drug AKB-9778 is showing promise as an alternative to VEGF inhibitors for DME. *(Brigell M, et al. ARVO E-Abstract 1757)*

In terms of new therapies, biomarkers and diagnostic approaches, there is

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

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

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

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

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

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

Alcon®
a Novartis company

For important safety information, please see adjacent page.

LenSx® LASER
Designed for Growth™

THE CATARACT REFRACTIVE SUITE BY ALCON

LenSx® LASER

Designed for Growth™

VERION™

IMAGE GUIDED SYSTEM

IMPORTANT SAFETY INFORMATION

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

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

RESTRICTIONS:

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

Contraindications:

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

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

PRECAUTIONS:

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

AES/COMPLICATIONS:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Alcon®

a Novartis company

never a shortage of presentations on dry eye. A series of posters describe our work at Ora in refining our ability to quantify and characterize blink behavior and pathophysiology. One study characterized our continuous, automated blink monitoring device, confirming that it provides valid metrics of blink dynamics. *(Rodriguez J, et al. ARVO E-Abstract 3681)* A second study then used the device to reveal dramatic differences in blinking behavior in subjects who wore either spectacle or contact lens correction. *(Heckley C, et al. ARVO E-Abstract 6062)* This study also showed large differences in blink between lens products, suggesting that blink monitoring may be a useful metric in lens development.

A number of studies presented approaches to ocular surface pathology, exploring novel methods to assess the corneal and conjunctival insults that occur in chronic allergy, dry eye and other conditions. One study correlated tear fluid biomarkers with various subgroups of dry-eye patients, and uncovered a strong correlation between the tear protein PRR4 and aqueous-deficient dry eye. *(Perumal N, et al. ARVO E-Abstract 2002)* Another group examined the utility of matrix-metalloproteinase-9 assays in tear samples from dry-eye patients. *(Messmer E, et al. ARVO E-Abstract 2001)* Objective assessments of dry eye are notorious for their lack of correlation, but this group found that MMP-9 levels in 101 subjects showed a strong positive correlation with OSDI scores, tear-film breakup times, Schirmer's scores and ocular surface staining. In addition, levels were significantly increased in females, subjects with autoimmune or thyroid disease and those who identified themselves as having Sjögren's syndrome. Combined with the simplicity of the assay, these findings suggest that MMP-9 may be a valid metric for both clinical diagnosis and drug development applications.

An animal model using an injection of concanavalin A into the lacrimal gland may improve upon the conventional scopolamine-based model of dry eye. *(Belen L, et al. ARVO E-Abstract 3663)* Transiently elicited decreases in tearing and increases in corneal staining were reduced by oral dexamethasone, suggesting that dry-eye symptomology generated by ConA injection is modifiable and thus useful in testing novel dry-eye therapies.

One study found an increased incidence in signs of dry eye in patients with diabetic peripheral neuropathy when compared to age-matched controls. *(DeMill D, et al. ARVO E-Abstract 1483)* While the investigators saw no clear association between the severity of the two diseases, dry-eye signs (osmolarity, Schirmer's test) were significantly higher in diabetic neuropathy patients. As with other types of dry eye, there was a lack of association between signs and OSDI-based symptoms.[8]

A number of studies examined factors thought to contribute to dry-eye disease. One group examined tear cytokines before and after computer use. *(Kumar N, et al. ARVO E-Abstract 1859)* Even after only an hour of exposure, increases in galectin-3 and epithelial expression of MMP9 indicated the presence of surface inflammation. Though the study was small (n=5), results suggest that the inflammatory effects of ocular stress occur within a very short time period. Another study compared 20 patients with dry eye to 20 age-matched controls using a driving simulator in combination with traditional DE metrics. *(Deschamps N, et al. ARVO E-Abstract 1987)* Subjects with DE show significantly longer reaction times and a decreased ability to avoid randomly displayed targets.

One of the biggest issues with dry-eye patients is reading, which is a major contributor to visual stress and ocular discomfort, while at the same time being a key aspect of a patient's quality of life. It's not surprising that impairment of reading is one of most important reasons patients seek help for their dry eye. Several studies examined this issue to understand how dry eye impacts reading function, assess these effects and determine the extent to which reading function can be used as a metric in dry-eye studies. A pilot study compared results of reading tests such as the Wilkins test and the IreST test in normals and in dry-eye patients and found a clear pattern of reduced scores in those with dry eye. *(Ousler G, et al. ARVO E-Abstract 160)* Another study surveyed patients to assess how dry eye impacted their reading tasks. *(Watson M, et al. ARVO E-Abstract 1997)* As a critical issue of quality of life, it seems that reading might be an appropriate clinical metric for dry-eye therapies in the future.

We enjoyed our visit to Orlando, and hope that next year's meeting can match the variety of science, technology and therapeutics at ARVO 2014. If past experience is any predictor of what's ahead, ARVO 2015 in Denver will not disappoint. REVIEW

Dr. Abelson is a clinical professor of ophthalmology at Harvard Medical School.

1. Kalatzis V, Hamel CP, MacDonald IM. First International Choroideremia Research Symposium. Choroideremia: Towards a therapy. Am J Ophthalmol 2013;156:433-7.
2. Huckfeldt RM, Bennett J. Promising first steps in gene therapy for choroideremia. Hum Gene Ther 2014;25:2:96-7.
3. MacLaren RE, Groppe M, Barnard AR, et al. Retinal gene therapy in patients with choroideremia: Initial findings from a phase I/II clinical trial. Lancet 2014;383:9923:1129-37.
4. Dalkara D, Sahel JA. Gene therapy for inherited retinal degenerations. C R Biol 2014;337:185-92.
5. Tucker BA, Mullins RF, Stone EM. Stem cells for investigation and treatment of inherited retinal disease. Human Mol Gen 2014;R1–R8.
6. Adhi M, Duker JS. Optical coherence tomography—current and future applications. Curr Opin Ophthalmol 2013;24:3:213-21.
7. Thurmond RL, Gelfand EW, Dunford PJ. The role of histamine H1 and H4 receptors in allergic inflammation: The search for new antihistamines. Nat Rev Drug Discov 2008;7:41-53.
8. Walker PM, Lane KJ, Ousler GW 3rd, Abelson MB. Diurnal variation of visual function and the signs and symptoms of dry eye. Cornea 2010;29:6:607-12.

The Latest Results With the LAL

An update on the Light-Adjustable Lens and a look at a potential application for it in broadening focal depth.

Walter Bethke, Managing Editor

The Calhoun Vision Light-Adjustable Lens is a technology that is intriguing for a lot of ophthalmologists, since it may enable them to avoid postop refractive "surprises" by letting them adjust the lens's power after it's been implanted, and may even be able to afford presbyopic patients a form of multifocal vision, as well. Here, surgeons who've worked with the unapproved lens, both outside of the United States and within the lens's U.S. Food and Drug Administration trial, discuss the current results.

Adjusting the Lens

The LAL is a silicone lens composed of both stable material and photosensitive silicone macromers. When the lens is exposed to ultraviolet energy emitted by a special radiation device, the macromers polymerize in whatever shape or pattern is imposed by the radiation application. Non-polymerized macromers will then migrate to the area of the polymerized ones, causing the lens to enlarge in that area. This shape change is what alters the refractive power of the lens. This process, known as adjustment and lock-in, takes place during the period following the cataract surgery and implantation of the lens.

"The FDA protocol requires implantation of the IOL and a wait of 17 days to start the adjustment process," says Indianapolis surgeon and LAL investigator Kevin Waltz. "The preop astigmatism is not treated during cataract surgery, and the refractive target at the time of cataract surgery is approximately +0.50. All post-implantation treatments are preceded by testing, including two independent refractions. The first treatment is called adjustment number one; it targets the cylinder and decreases the plus sphere toward zero. The next treatment is adjustment number two, and is used if some refractive error remains after adjustment one. If there is very little refractive error after adjustment one, we go directly to lock-in number one. The purpose of this lock-in step is to consume the remainder of the reactive macromer in order to stabilize and 'lock' the refraction. There is some inefficiency in lock-in number one, though, because, for technical reasons, it can't consume all of the unused macromer. Lock-in one does draw all of the unused macromer into a part of the lens where it can be consumed, however, and lock-in two consumes all of the unused macromer that lock-in one does not. After lock-in two, the IOL power is fixed and stable." At this point in its development, the lens can be adjusted to eliminate up to 2 D of spherical error and up to 2 D of astigmatism (which is 3 D of cylinder at the corneal plane).

During this adjustment process, it's important for the patient to wear UV eye protection, since UV light can actually alter the lens before it's shape is finally locked in. "We have some patients we suspect of being less than perfect with their UV protection," says Dr. Waltz. "But it doesn't appear to have harmed them, or to have had a serious adverse effect on the adjustment process. We don't have any patients that we've confirmed as non-compliant with the UV protection requirement."

Current Results

Calhoun Vision's medical monitor R. Doyle Stulting presented results from one of the LAL investigational sites

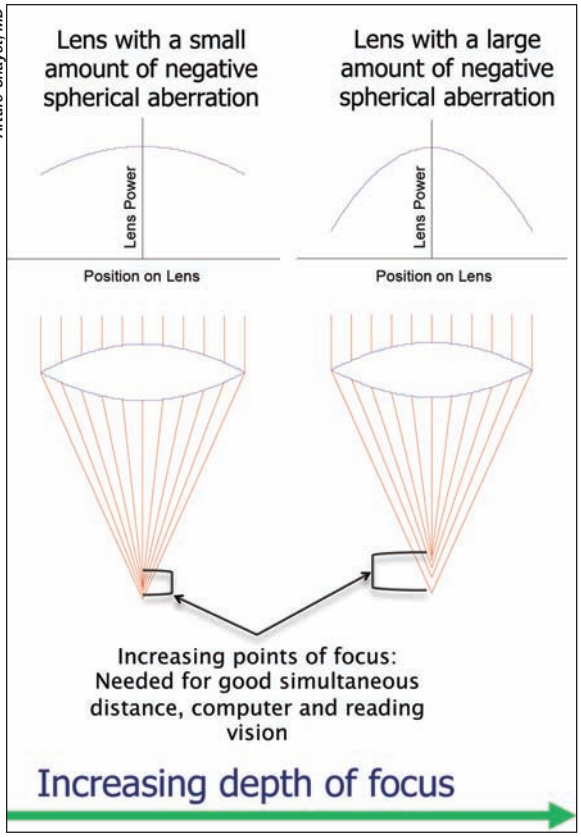
This article has no commercial sponsorship.

at the 2014 meeting of the American Society of Cataract and Refractive Surgery. The results he presented were after one adjustment. In the eyes presented, one week after lock-in, 83 percent achieved 20/20 or better uncorrected vision vs. zero who saw at that level before the adjustment, with a quarter of the eyes seeing 20/12 or better.

Dr. Stulting also provided data on how well patients see uncorrected postop versus how well they'd see with correction. Before the lens adjustment, only 8 percent of the cases had less than one line of difference between uncorrected and best-corrected vision. After adjustment, 83 percent were in this category.

In terms of astigmatism control, after lock-in, 67 percent of the eyes had zero astigmatism. All of the eyes had 0.5 D or less of astigmatism (preop range: 0.5 to 1.75 D) post lock-in.

At Dr. Waltz's practice, he notes that all of his patients, if done without the LAL, would have required a toric lens. "All patients in the FDA Phase III Calhoun trial must have between 0.75 and 2.25 D of anterior corneal astigmatism to enter the trial," he says. "This makes them very challenging patients to achieve a plano endpoint. Given this, in my site's experience, approximately one-third of our patients have uncorrected vision of 20/20 postop, one-third see 20/16 and a third see 20/12. There is an occasional patient with less than 20/20 after treatment, but it's rare."



Though increasing the amount of negative spherical aberration in a lens decreases its distance acuity, it also increases its depth of focus. This is the mechanism behind the Light-Adjustable Lens's adjustable blended vision. In ABV, the dominant eye's LAL gets a small amount of SA while the non-dominant eye's lens gets a greater amount.

Presbyopic Correction

Researchers and investigators are also using the UV light to make special aspheric adjustments to the LAL in a process called adjustable blended vision. The goal of these adjustments is to broaden patients' range of vision.

Tijuana surgeon Arturo Chayet, who consults for Calhoun Vision, says the ABV treatment relies on inducing different levels of asphericity in the lenses. "First of all, we make sure the patient can see well for distance, because individuals like to have good distance vision," Dr. Chayet explains. "We do that by making sure the dominant eye will have great distance vision, though we still give that eye a little negative asphericity so it can have the so-called 'summation' with the other eye, and have some improved intermediate acuity. Then, in the non-dominant eye, we'll give high asphericity. The non-dominant eye will lose a little bit of distance vision because any time you create a multifocal effect or a different focus in one eye, the eye loses a little at some focal distance. Basically, the eye will go from 20/20 to 20/25 in order to gain near vision. Typically, that eye will be able to see between J2 and J3. If the patient wants J1 because his lifestyle requires very good vision at, say, 40 cm, then you can leave that eye around -0.5 D. The patient will still have very good intermediate vision, and the eye will typically have an uncorrected vision between 20/30 and 20/40. The difference between the eyes is well-accepted by the brain, as opposed to the typical monovision treatment in which there is more than a 1.5-D difference between the eyes."

In a study of binocular vision results in 20 ABV patients at Dr. Chayet's practice, 75 percent could see 20/16 or better at distance after lock-in. Eighty-five percent now see 20/20 or better and 100 percent see 20/32 or better. In terms of binocular intermediate vision at 60 cm, 60 percent see J1+ versus zero patients preop, 75 percent see J1 versus 20 percent at this level preop and 100 percent see J2 or better compared to 45 percent preop. Ninety percent see J2 or better binocularly at near (40 cm) versus 15 percent preop. Fifty-five percent now see at least J1, compared to 5 percent who could see that well preop.

"Right now, I think we're learning a lot about how to present the technology to patients and create the right expectations in them," says Dr. Chayet. "This is a new technology and, as with any new technology, we're learning more about it, but we're making very good progress." REVIEW


Meeting the Needs of the Emerging 'Super Senior'

Elderly patients are an ever-increasing part of our patient populations, bringing special challenges and considerations.

Carla J. Siegfried, MD, St. Louis

There's an old saying that the first 20 years of managing a patient with glaucoma are pretty easy. (There's also a saying that the best thing to do when managing glaucoma patients is to move every 10 years!) In fact, in the past it was very unusual to manage a patient for 40 or 50 years, unless the patient was very young at the time of the original diagnosis.

Today, however, Americans are living healthier lives with better medical care and preventive care, and this is increasing our life expectancy. The U.S. population over the age of 65 has doubled since 1980, and if current trends continue, the U.S. population over the age of 80 will triple by 2050. In fact, children born today are very likely to live to 100. Of course, this means an increasing number of glaucoma patients; age is a very important risk factor for the disease. As a result, many of us find ourselves managing patients for an extended period of time—and more patients who are over 80 or 90 years old.

The Super Senior

For our purposes here, let's define a "super senior" as someone over the age of 90. The individuals in this age group are different from those of this age a few decades ago. Today these individuals may have some chronic medical conditions, but they often don't have anything imminently life-threatening; they desire a continued high quality of life. These are people who are active, not sitting around in skilled nursing facilities. Many of them are still living independently.

These are not patients that you'd want to give up on or manage half-heartedly. You know that as their ability to ambulate decreases they're going to depend more and more on their vision to lead a high-quality life. Good vision helps keep these individuals safe; among other things, they'll have less risk of falling. And if someone has severe arthritis and can't get around, his world gets smaller—but he really needs to see that world. So it's important to not have someone in this group succumb to vision loss because of a progressive disease like glaucoma.

Given that we're going to follow these patients for a much longer time than ophthalmologists would have in the past, we really have to think about how aging affects all of the aspects of managing glaucoma—from diagnosis to therapy to monitoring progression. We also have to be prepared to offer more help to the patient. Patients with arthritis may have more difficulty instilling drops; being on a fixed income can make costs a major issue; memory difficulties may lead to adherence problems; being on many systemic medications can lead to unexpected drug interactions and adverse effects; and so on.

The reality is, when you see somebody for the first time at the age of 70 and know that he or she could easily live another 20 to 30 years, you're looking at a disease process that's somewhat different from what you'd encounter in a younger patient. And today, you have to think about it in terms of the long run.

Monitoring the Patient

Visual field testing is an important part of monitoring progression in most glaucoma patients, but automated visual field testing may be much more difficult in elderly patients. Their

This article has no commercial sponsorship.

reaction time is different and their attention span is shorter.

One helpful alternative is to try a kinetic (e.g., Goldmann) visual field test, which is much more user-friendly than automated static visual fields. In this type of testing, there's a technician sitting with the patient who can alter the speed of the test and respond to the patient's limitations. The Goldmann visual field test is not always reliable, but it's often better than no formal testing at all.

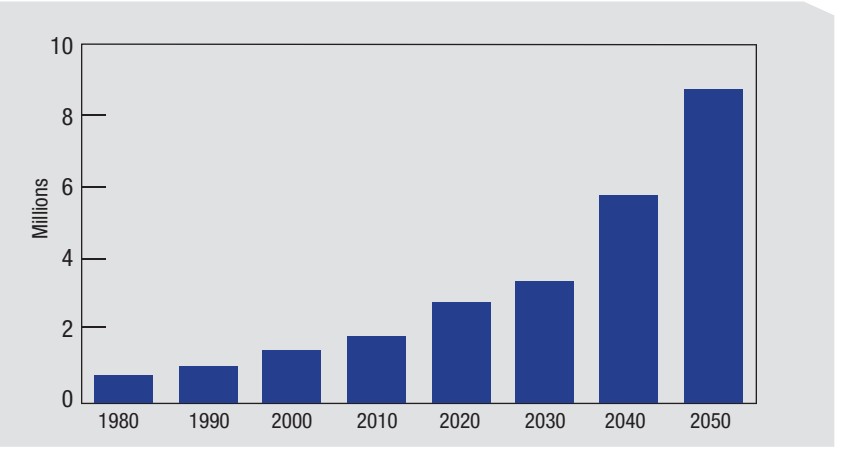
Unfortunately, not all offices have the Goldmann technology today, and the instrumentation is no longer manufactured. Furthermore, fewer and fewer people are being trained to perform this test. That means this method of testing may soon be unavailable, but there are newer versions of automated kinetic visual field testing that are increasing in use. Hopefully, in the future there will be improved objective methods to obtain this functional data from patients.

Structural information about the optic nerve is very important and requires interpretation of optic nerve and retinal nerve fiber layer imaging scans; you'll depend on them much more as an objective measure of progression with this group of patients. Of course, a key issue will be deciding whether a change is attributable to aging or progression. Unfortunately, most studies of optic nerve imaging have been cross-sectional; they look at different patients at a specific point in time. As a result, we don't know a lot about longitudinal changes in OCT or HRT scans, or about what is normal for an aging individual.

One study from 2007 by Don Budenz, MD, and colleagues looked at the changes in the retinal nerve fiber layer for every decade of increased age.[1] They found an average 2-µm decrease in thickness for every decade, after making adjustments for age, ethnicity and axial length (all of which can affect the optic disc size and the retinal nerve fiber layer). A more recent paper from the *Journal of Glaucoma* looked specifically at the changes in the different quadrants of the retinal nerve fiber layer over time.[2] It found more age-related change in the superior and inferior quadrants; in contrast, glaucomatous loss paralleled the decline in average thickness. The study also found that true glaucomatous progression was much more rapid than age-related decline; even the fastest age-related decline was still slower than most glaucomatous loss. So if you look carefully, you can probably distinguish one from the other in most patients.

Ultimately, you may not be able to get visual field information or measure retinal nerve fiber layer loss in some of these patients because of advanced optic nerve damage. In that situation you're left with just the patient's IOP and your gut instinct as to whether the patient is getting worse. If the mean pressure is 18 or 20 mmHg and the patient has advanced nerve damage and visual field loss and you feel the patient is getting worse, you're probably right. But if the pressure is 12 or 10, it's a lot harder to say whether the patient is getting worse; and its really hard to judge when the pressure is 14 or 16. Still, you have to make those difficult decisions and recommendations for therapy.

Population Aged 90 and Over: 1980 to 2050



Data from United States Census Bureau, 1980 to 2010. Projections calculated by the Census Bureau in 2008.

Treating the Super Senior

Given the limitations and special concerns that accompany treating an elderly patient, it's important to approach this as a special case. A few points to keep in mind:

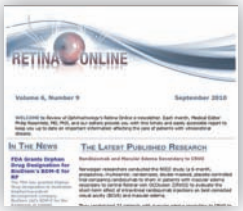
• ***Older treatment options may be worth considering.*** We do tend to treat elderly patients more with medications than with surgery, because we're trying to avoid taking them to the operating room —especially if they have other co-morbidities. In addition, many of them are resistant to having surgery. For that reason it often makes sense to try alternatives you might not try with a younger patient. Some of the older medications, like pilocarpine and phospholine iodide, may be worth trying. Laser trabeculoplasty can also be a very good adjunct to medical therapy, and even transcleral diode cyclophotocoagulation may be beneficial in this population. I've had some very good results with diode CPC in elderly patients who didn't want to have intraocular surgery in

REVIEW® of Ophthalmology

ENRICH YOUR PRACTICE

Review of Ophthalmology delivers current and comprehensive information focusing on topics such as disease diagnosis, surgical techniques and new technologies.

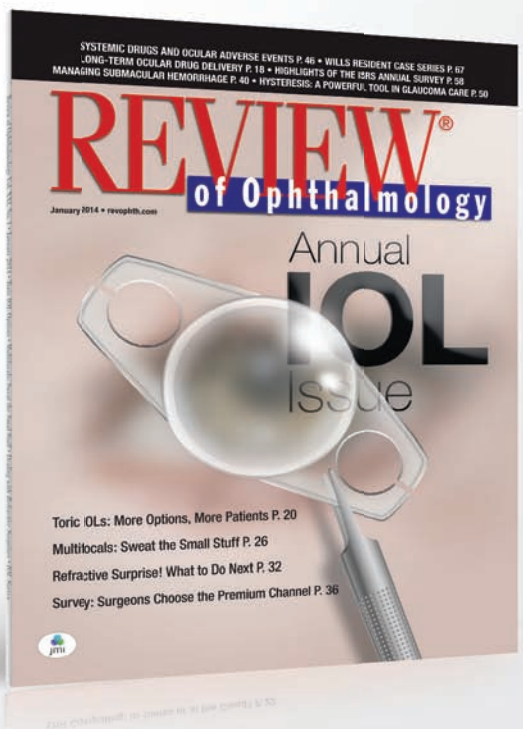
The *Review* Group's *Ophthalmic Product Guide* brings you the latest products and technology on the market. Published every February and July.



The *Review* Group also distributes a variety of supplements, guides and handbooks with your subscription to *Review of Ophthalmology*. These publications are designed to keep you informed on what's new and innovative in the industry on topics ranging from cataract refractive surgery to ocular surface disease.

The *Review* Group also offers valuable continuing medical education sessions in both print and online formats, allowing a convenient way for you to earn CME credits. In addition, we also offer an impressive fleet of free e-newsletters—such as *Review of Ophthalmology Online* and *Review of Ophthalmology's Retina Online*—so you can keep up to date on breaking news and the latest research.

The *Review Group* offers eyecare practitioners quality informational resources dedicated to the growth and education of the profession. The *Review Group* offers a variety of print and online products to enrich your patient care and practice needs.



The *Review* Group also spearheads meetings and conferences, bringing together experts in the field and providing a forum for practitioners that allows you to educate, and learn from others in the profession. These meetings cover a broad range of topics in the form of educational or promotional roundtables and forums.

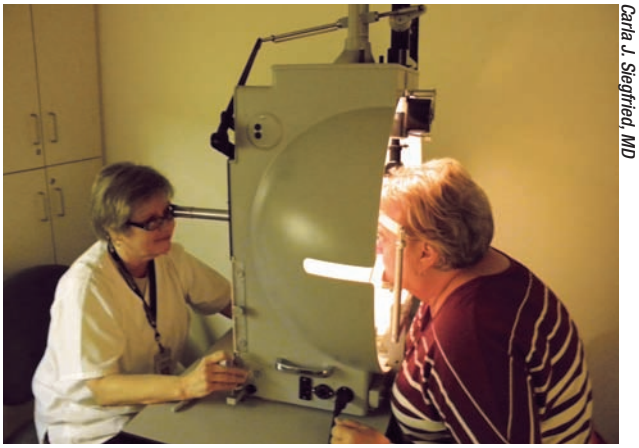
www.revophth.com

Jobson Medical Information LLC
The *Review* Group

the OR.

• ***Make sure the patient and family understand that glaucoma eye drops are medications.*** The reality is that these drugs may have systemic effects, not just local effects on the eye. The patient and the family must be made aware of this.

Use of topical medications is sometimes overlooked by primary-care physicians, for example. I've had patients on beta blockers come back and say, "I had a pacemaker implanted a couple of months ago." I look through their medication list and see that they're on a topical beta blocker; beta blockers may cause bradycardia in some patients. I ask whether their cardiologist was aware of that. They say, "Oh yes, she made a list of all of my medicines." But did the cardiologist consider that the topical beta blocker might be contributing to the patient's need for a pacemaker?



Carla J. Siegfried, MD

A kinetic visual field test such as the Goldmann (pictured above) is more user-friendly for senior patients than an automated perimetry test. A technician sits with the patient, able to alter the speed of the test in response to patient limitations. For some patients, this may be the only visual field test that's manageable.

• ***Be prepared to manage pressure-independent factors.*** In addition to IOP, blood flow-related factors such as ocular perfusion pressure and blood pressure are important; these may help us determine how much blood flow is reaching the optic nerve. Of course, when we're managing these patients we lower intraocular pressure as much as we can, but if they're still progressing and we don't think we can easily lower the pressure further—i.e., surgery may be required—then it's helpful to examine these other factors. (Sleep apnea is another important condition to consider for diagnosis and management.)

Obviously, it's important for blood pressure to be properly controlled. However, sometimes patients get dizzy when they take their blood pressure medicine—indicating that their blood pressure is too low—so they take it right before they go to bed when they'll be lying down, figuring that's safer. Of course, that's actually not a good thing to do; their blood pressure can drop too low, along with the perfusion pressure to the optic nerve, placing their eye at risk. So, I take a history about some of these issues, including what time of day they're taking their blood pressure medicine. (I'll also have patients check their blood pressure at night.)

• ***If blood pressure is an issue, coordinate with the primary-care doctor.*** There's sometimes a disparity in what we feel the blood pressure should be and what the primary-care doctor believes the blood pressure should be. Many primary-care doctors want the pressure as low as possible, as long as the patient is not falling. From our perspective, that's not necessarily a good thing; we want to make sure the diastolic blood pressure stays over 60 mmHg so there will be less chance of hypotension, especially at night.

• ***Salt tablets at night may help keep blood pressure up.*** This is another strategy for helping to prevent hypotension. However, the best strategy is to coordinate your care with the primary-care doctor.

Seniors and Surgery

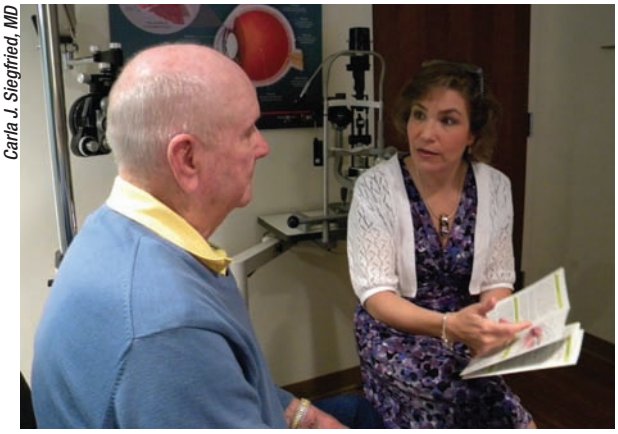
There are some special considerations when taking these patients to the OR, including issues surrounding informed consent (especially depending on the patient's cognitive status); risks associated with anesthesia, which can have more profound effects in this age group; questions involving hygiene and infection risk; and avoiding suprachoroidal hemorrhages, which is a greater risk because of these patients' vessel fragility, tissue quality and potential issues with their healing response.

Here are some strategies that will help make surgery go more smoothly:

• ***Make sure the informed consent involves the patient's family.*** This is especially true if the patient's cognition is impaired, and/or if the family is involved with managing the patient's day-to-day living situation and there are legal guardianship issues.

• ***At the same time, make sure the ultimate decision is the patient's.*** I've seen family members say, "Oh Grandma, you need to do this, the doctor says so." As long as I feel that the patient can make the decision, I encourage the patient to make the decision. I give her the information she needs; I spell out the risks and benefits and how it relates to her quality of life currently and in the future. Then I let the patient know that it has to be her decision. I won't schedule a procedure just because the patient's family says the patient needs to do it.

If patients are not prepared to make that decision, I urge them go home and think about it, unless the


Carla J. Siegfried, MD

It's important to make sure the patient and any caregivers—as well as the patient's primary care physician—understand that topical eye drops can have systemic interactions with other medications the patient may be taking.

procedure should be performed urgently. There's often no reason to rush, so allowing them to think about the issues and giving them time to consider more questions is appropriate.

• ***Only broach the idea of avoiding "vision-saving" surgery if the eye is no longer helping the patient.*** Very few patients ever say they don't care about their vision. The only time I hear that is when one eye is severely compromised in terms of visual acuity and visual field, and the other eye is perfectly normal. If a patient says, "You know doc, this eye is really not of any use to me," I have the patient cover the better eye and try to cross the room. If the patient can't make it to the door using only the worse eye—and I know the other eye is perfectly normal—then I'll give them the option of skipping the surgery. However, if I think there's any chance that the bad eye might become their better eye at some point in the course of their lifetime, then I'll encourage them to proceed. Again, the final decision has to be theirs.

On the day of surgery:

• ***Avoid general anesthesia.*** I nearly always recommend monitored local anesthesia and sedation rather than general anesthesia, if at all possible. IV sedation with a short-acting drug such as propofol, which causes amnesia about what happens during the surgery, can be a good option. Even if the patient claims to feel something during the surgery, he probably won't remember it. General anesthesia, where the patient is intubated on a breathing machine, is a much riskier procedure in this population.

Note that this is also a very important part of the informed consent with the patient and the family. Even if a patient says, "I don't want to know anything about the surgery, I want to be put completely to sleep," I really push against that. A trabeculectomy or tube shunt procedure is very safe for most of these patients when done using very short-acting sedative; there's no reason to increase the risk by using general anesthesia.

• ***If possible, work with an anesthesiologist who has experience working with elderly patients in these types of procedures.*** Such an individual will know better when to give a little sedation and will know how to make the patient more aware when you want the patient to be more aware. That makes the surgery safer for everybody.

• ***Be cautious with the use of antimetabolites.*** My experience suggests that these patients have a thinner Tenon's capsule, as it seems to become attenuated over time. They may have had prior surgery, leaving the conjunctiva scarred, more friable and easily torn, or the sclera more vulnerable, if the patient had a surgery such as an extracapsular cataract extraction, involving a large incision site at the limbus. Also, after decades of medication, their fibroblasts may be different. (We don't know that for certain because there aren't studies relating to that in this population, but we do know that long-term use of medication can alter the tissue.)

Fortunately, many of these patients do not have as much risk of scarring as a younger patient might, which means you can potentially cut back on the mitomycin or 5-fluorouracil and still achieve a good result. Given that fact, I titrate my antimetabolite use based on how the tissue looks at the time of surgery, with the goal of a low, diffuse posterior bleb.

• ***Be aware that the patient may have had large-incision extracap cataract surgery many years ago.*** This should be factored into consideration when deciding where to make your incision. If a patient had extracapsular cataract extraction, the sutures may be gone, but that incision site will always be there; your glaucoma surgery can get into trouble if you don't realize that and make your incision at that location. You may not find this information in the patient's record, either, if a 90-year-old patient had cataract surgery 30 years ago. So, make sure your physical exam considers this possibility.

If you determine that this is the case, you may want to alter which procedure you do. You might decide to put a tube in, rather than do a trabeculectomy or ExPress shunt, just because the tissue is not really amenable to a filtering procedure.

• ***Err on the side of higher postop pressures.*** Delayed suprachoroidal hemorrhage is probably our worst nightmare in glaucoma surgery; it's associated with aging, hypertension, hardening of the arteries, arterial sclerosis and anticoagulant therapy. Recovery following a limited suprachoroidal hemorrhage is certainly possible, but this event is often

devastating. Many super senior patients are on low-dose aspirin, and many others are on Plavix or Coumadin therapy because they've had some sort of cardiac procedure or have had a stroke in the past, putting them at greater risk. Patients with a suprachoroidal hemorrhage usually present to the office with acute, severe pain and loss of vision.

Delayed suprachoroidal hemorrhage can occur days or weeks after the surgery if the pressure in the eye drops low, so you need to be careful to avoid postop hypotony. I recommend putting in additional sutures at the end of surgery to keep the pressure a little bit higher for the first week or two after surgery. Avoiding lowering the head below the heart is also important.

• ***Make sure the family participates in post-surgery care.*** The family must be involved when it comes to follow-up appointments, and especially in terms of monitoring how the patient takes the medications after surgery. This can be a challenge for patients because the postop regimen may be very different from what they've been taking for their glaucoma. They may be accustomed to using drops once or twice a day, while the postoperative regimen could be every two to four hours. It's definitely a step up in frequency of medication.

They may also need to change their activities for a while, although this is not usually a big change. These patients are not necessarily doing heavy lifting, but they may want to work in the garden; however, they'll need to avoid doing this type of activity with a head-down position.

• ***Make sure the patient and family understand the signs and symptoms of infection.*** Infection does not appear to be a greater risk with elderly patients; at least there's not much data supporting a greater risk. As long as the patient displays good hygiene and is compliant with therapy, this isn't likely to become an issue. However, I've observed that sometimes when an infection does occur, the patient doesn't come in right away because she "doesn't want to bother anybody." Thus, it's very important to get the family involved, and say, "If you see any of these signs or symptoms, the patient needs to come in immediately."

What About MIGS?

Microinvasive glaucoma surgeries, or MIGS, have garnered a lot of attention recently; they've raised the possibility of lowering pressure surgically without the risks and drawbacks associated with trabeculectomy and tube shunts. For a super senior, however, such an approach may not be all that useful, for two reasons. First of all, many MIGS procedures are approved by the Food and Drug Administration to be performed only at the time of cataract surgery. The majority of these patients had cataract surgery years earlier, so they wouldn't be considered candidates for MIGS.

Second, while MIGS procedures are known for being safe, they don't lower pressure nearly as dramatically as the more invasive surgeries. That's a problem because if you don't get the pressure reduction the patient needs to halt or decrease progression you'll have to take the patient back into the OR for more surgery later. With a younger patient this may be very reasonable, but it doesn't necessarily make sense when the patient is in her 90s. Surgery is inherently riskier at this age, and these patients may not be enthralled with the prospect of more surgery.

Yes, in some circumstances it might be a good option, as long as the patient understands and agrees. It might help to control the pressure for a few years and reduce the number of medications the patient has to use. Performing a MIGS procedure at the time of cataract extraction could be ideal for select patients in this population.

Keeping Things Super

Thanks to increasing life expectancy, all of us will be seeing patients for longer and longer stretches of time—and seeing more patients in their 80s and 90s (and maybe over 100). With any glaucoma patient, the ultimate goal of therapy is to improve the patient's quality of life in terms of function and comfort. When the patient is a super senior, maintaining good vision is especially important: Being able to see well offsets some of the physical limitations that may come with aging and gives the individual a fighting chance to continue activities such as driving that are so important to quality of life. (If we can also find ways to reduce the treatment burden, so much the better. Taking eye drops that make you miserable is not an ideal way to live.)

Today, my own parents are 86 and 96 and blessed with good health, an experience that I believe is increasingly common. Our attitudes about the elderly need to reflect that reality. You wouldn't want to say to them, "Well, we'll just kind of manage your glaucoma, and if you slowly lose vision, that'll be OK." With a little extra thought and persistence, we can help them maintain their best possible vision—and their quality of life. REVIEW

Dr. Siegfried is a professor in the department of ophthalmology and visual sciences at Washington University in St. Louis.

1. Budenz DL1, Anderson DR, Varma R, et al. Determinants of normal retinal nerve fiber layer thickness measured by Stratus OCT. Ophthalmology 2007;114:6:1046-52.
2. Feuer WJ, Budenz DL, Anderson DR, Cantor L, Greenfield DS, Savell J, Schuman JS, Varma R. Topographic differences in the age-related changes in the retinal nerve fiber layer of normal eyes measured by Stratus optical coherence tomography. J Glaucoma 2011;20:3:133-8.



The Rick Bay Foundation

for Excellence in Eyecare Education

www.rickbayfoundation.org

Support the Education of Future Healthcare & Eyecare Professionals



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.

To those in the industry and the professions he served, he will be remembered for his unique array of skills and for his dedication to exceeding the expectations of his customers, making many of them fast friends.

Scholarships will be awarded to advance the education of students in both ***Optometry*** and ***Ophthalmology***, and will be chosen by their school based on qualities that embody Rick's commitment to the profession, including integrity, compassion, partnership and dedication to the greater good.

Interested in being a partner with us?

Visit www.rickbayfoundation.org

(Contributions are tax-deductible in accordance with section 170 of the Internal Revenue Code.)

THE RICK BAY FOUNDATION
for Excellence in Eyecare Education

(The Rick Bay Foundation for Excellence in Eyecare Education is a nonprofit, tax-exempt organization under section 501(c)(3) of the Internal Revenue Code.)

Vigabatrin and Visual Field Loss in Children

The drug has a long history outside the United States in the treatment of epilepsy. Its use in children requires close follow-up.

Christopher M. Fecarotta, MD, Brooklyn, N.Y.

Vigabatrin, used around the world to treat epilepsy, was approved a few years ago for use in the United States for the management of refractory, complex partial seizures in adults who have failed other anti-epileptic drugs. Ophthalmologists may be involved in the care of children who are receiving vigabatrin; this article will review the drug's uses and effects and the considerations to keep in mind in treating or monitoring this population of patients.

Background

Gamma-aminobutyric acid is the brain's major inhibitory neurotransmitter. Vigabatrin (Sabril) is a selective, irreversible, inhibitor of GABA transaminase that increases levels of GABA in the brain; it was synthesized in the 1980s and 1990s as an anti-epileptic medication.[1,2] The molecule resembles GABA, but the addition of an extra vinyl group allows it to sit in the active site of GABA transaminase and render it inactive. It has been used around the world since the 1990s and was recently approved for use in the United States. Vigabatrin is often effective for the management of refractory complex partial seizures in adults who have failed multiple medications. Such patients are often debilitated by their seizures and are desperate for treatment. Compared with other anti-epileptics, vigabatrin has a relatively low interaction rate with other medications, a lower overall rate of side effects, and is particularly effective when spasms are associated with tuberous sclerosis.[3,4] In children, it is an option for first-line therapy for infantile spasms (West syndrome), which are seizures hypothesized to be malfunctions of the GABA regulation process and are notoriously difficult to control. Adrenocorticotropic hormone (ACTH) can also be used as first-line treatment for infantile spasms, since excess production of corticotropin-releasing hormone is another possible etiology, but this treatment carries a higher risk profile.

In 1997, Dr. Tom Eke and colleagues described cases of peripheral visual field constriction associated with vigabatrin.[5] Since then, vigabatrin has clearly been shown to cause a dose-dependent, permanent peripheral field constriction.[2,6] Other, less common side effects include somnolence, headache, dizziness, fatigue and weight gain. Psychosis has also been reported, although this side effect is more common in adults than in children. The prevalence of visual field constriction is uncertain and ranges from 14 to 92 percent in various studies. Because of this side effect, nearly two decades of debate delayed the approval of vigabatrin in the United States until August 21, 2009. Prior to approval, patients and their family had to obtain vigabatrin from

Canada, Mexico and the United Kingdom. After approval, the Food and Drug Administration implemented a Risk Evaluation and Mitigation Strategy (REMS) to promote compliance with its screening recommendations. The earliest reports of toxicity were after 11 months of exposure. The vision loss is usually asymptomatic and spares the macula, but sub-clinical depression of macular function and color vision deficits have been reported. The mechanism has not yet been fully demonstrated, but most likely involves toxicity to both retinal photoreceptors and ganglion cells. There is some evidence that vigabatrin induces a taurine deficiency that leads to toxicity, and some authors have suggested taurine supplementation as a way to prevent toxicity.[7] Dr. Pedro Gonzalez and colleagues have recently suggested that, as an anti-epileptic medication with inhibitory effects, vigabatrin may also dampen the visual system as a whole.[8] The authors suggest that other anti-epileptic medications may have similar effects, but retinal toxicity caused by vigabatrin exacerbates this effect.

Current recommendations limit the dose of vigabatrin to 3 g per day in adults, or 50 to 100 mg/kg/day in children, and the drug should be withdrawn if it does not provide adequate seizure control.[9] Adult ophthalmologists will be seeing patients on vigabatrin more frequently as its uses expand. Robert Fechtner, MD, and colleagues recently showed that vigabatrin is effective in treating cocaine and methamphetamine dependence.[10] Their study enrolled 28 patients and found that 16 remained negative for substance use during the last six weeks of the study. Furthermore, no ocular adverse effects were reported.

Use of vigabatrin involves a continuous analysis of its risks and benefits. This approach requires cooperation among the patient's neurologist, ophthalmologist and family. Some families will accept risk of a visual field defect if vigabatrin provides freedom from seizures, while others would prefer not to risk visual impairment.

Toxicity Evaluation Options

The FDA has recommended that all patients have complete eye examinations and visual field testing before starting vigabatrin. Patients should return for follow-up exams every three months to monitor for side effects. Unfortunately, detection of visual field defects in this population of children is very difficult. The majority of children who require vigabatrin for seizure control are very young, non-verbal, or are unable to cooperate with the most sensitive tests. The American Academy of Pediatric Ophthalmology & Strabismus has recommended alternative ways to evaluate for toxicity:

• ***Serial fundus examinations.*** The appearance of the fundus may be completely normal despite toxicity and visual field constriction; however, indirect ophthalmoscopy may be the best method for a large proportion of pediatric patients. Optic nerve findings include thinning of the nasal retinal nerve fiber layer often referred to as "reverse optic atrophy."[11-13] Macular pigment epithelial changes have also been described.[14-16]

• ***Serial automated static perimetry.*** Reliable results are usually only achievable in older children, at least 9 years old, who are able to cooperate for the examination. Formal visual field testing performed on younger children, even those who can sit for the test, is not reliable or sensitive enough to detect early subtle changes. Recent studies also suggest that perimetry alone may not be enough to prove vigabatrin toxicity. Dr. Gonzalez and coworkers illustrated bilateral visual field constriction in 24 percent of vigabatrin-naive epileptic patients and concluded that visual fields constriction alone is not necessarily indicative of medication toxicity.[8]

• ***Optical coherence tomography.*** OCT has revolutionized our understanding of many different diseases that affect the nerve fiber layer and is a useful tool for detection of nerve fiber layer thinning in adults and older, cooperative children. Lisa Clayton and colleagues recently illustrated the effectiveness of OCT for evaluation of patients taking vigabatrin.[17] In this study, the average retinal nerve fiber layer thickness in patients taking vigabatrin was significantly thinner than in healthy controls. The extent of the nerve fiber layer thinning correlated well with the extent of visual field loss. The authors conclude that OCT is a reliable and objective tool for evaluating patients on vigabatrin. Unfortunately, it will not provide reliable information on younger children and patients who are unable to cooperate. Recent development of a handheld supine OCT may improve screening for vigabatrin toxicity in infants and young children. Such devices have been used successfully in a subset of these patients.

• ***Visual evoked potentials.*** Graham Harding, DSc, and colleagues illustrated that VEP can be used to detect visual field defects secondary to vigabatrin.[18] Their field-specific stimulus identified three of four abnormal perimetry results and seven of eight normal perimetry results, giving a sensitivity of 75 percent and a specificity of 87.5 percent. The authors conclude that field-specific VEPs are well-tolerated by children older than 2 years and are sensitive and specific enough to identify vigabatrin-associated defects. Unfortunately, despite the results of such studies, the authors conclude that " …in individual subjects, the tests are simply too unreliable to guide decision-making with regards to vigabatrin maintenance."[9]

• ***Electroretinograms.*** ERGs have been shown to detect early changes associated with vigabatrin toxicity; however, several problems prevent ERG from being an ideal screening tool. A

recent report warned against over-reliance on the ERG to detect vigabatrin toxicity. Their study found no significant association of any ERG parameter with visual field defects and could not determine if the ERG abnormalities they found were due solely to the effects of vigabatrin. Furthermore, there is no accepted "normal" waveform for very young children, and ERG in the pediatric population often requires general anesthesia, which may also alter the waveform. Finally, general anesthesia every three months is not convenient and is potentially dangerous. Most parents are hesitant to accept subjecting their child to the risks inherent in general anesthesia.

In conclusion, vigabatrin is a very effective drug for treatment of infantile spasms and seizure disorders refractory to other medications. Its use, however, is complicated by an irreversible, dose-dependent visual field constriction from photoreceptor toxicity. The majority of patients are asymptomatic since the macula is usually spared. Screening for this side effect in young children can be very difficult, especially given the fact that many children who need vigabatrin are non-verbal and poorly cooperative. Methods of screening for visual field constriction include serial fundus examination, serial automated static perimetry, OCT, VEP and ERG. Each method has its advantages and disadvantages. Most commonly, parents opt for serial fundus examination and prefer to avoid repetitive general anesthesia for their child. "Reverse" optic atrophy and macular pigment epithelial changes are the most common ophthalmoscopic findings. Any ophthalmologist screening children on vigabatrin should be ready to discuss the options with parents so they can make informed decisions. In addition, a periodic re-evaluation of the need for vigabatrin should be initiated by the patient's neurologist to ensure patients do not needlessly remain exposed to the risk of vision loss. The AAPOS policy statement on vigabatrin can be found at: http://www.aapos.org//client_data/files/2012/504_vigabatrin_05.09.12.pdf. Hopefully, future research will discover more effective tests of peripheral vision for patients who cannot comply with traditional methods. REVIEW

Dr. Fecarotta is an assistant clinical professor of ophthalmology at SUNY Downstate Medical Center in Brooklyn, N.Y.

1. Dichter MA, Brodie MJ. New antiepileptic drugs. N Engl J Med 1996;334:1583-90.
2. Ben-Menachem, E. 1995 Vigabatrin. Epilepsia 36 (Suppl. 2), S95-S104.
3. Camposano S, Major P, Halpern E, Thiele E. Vigabatrin in the treatment of childhood epilepsy: A retrospective chart review of efficacy and safety profile. Epilepsia 2008;49:1186-91.
4. Hancock E, Osborne J. Vigabatrin in the treatment of infantile spasms in tuberous sclerosis: Literature review. J Child Neurol 1999;14:71-74.
5. Eke T, Talbot JF, Lawden MC. Severe persistent visual field constriction associated with vigabatrin. BMJ 1997;314:180-1.
6. Bruni J, Guberman A, Vachon L, Desforges C. Vigabatrin as add on therapy for adult complex partial seizures: A double blind, placebo-controlled multicentre study. The Canadian Vigabatrin Study Group. Seizure 2000;9:224-232.
7. Jammoul F, Wang Q, Nabbout R, et al. Taurine deficiency is a cause of vigabatrin-induced retinal phototoxicity. Ann Neurol 2009 Jan: 65(1):98-107.
8. Gonzalez P, Sills GJ, Parks S. Binasal visual field defects are not specific to vigabatrin. Epilepsy Behav 2009 Nov;16(3):521-6. doi: 10.1016/j.yebeh.2009.09.003. Epub 2009 Oct 7.
9. http://www.aapos.org//client_data/files/2012/504_vigabatrin_05.09.12.pdf.
10. Fechtner RD, Khouri AS, Figureoa E, Ramirez M, et al. Short term treatment of cocaine and/or methamphetamine abuse with vigabatrin: Ocular safety pilot results. Arch Ophthalmol 2006;124:1257-62.
11. Frisen L, Malmgren K. Characterization of vigabatrin-associated optic atrophy. Acta Ophthalmol Scand 2003;81:466-73.
12. Wild JM, Robson CR, Jones AL, Cunliffe IA, Smith PE. Detecting vigabatrin toxicity by imaging of the retinal nerve fiber layer. Invest Ophthalmol Vis Sci 2006;47:917-24.
13. Buncic JR, Westall CA, Panton CM, Munn JR, McKeen LD, Logan WJ. Ophthalmology 2004;101:576-580.
14. French JA, Mosier M, Walker S, Sommerville K, Sussman N. A double-blind, placebo-controlled study of vigabatrin three g/day in patients with uncontrolled complex partial seizures. Vigabatrin Protocol 024 Investigative Cohort. Neurology 1996;46:54-61.
15. Guberman A, Bruni J. Long-term open multicentre, add-on trial of vigabatrin in adults resistant partial epilepsy. The Canadian Vigabatrin Study Group. Seizure 2000;9:112-118.
16. Sander JW, Trevisol-Bittencourt PC, Hart YM, Shorvon SD. Evaluation of vigabatrin as an add-on drug in the management of severe epilepsy. J Neurol Neurosurg Psychiatry 1990;53: 1008-1010.
17. Clayton LM, Devile M, Punte T, et al. Retinal nerve fiber layer thickness in vigabatrin- exposed patients. Ann Neurol 2011;69:845-854.
18. Harding GFA, Spencer EL, Wild JM, Conway M, Bohn RL. Field-specific visual evoked potentials: Identifying field defects in vigabatrin-treated children. Neurology 2002; 58(8):1261-1265.

REVIEW Advertising Index

Equipment and Supplies

EquipmentandSupplies

Practice Consulting

FOCUSED MEDICAL BILLING
A FULL SERVICE MEDICAL BILLING FIRM SPECIALIZING IN OPHTHALMOLOGY

Focused Medical Billing is a full service medical billing & practice consulting firm based out of New York servicing ONLY Ophthalmology practices.

We chose the name Focused Medical Billing because we wanted our clients to be certain of what they are getting with our firm. Our focus each and every day is to maximize our client's revenue by utilizing over a decade of experience and expertise in Billing, Coding, A/R Recovery, Forensic Billing, Practice Management and Consulting.

- Outsourced Billing lowers your overhead and maximizes revenue
- Full Service Billers specializing ONLY in Ophthalmology practices

Services include:
Billing | A/R Clean-Up | Practice Establishment
Practice Consulting & Management | Expert coding guarantees
maximum reimbursement and minimal denials

"Free, no obligation consultation"

- 14+ years experience in Ophthalmology billing, practice management & consulting
- No long term commitment or contract required.
- Your satisfaction with our service will make you a client for life.
- Electronic Claims Submission - 48 Hour Claim Submission Guarantee!
- 100% HIPAA Compliant

1-855-EYE-BILL
focusedmedicalbilling@yahoo.com • www.focusedmedicalbilling.com

Practice For Sale

Practice Consultants
Practice Sales • Appraisals • Consulting
www.PracticeConsultants.com

PRACTICES FOR SALE NATIONWIDE

Visit us on the Web or call us to learn more about our company and the practices we have available.

info@practiceconsultants.com
800-576-6935

www.practiceconsultants.com

Products and Services

P.M. MEDICAL BILLING AND CONSULTING

SPECIALIZING IN OPHTHALMOLOGY BILLING & CONSULTING

- *National, full service billing to ophthalmologists*
- *Maximum reimbursement is guaranteed*
- *Staff consists of Ophthalmic techs, expert coders & billers*
- *Increased revenue/low denial rate/complete & unrelenting follow up*

We specialize in old, outstanding AR, Practice Management & Credentialing

Contact us at:
pmmedbill@aol.com
or call us toll-free at:
1-888-PM-BILLING
for a free in-office consultation
WWW.PMOPHTHALMOLOGYBILLING.COM

Left your *Review of Ophthalmology* magazine at the office? No problem!

Get *Review* sent to your desktop or mobile device!

Just simply go to www.revophth.com and click on the digimag link to get your current issue.

Recent eyelid swelling appears to be resolved after an ER visit, but soon returns accompanied by headaches and eye pain.

Christine Talamini, MD

Presentation

A 19-year-old man presented to the Wills Eye Hospital Emergency Room for evaluation of intermittent right upper eyelid swelling that had been occurring for approximately one month. He noted temporary improvement with hot and cold compresses, but persistent recurrence. The swelling was accompanied by occasional tearing and blurry vision in the right eye. He denied history of prior trauma, recent insect bites or use of new facial products or detergents. His ocular exam was only notable for floppy eyelids and blepharitis, and he was prescribed erythromycin ointment at bedtime in both eyes, as well as warm compresses. At his two week follow-up appointment, the swelling was nearly completely resolved. The patient mentioned at this time that he was experiencing right-sided headaches, and he was referred to his primary-care provider for further evaluation. Five weeks after his initial presentation, the patient presented with recurrence of the right upper eyelid swelling, which had rapidly progressed over three days. He also reported right-sided periorbital pain, and new diplopia on upgaze.

Medical History

The patient had no prior ophthalmic history. He had chronic anxiety and underwent surgical repair of an umbilical hernia as an infant. He was not on any chronic medications. Family history was significant for glaucoma in his paternal grandmother. He reported occasional marijuana use, but did not smoke cigarettes or drink alcohol.

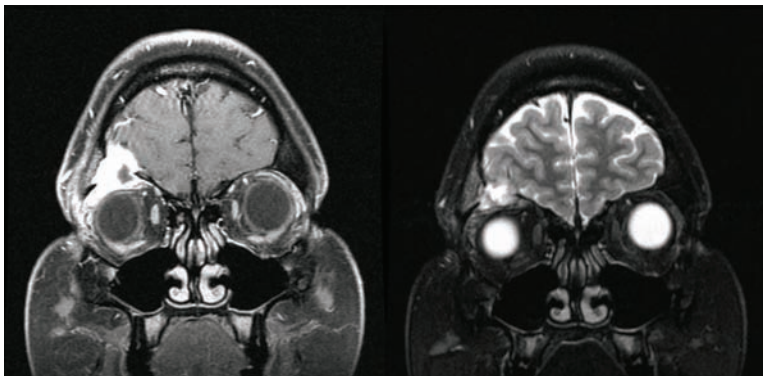
Examination

Visual acuity was 20/25 in the right eye, 20/20 in the left eye. Pupils were briskly reactive in both eyes with no afferent pupillary defect. Color vision was full in both eyes. Ocular motility was full, and visual fields were full to confrontation in both eyes. Intraocular pressure was within normal limits. There was significant swelling of the right upper eyelid, as well as suggestion of hypoglobus in the right eye.

What is your differential diagnosis? What further workup would you pursue? Please turn to p. 64

Diagnosis, Workup and Treatment

The patient underwent CT imaging of the orbits which revealed a mass in the right orbital roof with bony erosion. Further workup with MRI demonstrated a 2.4-cm aggressive enhancing lesion in the right orbit with extension to the right frontal calvarium and intracranial involvement with dural and epidural extension *(See Figure 1)*. Neurosurgery was consulted and a collaborative neurosurgery-ophthalmology team completely resected the mass. Pathology of the tissue biopsy demonstrated proliferation of macrophages or dendritic cells, and positive staining with CD1a confirmed a diagnosis of Langerhans' cell histiocytosis *(See Figure 2)*.



MRI, T1 post contrast with fat suppression (left) and MRI, T2-weighted (right), demonstrating a large enhancing mass in the right superior orbit.

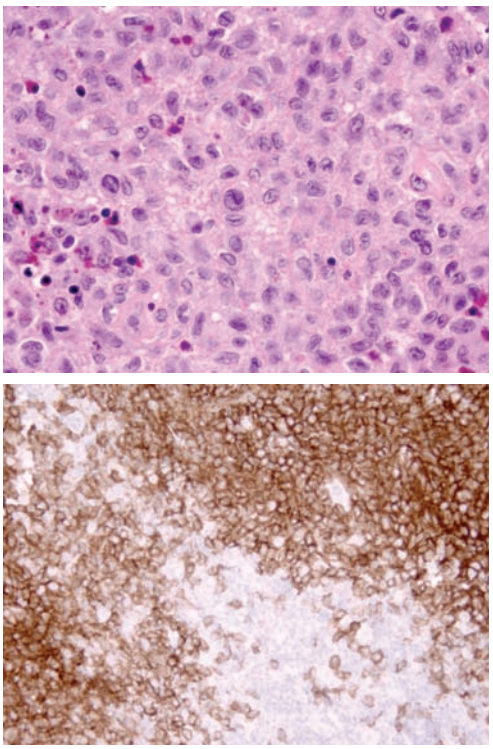


Figure 2. Microscopic review of the tissue specimen revealed proliferation of histiocytes (top) with positive CD1a staining, a marker for Langerhans' cells (bottom).

Discussion

Langerhans' cell histiocytosis (LCH), previously known as histiocytosis X, describes a rare spectrum of conditions with abnormal proliferation of histiocytes, occuring in various locations throughout the body. Three diagnoses historically fell under the classification of Langerhans' cell histiocytosis, differentiated by the extent and the number of organ systems involved: eosinophilic granuloma (unifocal, uni-system disease); Hand-Schuller-Christian disease (multifocal, uni-system disease); and Letterer-Siwe disease (multifocal, multi-system disease), the last being the most severe, with a 50-percent five-year survival rate. Its underlying pathogenesis remains unclear, as it has been characterized as both a neoplastic and reactive inflammatory process. Several triggers have been posited in the literature, including viruses and minor trauma, but these remain controversial.[1,2]

LCH classically presents in children, with a peak incidence at 1 to 4 years of age and a male predominance. Younger children tend to present with multi-system disease, with a worse prognosis.[2] The characteristic presentation in the orbit is anterior superolateral orbital swelling, which can be mistaken for periorbital cellulitis. LCH of the orbit commonly involves the frontal bone, as seen in our patient, which is thought to be derived from the ongoing hematopoiesis in the frontal bone through adulthood. Less commonly, LCH may also arise in the eyelids, conjunctiva, caruncle, choroid, optic chiasm, orbital apex or cavernous sinus.

Imaging with both CT and MRI allows for enhanced characterization of both the bony changes and soft tissue extension into the orbit and cranial fossae. Biopsy of the lesion is necessary to confirm the diagnosis as other orbital lesions in children, such as neuroblastoma, Ewing sarcoma and Wilms tumor, and other bony tumors may also present similarly on clinical exam and radiographic imaging. Positive immunohistological staining with neuronal markers S100 and CD1a are specific for Langerhans' cells and help to confirm the diagnosis. Other tissue markers may also be positive, including adenosine triphosphatase, acid phosphatase, peanut lectin, alpha-mannosidase,

CD207, fascin, CD4, CD45, CD101, HLA-DR, MHC Class II antigens and receptors for the Fc fragment of immunoglobulins.[2] Birbeck granules, rod or racquet-shaped inclusion bodies seen on electron microscopy, are considered pathognomonic. However, the absence of Birbeck granules, which are present in 50 to 70 percent of cases, does not exclude a diagnosis of LCH.

Once the diagnosis is established by tissue biopsy, systemic evaluation is necessary for proper staging of the disease. This includes laboratory testing with complete blood count, comprehensive metabolic panel, coagulation studies, urine osmolality, and imaging with skeletal survey and CT or MRI to search for metastases. Our patient had an extensive workup that did not demonstrate any other concerning lesions or multi-system involvement. The usual treatment strategies for LCH include observation, biopsy with either subtotal or total curettage, intra-lesional steroid injections, systemic steroid therapy or chemotherapy. Excision and intra-lesional steroid injections can spare children from the adverse effects of chemotherapy, with systemic chemotherapy and systemic steroid therapy reserved for recurrent lesions or lesions that fail to respond to initial excision. REVIEW

The author would like to thank Edward Bedrossian, MD, Wills Eye Hospital Oculoplastics and Orbital Surgery Service, Ralph Eagle, MD, Wills Eye Pathology Service, and Brian Doyle, MD, for their time and assistance in preparing this report.

1. Maccheron LJ, McNab AA, Elder J, Selva D, Martin FJ, Clement CI, Sainani A, Sullivan TJ. Ocular adnexal Langerhans cell histiocytosis clinical features and management. Orbit 2006 Sep;25(3):169-77.
2. Harris GJ. Langerhans Cell Histiocytosis of the Orbit: A Need for Interdisciplinary Dialogue. Am J Ophth 2006; 141: 374-78.
3. Herwig MC, Wojno T, Zhang Q, Grossniklaus HE. Langerhans Cell Histiocytosis of the Orbit: Five Clinicopathologic Cases and Review of the Literature. Surv Ophthalmol 2013 Jul-Aug;58(4):330-40.

(continued from page 41)

ophthalmology at Thomas Jefferson University in Philadelphia. He can be reached at johndpitcher@gmail.com.

Dr. Hsu is an assistant professor of ophthalmology on the Retina Service of Wills Eye Hospital and practices at Mid Atlantic Retina. He can be reached at jhsu@midatlanticretina.com.

1. Wang M, Munch IC, Hasler PW, et al. Central serous chorioretinopathy. Acta Ophthalmologica 2008;86:126-45.
2. Kitzmann AS, Pulido JS, Diehl NN, et al. The incidence of central serous chorioretinopathy in Olmsted County, Minnesota, 1980–2002. Ophthalmology 2008;115:169-73.
3. Gass JD. Pathogenesis of disciform detachment of the neuroepithelium. Am J Ophthalmol 1967;63:1-139.
4. Ross A, Ross AH, Mohamed Q. Review and Update of Central Serous Chorioretinopathy. Curr Opin Ophthalmol 2011;22:166-73.
5. Yamada K, Hayasaka S, Setogawa T. Fluorescein-angiographic patterns in patients with central serous chorioretinopathy at the initial visit. Ophthalmologica 1992;205:69-76.
6. Spitznas M, Huke J. Number, shape, and topography of leakage points in acute type I central serous retinopathy. Graefe's Arch Clin Exp Ophthalmol 1987;225:437-40.
7. Kitaya N, Nagaoka T, Hikichi T, et al. Features of abnormal choroidal circulation in central serous chorioretinopathy. Br J Ophthalmol 2003;87:709-12.
8. Maruko I, Iida T, Sugano Y, Ojima A, Ogasawara M, Spaide RF. Subfoveal thickness after treatment of central serous chorioretinopathy. Ophthalmology 2010;117:1792-9.
9.Shinojima A, Hirose T, Mori R, et al. Morphologic findings in acute CSC using spectral domain OCT with simultaneous angiography. Retina 2010;30:193-202.
10. Imamura Y, Fujiwara T, Margolis RON, Spaide RF. Enhanced depth imaging optical coherence tomography of the choroid in central serous chorioretinopathy. Retina 2009; 29:1469-73.
11. Gilbert CM, Owens SL, Smith PD, Fine SL. Long-term follow-up of central serous chorioretinopathy. Br J Ophthalmol 1984;68:815-20.
12. Bujarborua D. Long-term follow-up of idiopathic central serous chorioretinopathy without laser. Acta Ophthalmologica Scandinavica 2001; 79:417–21.
13. Singer M, et al. Non-steroidal anti-inflammatory topical therapy speeds recovery in central serous chorioretinopathy. AAO 2013 meeting, New Orleans. Unpublished data.
14. Leaver P, Williams C. Argon laser photocoagulation in the treatment of central serous retinopathy. Br J Ophthalmol 1979;63:674-77.
15. Yannuzzi LA, Slakter JS, Gross NE, et al. Indocyanine green angiography-guided photodynamic therapy for treatment of chronic central serous chorioretinopathy: A pilot study. Retina 2003;23:288-298.
16. Piccolino FC, Eandi CM, Ventre L, et al. Photodynamic therapy for chronic central serous chorioretinopathy. Retina 2003;23:752-763.
17. Smretschnig E, Ansari-Shahrezaei S, Hagen S, Glittenberg C, Krebs I, Binder S. Half-fluence photodynamic therapy in chronic central serous chorioretinopathy. Retina 2013:33:316-23.
18. Chan W, Lai TY, Lai RY, Liu DT, Lam DS. Half-dose verteporfin photodynamic therapy for acute central serous chorioretinopathy. Ophthalmology 2008;115:1756-1765.
19. Shin JY, Woo SJ, Yu HG, Park KH. Comparison of efficacy and safety between half-fluence and full-fluence photodynamic therapy for chronic central serous chorioretinopathy. Retina 2011;31:119-126.
20. Bae SH, Heo J, Kim C. Low-Fluence Photodynamic Therapy versus Ranibizumab for Chronic Central Serous Chorioretinopathy: One-Year Results of a Randomized Trial. Ophthalmol 2013 Nov 20. S0161-6420(13)00844-0. doi: 10.1016/j.ophtha.2013.09.024. [Epub ahead of print]
21. Witkin AJ, Brown GC. Update on nonsurgical therapy for diabetic macular edema. Curr Opin Ophthalmol 2011;22:185-9.
22. Chiang A, Regillo CD. Preferred therapies for neovascular age-related macular degeneration. Curr Opin Ophthalmol 2011;22:199-204.
23. London NJ, Brown G. Update and review of retinal vein occlusion. Curr Opin Ophthalmol 2011;22:159-65.
24. Lim JW, Kim MU, Shin M-C. Aqueous humor and plasma levels of vascular endothelial growth factor and interleukin-8 in patients with central serous chorioretinopathy. Retina 2010;30:1465-1471.
25. Kim H-S, Lee JH. The short-term effect of intravitreal bevacizumab for treatment of central serous chorioretinopathy. J Korean Ophthalmol Soc 2010;51:860-864.
26. Torres-Soriano M, Garcı´a-Aguirre G, Kon-Jara V, et al. A pilot study of intravitrealbevacizumab for the treatment of central serous chorioretinopathy (case reports). Graefe's Arch Clin Exp Ophthalmol 2008;46:1235-1239.
27. Seong HK, Bae JH, Kim ES, et al. Intravitreal bevacizumab to treat acute central serous chorioretinopathy: Short-term effect. Ophthalmologica 2009;223:343-347.
28. Lim JW, Ryu SJ, Shin M-C. The effect of intravitreal bevacizumab in patients with acute central serous chorioretinopathy. Korean J Ophthalmol 2010;24:155-158.
29. Bae SH, Heo JW, Kim C, et al. A randomized pilot study of low-fluence photodynamic therapy versus intravitreal ranibizumab for chronic central serous chorioretinopathy. Am J Ophthalmol 2011;152:784-92.
30. Artunay O, Yuzbasioglu E, Rasier R, et al. Intravitreal bevacizumab in treatment of idiopathic persistent central serous chorioretinopathy: A prospective, controlled clinical study. Curr Eye Res 2010;35:91-98.
31. Chung Y-R, Seo EJ, Lew HM, Lee KH. Lack of positive effect of intravitreal bevacizumab in central serous chorioretinopathy: Meta-analysis and review. Eye 2013;27:1339-46.
32. Pikkel J, Beiran I, Ophir A, Miller B. Acetazolamide for central serous retinopathy. Ophthalmology 2002;109:1723-5.
33. Avci R, Deutman AF. Treatment of central serous choroidopathy with the beta receptor blocker metoprolol (preliminary results). Klin Monbl Augenheilkd 1993;202:199-205.
34. Tatham A, Macfarlane A. The use of propranolol to treat central serous chorioretinopathy: An evaluation by serial OCT. J Ocular Pharmacol Therapeut 2006;22:145-9.
35. Golshahi A, Klingmuller D, Holz FG, Eter N. Ketoconazole in the treatment of central serous chorioretinopathy: A pilot study. Acta Ophthalmologica 2010;88:576-81.
36. Nielsen JS, Jampol LM. Oral mifepristone for chronic central serous chorioretinopathy. Retina 2011;31:1928-36.
37. Forooghian F, Meleth AD, Cukras C, Chew EY, Wong WT, Meyerle CB. Finasteride for chronic central serous chorioretinopathy. Retina 2011;31:766-71.
38. Zhao M, Célérier I, Bousquet E, et al. Mineralocorticoid receptor is involved in rat and human ocular chorioretinopathy. J Clin Invest 2012;122(7):2672-9.
39. Bousquet E, Beydoun T, Zhao M, Hassan L, Offret O, Behar-Cohen F. Mineralocorticoid receptor antagonism in the treatment of chronic central serous chorioretinopathy: A pilot study. Retina 2013;33:2096-102.
40. http://clinicaltrials.gov/ct2/show/NCT01990677
41. Yavas GF1, Küsbeci T, Kasikci M, Günay E, Dogan M, Unlü M, Inan UÜ. Obstructive sleep apnea in patients with central serous chorioretinopathy. Curr Eye Res 2014 39(1):88-92..

RESTASIS® (Cyclosporine Ophthalmic Emulsion) 0.05%

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

INDICATION AND USAGE

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Potential for Eye Injury and Contamination

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

Use with Contact Lenses

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

ADVERSE REACTIONS

Clinical Trials Experience

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

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

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

Post-marketing Experience

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C

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

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

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

PATIENT COUNSELING INFORMATION

Handling the Container

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

Use with Contact Lenses

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

Administration

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

Rx Only

ALLERGAN

D-KAT Digital

The first FDA 510(k) digital applanation tonometer

40H Slit Lamp

The next generation slit lamp featuring advanced Keeler optics

Vantage Plus Wireless

The world's best selling binocular indirect ophthalmoscope

MULTIPLY YOUR SAVINGS

BUY MORE SAVE MORE

Keeler's 40H Slit Lamp is quickly gaining the reputation as a world class device.

Featuring Keeler's famous optics, 6 to 40x magnification, LED Illumination in a beautifully crafted, thoughtful design, giving you the functionality and performance you want, need and expect from a Keeler Slit Lamp.

BUY 1 / GET 1
Purchase a Keeler 40 H Slit Lamp and you'll receive a FREE Keeler D-KAT Digital

BUY 2 / GET 2
Purchase 2 Keeler 40H Lamps and you'll receive 2 FREE Keeler D-KAT Digitals

BUY 3 / GET 3 + 1
Purchase 3 Keeler 40H Slit Lamps and you'll receive 3 FREE Keeler D-KAT Digitals + a FREE Keeler Vantage Plus BIO

Outfit your offices with Keeler 40H Slit Lamps before October 31, 2014 and take advantage of these great offers!

Offer valid: May 1st to October 31, 2014. No other Keeler offers can be combined.

Keeler OPTICS

Keeler Instruments, Inc. • 456 Parkway • Broomall, PA 19008
Tel: (800) 523-5620 • Fax: (610) 353-7814 • email: keeler@keelerusa.com

Restasis®
(Cyclosporine Ophthalmic Emulsion) 0.05%

restasis.com

For patients with decreased tear production presumed to be due to ocular inflammation associated with Chronic Dry Eye

RESTASIS® MAKES MORE OF THEIR OWN REAL TEARS POSSIBLE

Prescribe RESTASIS® for your appropriate moderate and severe Dry Eye patients and increase their own real tear production over time with continued use

For local co-pays, scan QR-code or visit restasiscopay.com

Indication and Usage

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

Important Safety Information

Contraindications

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

Warnings and Precautions

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

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

Adverse Reactions

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

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

ALLERGAN