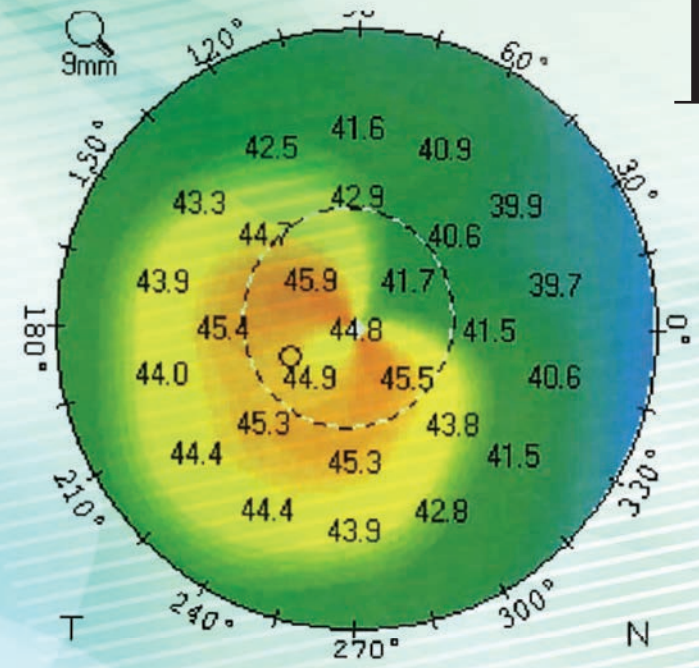
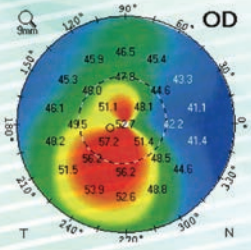
REVIEW® of Ophthalmology

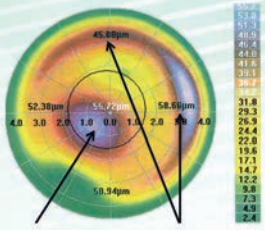
February 2015

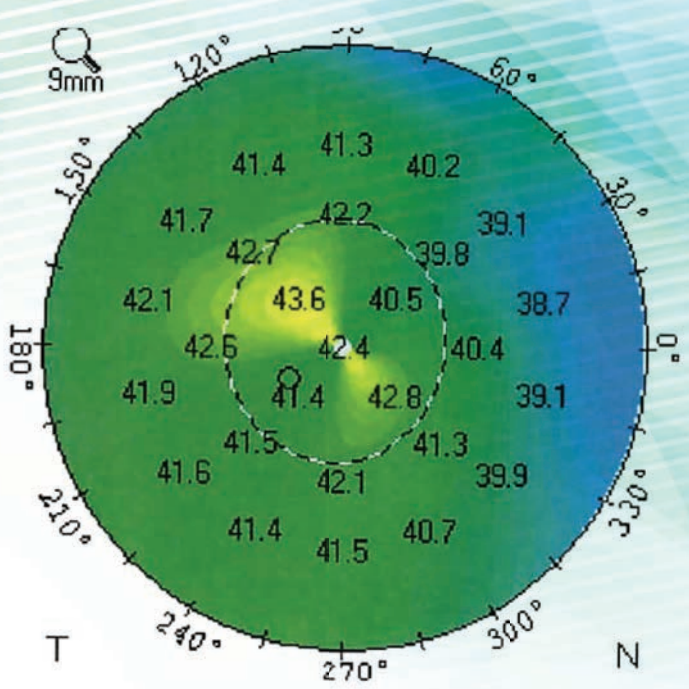
reviewofophthalmology.com

Refractive Surgery Issue









PATADAY® Solution: The #1 Prescribed Allergy Eye Drop[1]

THE SOLUTION YOU'VE TURNED TO, SEASON AFTER SEASON[1]

Your allergic conjunctivitis patients can rely on PATADAY® Solution for proven ocular itch relief[2] with excellent payer coverage and affordability

- Broad Tier 2 formulary coverage for both commercial and Medicare Part D plans[3]
- Patient Rebate Programs for eligible patients*

*This offer is not valid for patients who are enrolled in Medicare Part D, Medicaid, Medigap, VA, DOD, Tricare, or any other government run or government sponsored healthcare program with a pharmacy benefit. Please refer to complete terms and conditions on the rebate materials.

INDICATION AND DOSING

PATADAY® Solution is a mast cell stabilizer indicated for the treatment of ocular itching associated with allergic conjunctivitis. The recommended dose is one drop in each affected eye once a day.

IMPORTANT SAFETY INFORMATION

PATADAY® Solution is for topical ocular use only. It is not for injection or oral use.

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

Patients should be advised not to wear contact lenses if their eyes are red.

PATADAY® Solution should not be used to treat contact lens-related irritation. The preservative in PATADAY® Solution, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses and **whose eyes are not red** should be instructed to wait at least ten minutes after instilling PATADAY® Solution before they insert their contact lenses.

Symptoms similar to cold syndrome and pharyngitis were reported at an incidence of approximately 10%.

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

References: 1. IMS Health, IMS National Prescription Audit™, August 2010 to November 2013, USC 61500 OPHTH ANTI-ALLERGY. **2**. PATADAY® Solution package insert. **3**. Formulary data provided by Pinsonault Associates, LLC, PathfinderRx, November 2013.

Alcon
a Novartis company

Visit myalcon.com/pataday

Once Daily Pataday®
(olopatadine hydrochloride ophthalmic solution) 0.2%

Pataday®
(olopatadine hydrochloride ophthalmic solution) 0.2%

BRIEF SUMMARY OF PRESCRIBING INFORMATION.

FOR ADDITIONAL INFORMATION REFER TO THE FULL PRESCRIBING INFORMATION.

INDICATIONS AND USAGE

PATADAY® Solution is indicated for the treatment of ocular itching associated with allergic conjunctivitis.

DOSAGE AND ADMINISTRATION

The recommended dose is one drop in each affected eye once a day.

DOSAGE FORMS AND STRENGTHS

Ophthalmic solution 0.2%: each ml contains 2.22 mg of olopatadine hydrochloride.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

For topical ocular use only.

Not for injection or oral use.

Contamination of Tip and Solution

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

Contact Lens Use

Patients should be advised not to wear a contact lens if their eye is red.

PATADAY® (olopatadine hydrochloride ophthalmic solution) 0.2% should not be used to treat contact lens related irritation.

The preservative in **PATADAY®** Solution, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses **and whose eyes are not red**, should be instructed to wait at least ten minutes after instilling **PATADAY®** (olopatadine hydrochloride ophthalmic solution) 0.2% before they insert their contact lenses.

ADVERSE REACTIONS

Symptoms similar to cold syndrome and pharyngitis were reported at an incidence of approximately 10%.

The following adverse experiences have been reported in 5% or less of patients:

Ocular: blurred vision, burning or stinging, conjunctivitis, dry eye, foreign body sensation, hyperemia, hypersensitivity, keratitis, lid edema, pain and ocular pruritus.

Non-ocular: asthenia, back pain, flu syndrome, headache, increased cough, infection, nausea, rhinitis, sinusitis and taste perversion.

Some of these events were similar to the underlying disease being studied.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic effects: Pregnancy Category C

Olopatadine was found not to be teratogenic in rats and rabbits. However, rats treated at 600 mg/kg/day, or 150,000 times the maximum recommended ocular human dose (MROHD) and rabbits treated at 400 mg/kg/day, or approximately 100,000 times the MROHD, during organogenesis showed a decrease in live fetuses. In addition, rats treated with 600 mg/kg/day of olopatadine during organogenesis showed a decrease in fetal weight. Further, rats treated with 600 mg/kg/day of olopatadine during late gestation through the lactation period showed a decrease in neonatal survival and body weight. There are, however, no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human responses, this drug should be used in pregnant women only if the potential benefit to the mother justifies the potential risk to the embryo or fetus.

Nursing Mothers

Olopatadine has been identified in the milk of nursing rats following oral administration. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in the human breast milk. Nevertheless, caution should be exercised when **PATADAY®** (olopatadine hydrochloride ophthalmic solution) 0.2% is administered to a nursing mother.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 2 years have not been established.

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Olopatadine administered orally was not carcinogenic in mice and rats in doses up to 500 mg/kg/day and 200 mg/kg/day, respectively. Based on a 40 µL drop size and a 50 kg person, these doses were approximately 150,000 and 50,000 times higher than the MROHD. No mutagenic potential was observed when olopatadine was tested in an *in vitro* bacterial reverse mutation (Ames) test, an *in vitro* mammalian chromosome aberration assay or an *in vivo* mouse micronucleus test. Olopatadine administered to male and female rats at oral doses of approximately 100,000 times MROHD level resulted in a slight decrease in the fertility index and reduced implantation rate; no effects on reproductive function were observed at doses of approximately 15,000 times the MROHD level.

Rx only

Reference: 1. IMS Health, IMS National Prescription Audit, August 2010 to October 2013, USC 61500 OPHTH ANTI-ALLERGY.

Alcon
a Novartis company

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 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.reviewofophthalmology.com

jmi

Imaging With Depth-of-field. Just Dandy.

What if none of your slit images or video had blurry edges? You would have a Haag-Streit, of course. Invest in one and submerge yourself into our extreme world of depth of field.

Visit haag-streit-usa.com to learn about our entire range of slit lamps and imaging systems.

800.787.5426
haag-streit-usa.com

HAAG-STREIT USA

REVIEW NEWS
Volume XXII • No. 2 • February 2015

This Time, Could Congress Slay the SGR for Good?

With the clock running down on the latest "patch" to the Medicare Sustained Growth Rate (SGR), Congress next month may finally take up whether to scrap the formula Medicare uses to set physician payments, but short of that, it will probably forestall a looming 24 percent decrease in physician reimbursements with another patch.

In the process, Congress could have an opportunity to delay another government mandate: implementation of ICD-10 codes. While dismantling key Affordable Care Act components and outright repeal are dominating the attention of health policy experts since Republicans gained control of both houses of Congress, physicians are more focused on what will happen as the latest SGR patch runs out March 31.

"The answer to SGR relief is probably what's happened all the other times; if the SGR doesn't get fixed, there will almost certainly will be a patch and of course, it will probably be at the last minute," says Michael X. Repka, MD, AAO medical director for governmental affairs.

A better answer would be to permanently fix the SGR by repealing or restructuring it. The American College of Physicians, for example, has called on Congress to replace SGR with a program of incentives for physicians to improve quality and participate in innovative delivery systems like patient-centered medical homes.

The current price tag for a permanent SGR fix is about $144 billion, and last year Congress was close to doing just that but then backed away when Democrats and the GOP could not agree on how to pay for it, Dr. Repka says. "In terms of getting it fixed, I guess one would say we have both houses that are run by a single party; maybe there's a better chance of getting an agreement to have something passed," he says.

However, Congress must contend with the "pay-for rule," the Congressional mandate that federal budget cuts must offset any new spending. If Congress can waive that and reach agreement on an SGR fix, President Obama would probably sign it unless the fix taps into the Affordable Care Act to fund it, Dr. Repka says. Both Congressional caucuses discussed a permanent SGR fix at their respective retreats last month, according to Dr. Repka. "Maybe they'll have a plan," he says.

Without a permanent solution, continuous patching will only cost more. The Congressional Budget Office has estimated the cost of patches over the next 10 years at around $16 billion.

When Congress passed the SGR patch last year, it also voted to delay implementation of ICD-10 by a year to October 1, 2015. A similar scenario could play out again this year, says Rob Tennant, Medical Group Management Association senior policy adviser for government affairs. Since last year, resistance to another delay has hardened, led by the so-called Coalition for ICD-10 comprised of health insurers and health information management groups. While the AMA is pushing for another delay, the MGMA has not taken a position.

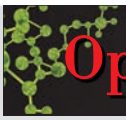
The AAO does have reservations about the ICD-10 deadline. "We have commented before to CMS that we thought that Oct 1 was a bad date to do it because it was not in synch with all the other reporting requirements for PQRS, but that's more of a technical detail," Dr. Repka says.

A New Clue to the Trigger for AMD

New research from scientists at the University of Maryland School of Medicine has found that tiny lumps of calcium phosphate may be an important triggering factor for age-related macular degeneration. This is the first time these mineral deposits have been implicated in the disease, which affects more than 10 million Americans. The article appeared in the *Proceedings of the National Academy of Sciences*.

Biochemist Richard Thompson, PhD, along with his colleague from University College, London, Imre Lengyel, PhD, and a multidisciplinary international team studied retinal samples from a group of elderly patients, some of whom had AMD. They found that the AMD

(continued on page 8)



Ophthalmic Product Development Insights

Sena Biswas, PhD, and Matthew Chapin • Ora Inc., Andover, Mass.

The Scientist-Entrepreneur as CEO

Scientist-entrepreneurs often feel as if nobody knows their product better than they do. They have often developed it based upon a deep understanding of clinical practice and/or basic research, possibly refined it with the feedback of patients, and are many times internationally recognized experts in their fields. Naturally, they feel that they should lead a new enterprise that is based on their products. This feeling is accentuated when scientist-entrepreneurs see that the alternative leaders are business and finance professionals, who may not have the same academic or clinical background.

Most scientist-entrepreneurs we have met are, in fact, usually the most knowledgeable about their product and the underlying technology around which a new company is based. However the commercialization, operational, managerial and financial skills that are vital to creating a successful enterprise are many times not part of a scientist-entrepreneur's tool box. In this article we highlight some of the key skills required to run a successful enterprise and the differences between these skills and—generally speaking—the training of scientist-entrepreneurs. We highlight some of the practices of successful scientist-entrepreneurs whom we have worked with. Of course there are many exceptions, including new physician-scientists who have successfully brought forward new ventures; we will simply be making general comments that we hope are helpful for new scientist-entrepreneurs to consider.

Commercialization

A study by Egon Zehnder International and McKinsey & Co. showed that the single biggest predictor of success for a CEO is customer impact.[1] At most established biopharmaceutical companies, commercial considerations, such as the cost-benefit profile of the therapy, addressable market and competitive products, are thoroughly examined prior to initiation of development. These considerations are critical to the success of a product or a company. Even an efficacious drug or device may have marginal benefit if there are cheaper alternatives and it cannot be commercialized. Physicians are in a good position to understand the multitude of factors—including benefit to a patient; efficacy; safety; drop comfort; mode of administration; convenience of dosing; container closure systems; ease of use—and what is needed to make the clinical decision to use one product over another. However, making the case for reimbursement to payers requires a different experience base, and it is important to take these factors into consideration during product development. In addition, a global focus is needed to ensure there aren't missed opportunities that could maximize the value of their product outside the home market.

Finance

For an emerging life-sciences company, the immediate customer is often the financial community that provides capital when there are no revenues to support the company. Scientist-entrepreneurs are accustomed to dealing with other scientists for access to funding; physicians can often override budgetary guidelines for the benefit of their patients. These experiences are quite different from raising capital for a new company, which requires constant selling of the company's vision to business executives who have financial and investment acumen, but sometimes different scientific or clinical experience.

When a scientist-entrepreneur is successful in getting funding, he then has to focus on cash management, and how that impacts sequencing of development activities and proper decision-making to get to the value inflection. In the start-up world, running out of cash has dire consequences. Either the enterprise must be shut down, or investors must put in additional capital to rescue the company. This often occurs before there's proof that the enterprise is viable, and at the cost of major dilution to the founder. Experienced entrepreneurs do not want to put their investors in this position, as it usually means a loss of faith in them as leaders, and they are understandably intensely focused on effective cash management. This highlights the importance of efficient deployment of capital and ensuring every investment is being made in activities that advance the program to value inflection and a successful exit. A general rule is to fail early, i.e., conduct experiments that clarify the odds of eventual success. Many times this is difficult for founders. Investors appreciate leaders who do not put more capital towards businesses that have a low probability of eventual success.

Management Leadership

In a clinical environment, physicians are expected to make tough decisions rapidly and independently. Similarly, scientists are rewarded for independent thinking and developing scientific insights not apparent to their peers. Effective business leaders, on the other hand, are rewarded for bringing on talented individuals and managing and leading teams of such individuals toward common goals. Decisions and company strategy must be co-developed by all members of the executive team to ensure buy-in. The most effective entrepreneurial managers score higher on collaborative and team-building skills than their less-effective peers.[1] Unilateral decision-making, rewarded in a clinical or research environment, can be counterproductive in the start-up company. When independence, not collaboration, has been rewarded throughout their training, it is not surprising that scientist-entrepreneurs may be surprised at the value of a collaborative management style in the business environment.

Operations

Bringing a new drug or device from the bench to the clinic is a completely different process from identifying the target and molecule in the first place. Whereas identifying a molecule that intervenes in a novel pathway requires scientific curiosity and imagination, a completely different skill set is needed for defining the target product profile up front, up-scaling manufacturing, testing the molecule for toxicity and navigating through the regulatory challenges to conduct a clinical study. Suddenly, the free-minded researcher is confronted with quality systems, documentation requirements and other regulations. Many researchers initially feel limited in their ability to be creative in such an environment. In addition, almost all academic institutions educate and train their students to become researchers; however, there are only very few training programs available that teach drug development, including regulations and processes. Therefore, almost all successful development professionals acquired their skills through hands-on experiences in start-ups or large pharmaceutical companies.

Extrinsic Barriers to Success

In addition to successfully acquiring new skills, the scientist-entrepreneur faces long odds that he remains CEO through multiple rounds of fundraising. Numerous studies have shown that the probability of a CEO being replaced increases with venture capital financing,[2] with reports of 80 percent of founding CEOs being fired by the time multiple rounds of funding are raised.[3] While the data is mixed on whether companies perform better with or without a founding CEO,[3] the fact remains that most will be replaced. This may be why many

successful scientist-entrepreneurs choose to take scientific or advisory roles in companies they founded. This allows them to function in roles that they are more familiar with, as well as found multiple companies. It also allows them to acquire skills and gain valuable start-up experience prior to taking the helm of a start-up company.

Successful Entrepreneurs

We have had the good fortune of working with Professor Robert Langer, ScD, of MIT, perhaps the most successful and prolific scientific founder in biotechnology. He is the author of more than 1,100 patents and has started well over two dozen companies, with over 100 products on sale or in clinical trials. Dr. Langer has enjoyed great financial, scientific and clinical success without ever having to be primarily responsible for the challenges highlighted here. Interestingly, he is well known for his collaborative nature and ability to motivate individuals, two of the key characteristics of successful entrepreneurs.

Serial entrepreneurs are good role models for new scientists with ideas they hope to move forward. Allowing other experienced professionals to take on the tasks that the scientist-entrepreneur does not have experience with or ability to focus on, and learning the keys to repeating that success, enables the founding of multiple companies. While some new scientist-entrepreneurs (and who do not have industry experience) have succeeded in their first CEO role, we believe—generally speaking—it is wiser to take on advisory or scientific/medical roles in the new company and gain the experience required to successfully run future endeavors.

Dr. Biswas is a managing director at VIMAC Ventures, and Mr. Chapin is the senior vice president of corporate development at Ora Inc. Ora provides a comprehensive range of product development, clinical-regulatory and product consulting for developers, investors and buyers; clinical trial services and regulatory submissions; and asset and business partnering support in ophthalmology. We welcome comments or questions related to this or other development topics. Please send correspondence to mchapin@oraclinical.com.

1. Return on Leadership—The Competencies that Generate Growth. Egon Zehnder International, McKinsey and Company, February, 2011. http://www.mckinsey.de/sites/mck_files/files/Return%20on%20Leadership.pdf
2. Bains W. When should you fire the founder? J Comm Biotech 2007;13:139-149.
3. On average, how often do founding CEOs get replaced by a VC-controlled BoD candidate, and in what circumstances?, Firas Raouf, Quora.com

REVIEW of Ophthalmology
EDITORIAL STAFF

Editor in Chief
Christopher Glenn
(610) 492-1008
cglenn@jobson.com

Managing Editor
Walter C. Bethke
(610) 492-1024
wbethke@jobson.com

Senior Editor
Christopher Kent
(814) 861-5559
ckent@jobson.com

Associate Editor
Kelly Hills
(610) 492-1025
khills@jobson.com

Chief Medical Editor
Mark H. Blecher, MD

Senior Director, Art/Production
Joe Morris
(610) 492-1027
jmorris@jobson.com

Art Director
Jared Araujo
(610) 492-1023
jaraujo@jobson.com

Graphic Designer
Matt Egger
(610) 492-1029
megger@jobson.com

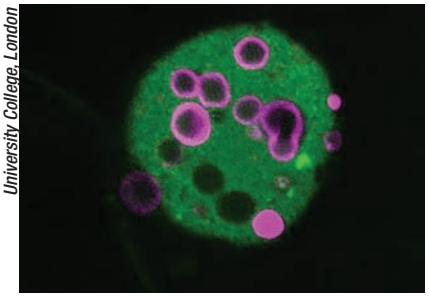
International coordinator, Japan
Mitz Kaminuma
Reviewophthalmo@aol.com

Business Offices
11 Campus Boulevard, Suite 100
Newtown Square, PA 19073
(610) 492-1000
Fax: (610) 492-1039

Subscription inquiries:
United States — (877) 529-1746
Outside U.S. — (847) 763-9630
E-mail:
rhsubs@halldata.com
Website: www.reviewofophthalmology.com

jmi BPA

REVIEW News


University College London

An image of HAP deposits, surrounded by fat and protein. The HAP is pink.

samples contained tiny spherules of a mineralized calcium phosphate known as hydroxyapatite, or HAP. HAP is common in the body—it comprises the hard part of bones and teeth—but it had never been identified in that part of the eye before.

AMD develops slowly over decades, with the buildup of fatty protein deposits in the retina, which cause damage by blocking the flow of nutrients into the light-sensitive portion of the eye, and of waste products out. Scientists have known about these deposits for over a century, but their origins remained a mystery. Dr. Thompson and Dr. Lengyel discovered that the deposits appear to form around the tiny bits of HAP. Once these chunks appear, the fatty protein material coalesces around it; over years, these globules build up.

They discovered the possible role of HAP by examining tissue samples from patients using X-ray diffraction and fluorescent staining chemicals. "We had no idea that HAP might be involved," says Dr. Thompson, who is an associate professor of biochemistry and molecular biology at the school. "That's what makes this work so exciting. It opens up a lot of new research opportunities."

The researchers are looking into the possibility of using the presence of HAP as an early warning signal for AMD risk with a hope that this will aid early intervention before patients have suffered irreversible vision loss. Eventually, they say, it may be possible to devise methods to reduce HAP deposits or limit the growth and progression of the disease. "We think HAP plays a key role in this process," said Dr. Lengyel. "This is a new explanation for how these deposits start."

"This work epitomizes the school's mission," said Dean E. Albert Reece, MD, PhD, MBA, who is vice president for Medical Affairs, University of Maryland, and the John Z. and Akiko K. Bowers Distinguished Professor and Dean of the School of Medicine. "Dr. Thompson and his colleagues have provided new insight into the deep mechanisms of this terrible disease, and in doing so, they have created new avenues of research that have the potential to help millions of people."

The work was supported in part by the Bright Focus Foundation in the United States and the Bill Brown Charitable Trust in the UK.

A New Tack in Avoiding TED

A University of Michigan study reports that patients with Graves' disease had a significantly reduced risk of developing thyroid eye disease after taking statins or undergoing surgical removal of the thyroid. The study, based on an analysis of health-care claims data and published in the December issue of *JAMA Ophthalmology*, suggests that physicians may, for the first time, be able to modify their patients' risk for TED through medical or surgical intervention.

Individuals with Graves' disease, an autoimmune condition characterized by overproduction of a thyroid hormone, often develop TED, which can cause bulging eyes, double vision, dry eye and in some cases, vision loss. "Previously, aside from

(continued on page 18)

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
Alessandra Intili, 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, WEST PALM BEACH, FLA.
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

REVIEW® of Ophthalmology

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
PUBLISHER
JAMES HENNE
(610) 492-1017 JHENNE@JOBSON.COM

REGIONAL SALES MANAGER
MICHELE BARRETT
(610) 492-1014 MBARRETT@JOBSON.COM

REGIONAL SALES MANAGER
MICHAEL HOSTER
(610) 492-1028 MHOSTER@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:
REVOPHTHALMOLOGY@CAMBEYWEST.COM

CIRCULATION
PO BOX 71, CONGERS, NY 10920-0071
(877) 529-1746
OUTSIDE USA: (845) 267-3065

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 71, Congers, NY 10929-0071. 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 (845-267-3065. Or email us at revophthalmology@cambeywest.com. Canada Post: Publications Mail Agreement #40612608. Canada Returns to be sent to Bleuchip International, P.O. Box 25542, London, ON N6C 6B2.

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 Carrying Case. Only Portable Slitlamps that have a binocular microscope allowed as trade-in. Offer expires March 31, 2015.

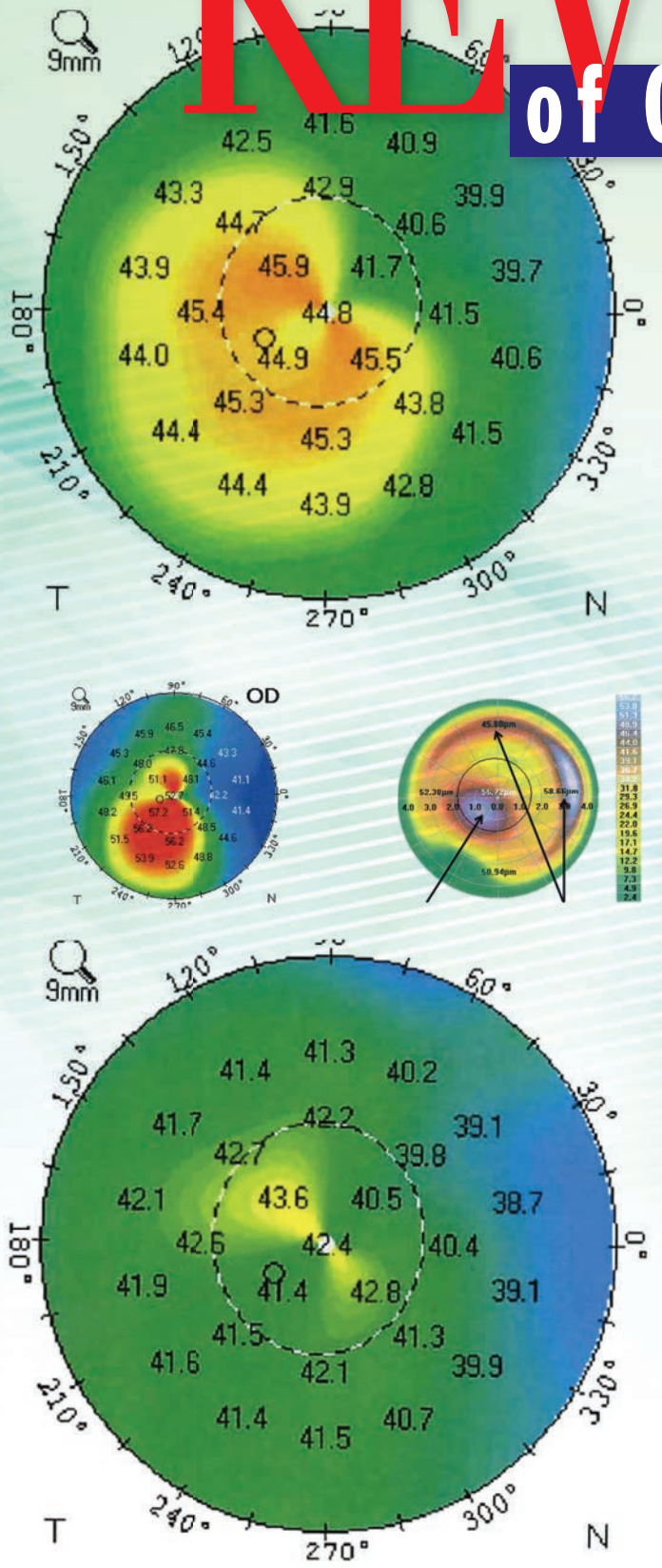
Buy Online!
keelerusa.com

Keeler
OPTICS

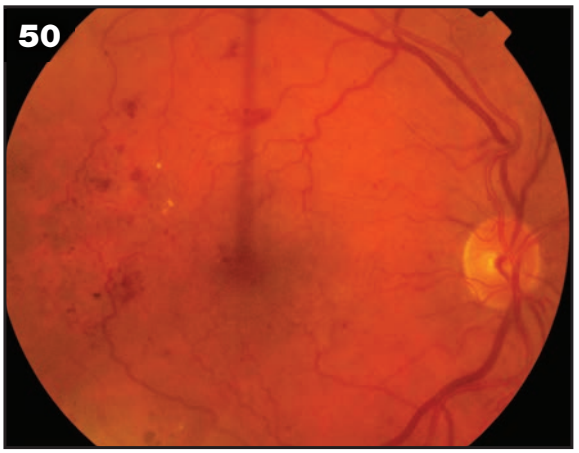
Keeler Instruments, Inc. • 456 Parkway • Broomall, PA 19008 • Tel: (800) 523-5620 • Fax: (610) 353-7814 • email: keeler@keelerusa.com

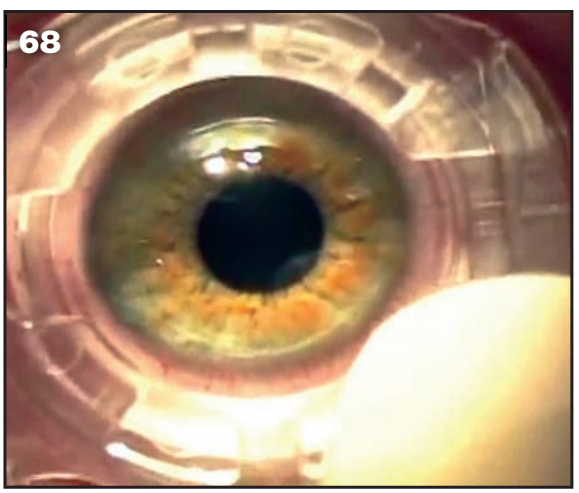
REVIEW® of Ophthalmology

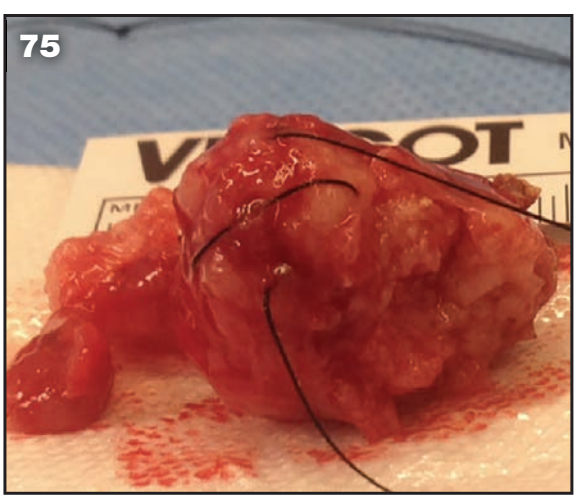
February 2015 • Volume XXII No. 2 | reviewofophthalmology.com



Departments







PROVEN

DO EVEN MORE WITH PROVEN *iFS* TECHNOLOGY

A comprehensive platform of surgical capabilities

As the leader in femtosecond technology with over 5 million procedures worldwide, the ***iFS*** Laser goes well beyond LASIK flaps to enable the creation of fully individualized incisions for all ophthalmic procedures, including refractive, corneal, and cataract surgery.

Contact your AMO representative or visit www.amo-ilasik.com/iFS.

iFS
Advanced Femtosecond Laser

INDICATIONS: The ***iFS*** Laser is a precision ophthalmic surgical laser indicated for use in patients undergoing surgery or treatment requiring initial lamellar resection of the cornea and to create tunnels for placement of corneal ring segments, in lamellar keratoplasty and corneal harvesting, in the creation of a corneal flap in patients undergoing LASIK surgery, and in the creation of a lamellar cut / resection of the cornea for lamellar keratoplasty (***IntraLase***-Enabled Keratoplasty or IEK), and in the creation of a penetrating cut/incision for penetrating keratoplasty (or IEK). The ***iFS*** Laser is also indicated for use in penetrating and/or intrastromal arcuate incisions. **CONTRAINDICATIONS:** Lamellar resection for the creation of a corneal flap is contraindicated in the presence of corneal edema, corneal lesions, hypotony, glaucoma, existing corneal implant or keratoconus. IEK procedures and arcuate incisions are contraindicated in the presence of any corneal opacity adequately dense to obscure visualization of the iris, descemetocele with impending corneal rupture, previous corneal incisions that might provide a potential space into which the gas produced by the procedure can escape, or corneal thickness requirements that are beyond the range of the system. **WARNINGS:** Check all treatment parameters for accuracy. Setting the posterior depth too deep could result in injury to other ocular structures. Patient Interface disposables should not be reused or resterilized. **PRECAUTIONS:** A surgeon should have successfully completed one or more training courses before attempting to create a corneal resection. The use of the ***iFS*** Laser for IEK procedures or for arcuate incisions is not recommended for certain patients. Please see the Operator's Manual for a complete listing. **ADVERSE EVENTS:** Possible complications resulting from LASIK flap creation include corneal edema/inflammation, corneal pain, epithelial ingrowth, epithelial defect, infection, photophobia, flap decentration, incomplete flap creation, flap tearing or incomplete lift-off, free cap, inflammation, thin or thick flaps, or flap striae. Arcuate incision complications include corneal edema/inflammation, corneal pain, epithelial ingrowth, epithelial defect, infection, photophobia or corneal endothelium perforation. Transient Light Sensitivity Syndrome (TLSS) and Peripheral Light Spectrum (PLS) have been sporadically reported and may occur following LASIK flap creation. TLSS (1% of patients) is characterized by symptoms of mild to severe light sensitivity which manifests between 2 and 6 weeks postoperatively. PLS (.03% of patients) is a temporary phenomenon whereby patients report the perception of a spoke-like spectrum of light in the periphery of their vision. **CAUTION:** Federal law restricts this device to sale, distribution, and use by or on the order of a physician or other licensed eye care practitioner who has been trained in the calibration and operation of this device, and who have experience in the surgical treatment and management of refractive errors.

Abbott
Medical Optics


Mobile Apps to Boost Productivity

New applications for documentation, organization and easy access to data let you raise your smartphone's IQ.

Walter Bethke, Managing Editor

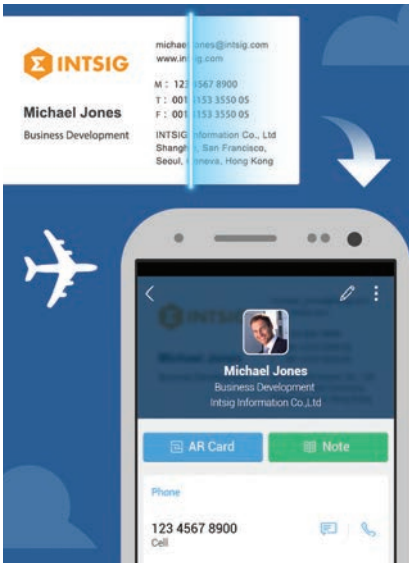
In the past several years, mobile phones morphed from convenient ways to communicate into virtual second brains, allowing users to manage all the various moving parts of their lives more efficiently. Applications for smartphones range from simple ones that help you manage your contacts, to complex apps that allow you to interact with your practice's electronic health records system remotely.

St. George, Utah, retinal specialist and software developer Ken Lord provided an evaluation of several burgeoning mobile apps at a new technology seminar at the most recent American Academy of Ophthalmology meeting. Here's a look at several apps that stood out, as well as an update on the ophthalmology app Dr. Lord helped develop, Eye Handbook.

Camcard

If you've ever been at one of the national ophthalmology meetings and found yourself sifting through a pile of business cards afterward in an effort to codify all the contacts you made, Camcard may be of use to you.

The app is designed to use optical character recognition technology to read a business card that's placed in front of your smartphone's camera. It then places all the relevant data it pulls off the card into a contact file. It will populate the file's fields with information such as the contact's name, place of business, mailing address, phone number and e-mail address. The app even has a locator feature that will use your phone's global positioning system to show the position of your contacts around you.



Camcard reads text and numbers from cards and zaps them to your phone.

"It works pretty well, considering how many business cards are being handed out at major meetings," says Dr. Lord. "It's a nice way to keep track of all the contacts you meet."

Like any program that uses OCR to read text, Camcard can still make mistakes when it attempts to interpret the letters and words. "Business cards aren't always the same, so it's not always perfect, but it comes pretty close." Dr. Lord says. "It will also store the picture of the business card for you so you can access it later if it doesn't recognize the fields properly. The app's user interface is easy to understand, though, and you can make on-the-spot corrections to someone's information if you have to."

For information, visit camcard.com.

Citrix ShareFile and XenMobile

Citrix is a software company that makes programs for both desktop and mobile devices that allow physicians to access and interact with their practice's electronic health records system from anywhere.

This article has no commercial sponsorship.

In the face of elevated IOP after monotherapy

RELEASE THE POWER

Most Covered Branded Combination
92% of Commercial and Part D member lives covered[1,a]
As of December 2013.

Individual plans and out-of-pocket costs will vary.

Most covered based on lives vs *Cosopt*®, *Cosopt*® *PF*, and *Simbrinza*™.

POWER: Still a reason you choose COMBIGAN®

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

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS: COMBIGAN® is contraindicated in patients with bronchial asthma; a history of bronchial asthma; severe chronic obstructive pulmonary disease; in patients with sinus bradycardia; second or third degree atrioventricular block; overt cardiac failure; cardiogenic shock; in neonates and infants (under the age of 2 years); in patients with a hypersensitivity reaction to any component of COMBIGAN® in the past.

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

Sympathetic stimulation may be essential to support the circulation in patients with diminished myocardial contractility and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure. In patients with no history of cardiac failure, continued depression of the myocardium with beta-blocking agents over time can lead to cardiac failure. Discontinue COMBIGAN® at the first sign or symptom of cardiac failure.

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

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

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS: (continued)

Patients taking beta-blockers with a history of atopy or severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

Although rare, timolol can increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

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

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

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

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

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

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

[a]Includes preferred, approved, and tiers 1-4, with and without step-edits, and also includes prior authorization, based on 203,671,234 total lives.

1. Managed Markets Insight & Technology, LLC, database as of December 2013.

ALLERGAN

Combigan®

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

COMBIGAN®

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

BRIEF SUMMARY

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

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

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

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

OVERDOSAGE

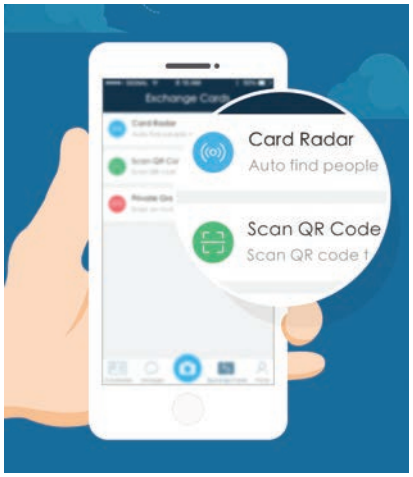
No information is available on overdosage with **COMBIGAN®** in humans. There have been reports of inadvertent overdosage with timolol ophthalmic solution resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath,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

Rx Only

Based on package insert 72060US13 revised 10/2012.
Patented. See: www.allergan.com/products/patent_notices

APC33KM13

ALLERGAN



The Camcard app's Card Radar will show you which of your contacts are nearby.

Through the use of the company's XenMobile technology, an ophthalmologist can access his practice's network and health records from the road, using a cellular connection. It does this through the use of virtual private network technology, which allows you to extend your practice or hospital's private network securely over a public network, usually the Internet. Using XenMobile, the physician can review exam notes and images from his computer at work, as well as provide a consultation to a colleague based on a particular patient record.

If the ophthalmologist needs to communicate securely with another physician, he can use Citrix's HIPAA-compliant WorxMail to discuss a patient and even securely attach an image of the patient's eye. The system also allows large, color graphics and images to be manipulated quickly, even on mobile devices, because the actual program is resident on a more powerful computer elsewhere.

Dr. Lord uses the Citrix applications and says they comes in handy. "All of your records are available to me when I'm away from the office," he says. "And all of the records are HIPAA-compliant and secure."

The one caveat with Citrix's apps is that they may not be compatible with your practice's particular EHR system, though other software providers' mobile solutions may be. Because of this possibility, Dr. Lord advises that you check with your EHR provider before adopting XenMobile or ShareFile.

For information, call 1 (800) 424-8749 or visit citrix.com.

SpeechTrans

SpeechTrans is a family of programs, some for mobile devices and some for desktop computers, that translate your spoken sentences into any of 40 other languages. Having this ability can be useful in a business setting when interacting with colleagues and new clients from other countries, as well as in health care, when trying to discuss a disease or diagnosis with someone for whom English isn't his first language.

"This technology is now becoming more available to the consumer market," says Dr. Lord. "For any medical practice or hospital that serves a multilingual population, interpreters are expensive, and an app like this helps reduce translation costs."

To use the app, you first select a language for translation, press a microphone icon on your screen, and then speak into your phone or your computer's desktop microphone. The program will then speak aloud your sentence, but in the foreign language you've selected. A patient in your office can also respond to you in his language using the device, and the application will translate his words into English and say them out loud for you.

"As far as accuracy, they aren't as good as an interpreter, of course, but they're continuing to improve," Dr. Lord says. "I wouldn't be surprised if they supplant the interpreter services at some hospitals in a year or two."

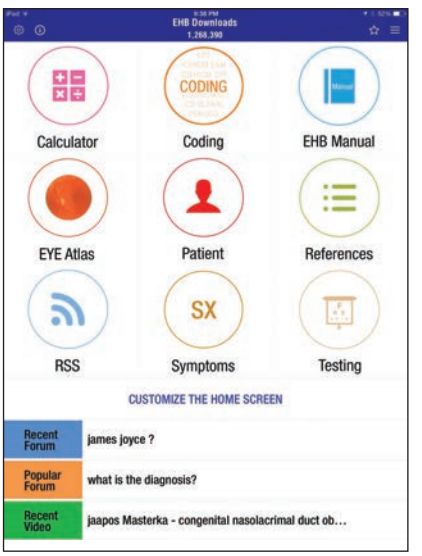
The SpeechTrans app is available on Apple iOS at the App Store and Android devices on Google Play. Desktop versions are also available from the company's website. For information, visit speechtrans.com.

Eye Handbook

Eye Handbook is an eye-care app created by Dr. Lord and his fellow ophthalmologists Rohit Krishna, director of the glaucoma service at the University of Missouri, and Vinay Shah, an associate professor at the University of Oklahoma's Dean McGee Eye Institute.

The app has various sections of interest to eye-care providers, including an eye atlas with images of ocular pathology, a vision symptoms area to help with diagnosing patients, a battery of vision tests and a guide to medications.

Dr. Lord says the group's current efforts for enhancing the app involve improving the medication section as well as the app's ability to get news to users. "The medications area has been kind of a static design in the past so now we're in the process of updating it to be more dynamic," he explains. "It will load its information from a



Users can now customize Eye Handbook's homescreen to show their preferred topics.

credentialed .gov website. We've tried to eliminate some of the less-reliable information and really just include hard data in the app."

To keep its users updated on eye care, Dr. Lord says they're changing the app's "push notifications," or updates that are sent directly to users. "We're trying to make sure we have a good ability to use the push notification features of the app," he says. "For instance, as the latest headline in ophthalmology comes out, we want to have the ability to notify our users about it. We've used it in the past, but now we have upgraded to a more advanced feature set for that specific ability. We hope to use it more in the future."

The Eye Handbook app is free, and is available at the App Store and on Google Play for Android devices. More information is also available at eyehandbook.com.

Turboscan

If you've ever needed to scan or photocopy a document quickly, but were nowhere near the right equipment, Turboscan can help.

Turboscan turns your phone into a handheld scanner for use with different types of documents, including forms, receipts, notes, articles and even whiteboards. Rather than just taking a picture of a document, however, Turboscan's maker, Piksoft, says it also uses proprietary algorithms to analyze the scanned material and detect a document's edges, correct the viewing perspective, remove shadows and find the best contrast for viewing later. The documents can be saved in PDFs, JPEGs or PNG format. You can also e-mail them to yourself right from within the application.

"I use it occasionally along with my Google Documents app," says Dr. Lord. "So, if I have an important document I want to store for later, I'll take a picture of it, turn it into a PDF, and upload it to Google Documents. Also, if it's a text page, Google has some optical character recognition in its software that will convert the scan into digital text for me in some cases. This allows me to convert a printed page into text in a few clicks.

"I use it mainly if I need to get a signature to someone across town or in another state," Dr. Lord adds. "If you needed to get someone a real estate document right away, for instance, you can sign it, convert it to a PDF and send it to them. They won't be able to tell it didn't come off of a photocopier, scanner or fax machine. In fact, the image sensor on your phone far surpasses the scanning resolution of a fax machine."

Turboscan is available at the App Store and on Google Play. REVIEW

(continued from page 8)

recommending not smoking cigarettes, we did not know of ways to prevent TED from developing in patients with Graves' disease," says Joshua D. Stein, MD, MS, a study author and health-services researcher at the University of Michigan Kellogg Eye Center. "There are only a few known risk factors that can be modified, for example, smoking and exposure to radioactive iodine."

Dr. Stein and colleagues analyzed longitudinal health-care claims data for 8,404 individuals with newly diagnosed Graves' disease. The data included the patients' diagnoses, tests ordered, medications prescribed and surgeries performed. Of that group, 8.8 percent eventually developed TED.

The study found that surgical thyroidectomy, alone or combined with medical therapy, was associated with a 74-percent decrease in risk for TED, compared with radioactive iodine therapy (RAI) treatment alone. Statin use for 60 or more days was associated with a 40 percent reduced risk for developing TED compared to less or no use of statins.

"We wanted to know whether medications or other interventions could keep patients with Graves disease from developing TED," says coauthor, Raymond S. Douglas, MD, PhD, oculoplastics surgeon and director of Kellogg's Thyroid Eye Disease Center. "Specifically, we investigated whether standard approaches for managing hyperthyroidism in Graves' disease—anti-thyroid medications, RAI therapy and thyroidectomy—altered the risk of developing TED."

The team chose to investigate statins, a drug class typically used to lower cholesterol, after reviewing recent studies showing that statins also reduce inflammation, which is believed to play a role in TED. The study authors also say that several reports have shown that statins reduce fibrosis and excess connective tissue in the orbit associated with the eye disease.

While the findings are promising, the authors propose to conduct a clinical trial before recommending any changes in treatment. Dr. Stein adds that because all treatments have side effects, it will be important to learn whether statins or thyroidectomy offer patients with Graves' disease benefits that outweigh the risks associated with these interventions. REVIEW

Save the Date

An interdisciplinary faculty of ophthalmic subspecialists will review the continuing progress in cataract and refractive surgery, glaucoma, retina, neuro-ophthalmology, oculoplastics, ocular surface disease, cornea and oncology.

Ophthalmology Update

2015

FEBRUARY 13-15

PROGRAM CHAIRS

Don O. Kikkawa, MD
Robert N. Weinreb, MD

KEYNOTE SPEAKER:

Robert Lustig, MD

FEATURED FACULTY:

Alexander J. Brucker, MD
Mandi Conway, MD
Marjan Farid, MD
Ray Gariano, MD
Kevin Miller, MD
Stephen Pflugfelder, MD
Arthur Sit, MD
Carlo Traverso, MD

UCSD SPEAKERS:

Natalie Afshari, MD, FACS
Henry Ferreyra, MD
William Freeman, MD
Michael Goldbaum, MD
Jeffrey Goldberg MD, PhD
David Granet, MD
Weldon Haw, MD
Christopher Heichel, MD
Bobby Korn, MD, PhD
Jeffrey Lee, MD
Felipe Medeiros, MD, PhD
Eric Nudleman, MD, PhD
Shira Robbins, MD
Peter Savino, MD
Kang Zhang, MD, PhD

PROGRAM TIMES

New Section:
Oculoplastics and Cosmetics

Friday, February 13
2:00pm - 4:15pm

Saturday, February 14
8:00am - 5:00pm
Reception to follow

Sunday, February 15
8:00am - 12:05pm

Please check www.revophth.com/Update2015 for up-to-date information.

LOCATION

Hilton La Jolla Torrey Pines
10950 North Torrey Pines Rd.
La Jolla, CA 92037
P: 858-558-1500

Discounted room rates are available at $209 per night. See registration site for further information.

3 WAYS TO REGISTER

Online: www.revophth.com/Update2015
Email: ReviewMeetings@Jobson.com
Call: Lois DiDomenico at 877-451-6512

This activity has been approved for *AMA PRA Category 1 Credit ™*

UC San Diego Shiley Eye Center | *Review of Ophthalmology®*

Jointly Provided by IAHB PHE

Supported by Independent Educational Grants from Allergan Alcon

Donna McCune, CCS-P, COE, CPMA

2015 Brings New Codes, Fee Schedule Changes

Regulatory issues and reimbursement rates are only some of the things to know about in the new year.

Q Were there changes made to the values of some ophthalmic codes in the 2015 *Current Procedural Terminology* manual?

A There are several changes to the *Medicare Physician Fee Schedule*, which was published in November 2014. Please see the table, below, for examples of some of the relative value units changing and the percentage of change from 2014.

Q Will there be more than one fee schedule in 2015?

Table 1. 2015 Relative Value Unit Changes

CPT Code	Percent Change
E/M new patient level 3 (99203)	1%
Comprehensive eye exam (92014)	-1
SCODI retina (92134)	-2
Intravitreal injection (67028)	-3
Cataract surgery w/IOL (66984)	-4
Gonioscopy (92020)	-4
PPV (67036)	-9
Scleral reinforcement w/graft (67255)	-23
PPV w/removal of ILM (67042)	-26
PPV w/endolaser PRP (67040)	-29

A On November 13, 2014, the *Federal Register* contained the final rule for the physician fee schedule and other Medicare Part B payment policies. Several factors affect payment policies:

- The Protecting Access to Medicare Act 2014 preserves a 0 percent physician fee schedule update for January 1 to March 31, 2015.
- The conversion factor changes slightly from $35.8228 to $35.7547 on January 1. If Congress does not intervene prior to April 1, the conversion factor will drop to $28.2239 for April 1 through December 31, 2015.
- Relative Value Unit changes will occur on January 1, creating a new fee schedule for the first quarter of 2015. In addition, the Centers for Medicare & Medicaid Services corrected an error in the malpractice RVUs, which results in an approximately 1 to 2 percent reimbursement reduction for ophthalmology.

Q What is happening to ambulatory surgery center facility fees in 2015?

A For 2015, the wage adjustment for budget neutrality, in addition to the multifactor productivity adjusted update factor, increases the

ASC conversion factor by 1.4 percent for those centers that meet quality reporting requirements, resulting in small increases in facility reimbursement. ASCs began reporting National Quality Forum Measures in October 2012. The reporting of these measures also affects reimbursement. Nonparticipation or failure to meet the necessary requirements results in a 2-percent reduction to facility Medicare reimbursement.

Q Did hospital outpatient department rates increase similarly to ASC facility rates?

A Yes. Various adjustments to hospital reimbursement result in a Hospital Outpatient Department rate increase of 2.3 percent.

Q What changes were published with Category I codes in *CPT 2015*?

A The *CPT 2015* coding manual contains a number of new codes, revisions and deletions applicable to ophthalmology. Category I CPT code changes are as follow:

• *66179 Aqueous shunt to extraocular equatorial plate reservoir, external approach; without graft* (new);

• *66180 with graft* (revised) (Do not report 66180 in conjunction with 67255);

• *66184 Revision of aqueous shunt to extraocular equatorial plate reservoir; without graft* (new);

• *66185 with graft* (revised) (Do not report 66185 in conjunction with 67255);

• *92145 Corneal hysteresis determination, by air impulse stimulation, unilateral or bilateral, with interpretation and report* (replaces 0181T).

The following code was revised:

• *67399 Unlisted procedure, ~~ocular~~ extraocular muscle.*

The following code was deleted:

• *66165 Fistulization of sclera for glaucoma; iridencleisis or iridotasis.*

Q Were there any Category III code changes published in 2015?

A There were a number of changes. These Category III codes, implemented on July 1, 2014 now appear in the hardcopy *CPT 2015*:

• *0341T Quantitative pupillometry with interpretation and report, unilateral or bilateral*;

• *0356T Insertion of drug-eluting implant (including punctal dilation and implant removal when performed) into lacrimal canaliculus, each.*

New Category III codes include:

• *0378T Visual field assessment, with concurrent real time data analysis and accessible data storage with patient initiated data transmitted to a remote surveillance center for up to 30 days; review and interpretation with report by a physician or other qualified health care professional*;

• *0379T Technical support and patient instructions, surveillance, analysis, and transmission of daily and emergent data reports as prescribed by a physician or other qualified health care professional*;

• *0380T Computer-aided animation and analysis of time series retinal images for the monitoring of disease progression, unilateral or bilateral, with interpretation and report.*

Revised Category III codes include:

• *0191T Insertion of anterior segment aqueous drainage device, without extraocular reservoir,* ***internal approach, into trabecular meshwork; initial insertion*** (revised text in bold).

+ 0376T each additional device insertion (List separately in addition to code for primary procedure) (new);

• *0253T Insertion of anterior segment aqueous drainage device, without extraocular reservoir,* ***internal approach, into the suprachoroidal space*** (revised text in bold).

Coverage and payment for Category III codes remains at carrier discretion.

No new ICD-9 codes were published in anticipation of ICD-10 implementation on October 1, 2015.

Q Are there new drug codes pertinent to ophthalmology in 2015?

A Yes; one new HCPCS Code that is effective January 1, 2015 is for the proprietary combination of phenylephrine 1.0% combined with ketorolac 0.3% (Omidria), which received pass-through status at the end of October 2014. Omidria is used during cataract and lens-replacement surgery to maintain pupil size by preventing intraoperative miosis and to reduce postoperative pain.

• *C9447 Injection, phenylephrine and ketorolac, 4 ml vial.*

This is submitted by the ASC or HOPD.

Q Were there any changes to diagnosis codes or the implementation of ICD-10?

A No new ICD-9 codes were published in anticipation of ICD-10 implementation on October 1, 2015. During 2015, CMS plans a

series of testing weeks with ICD-10 codes. The purpose of the testing weeks is to confirm that claims with ICD-10 codes can be submitted electronically through to the individual Medicare Administrative Contractors from providers. Watch contractor websites for sign-up opportunities for dates in March and June 2015.

Q What types of regulatory issues were identified in the annual *Office of Inspector General Work Plan* as areas of concern for ophthalmology in 2015?

A The annual publication included a series of initiatives that will continue through 2015. No "new" initiatives appear pertinent to ophthalmology. The returning targets for scrutiny include:

- Place of Service Errors;
- Payments for drugs;
- Ambulatory Surgical Centers–Payment System;
- Ophthalmological Services–Questionable billing during 2012;
- Imaging services–Payments for Practice Expense;
- Medicare Incentive Payments for Adopting Electronic Health Records;
- Anesthesia services–Payments for personally performed services;
- Payment for compounded drugs under Medicare Part B; and
- Security of Certified Electronic Health Record Technology under Meaningful Use.

Q Are there any changes to the Recovery Audit Contractor Program?

A Yes. The RAC program "paused" in February 2014 while CMS negotiated new contracts for the RACs. Some automated reviews resumed in August 2014 and changes to the program are expected in 2015. Total corrections since the Medicare Fee-for-Service Recovery Audit Program began in October 2009 stand at $7.26 billion with $6.8 billion in overpayments.

Q Are there penalties and/or bonus dollars for participation in the Physician Quality Reporting System in 2015?

A The Patient Protection and Affordable Care Act made PQRS mandatory by 2015. Those eligible professionals who did not successfully report PQRS in 2013 will be paid 1.5 percent less than the MPFS reimbursement rate in 2015. Unsuccessful reporters in 2014 will receive a 2 percent PQRS penalty adjustment (receiving 98 percent of the fee schedule amount) in 2016. Bonus payments ended with the 0.5 percent bonus paid to successful reporters in 2014. No bonus payments exist for 2015.

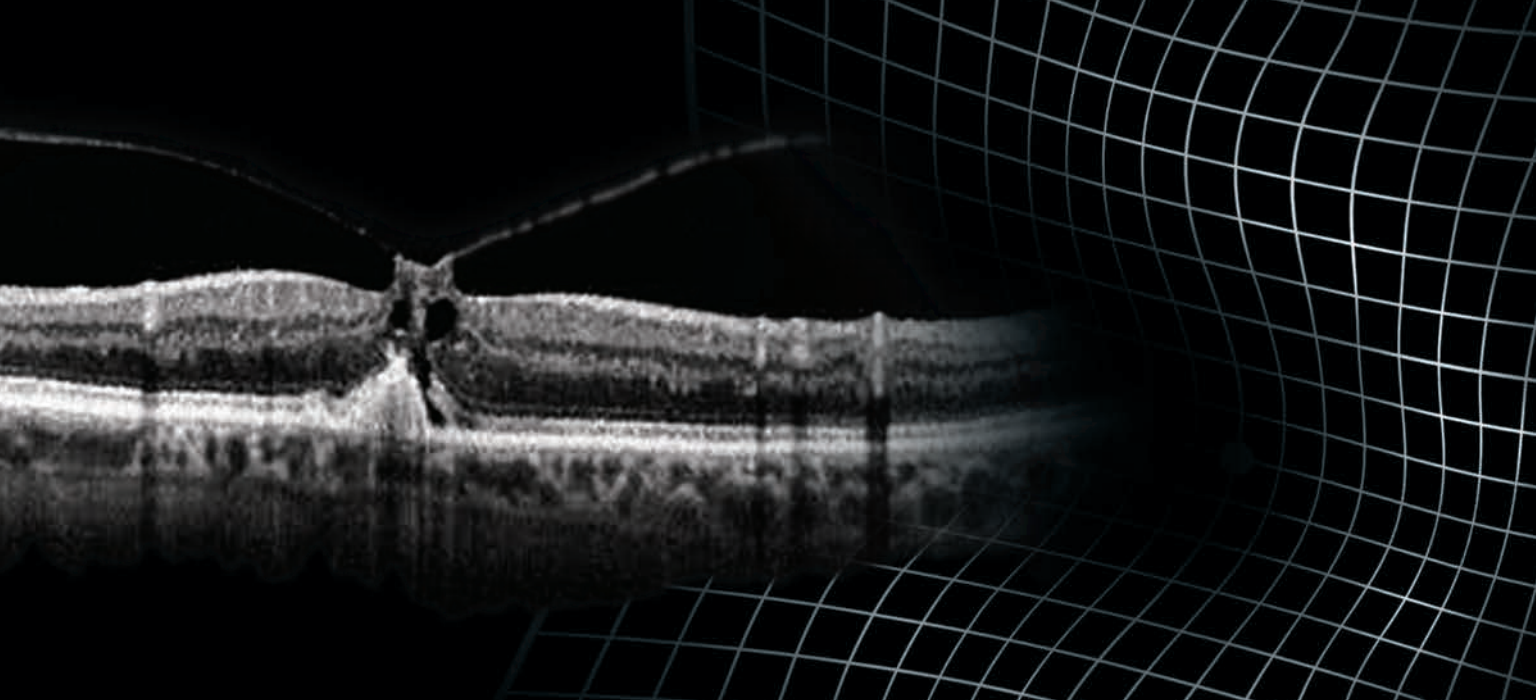
Q Is the Electronic Health Record Bonus Program continuing in 2015?

A As of September 2014, the EHR Incentive Bonus Program paid out $6.47 billion to eligible providers; $187 million was to ophthalmologists and $261 million was to optometrists. Providers expected to attest to Stage 2 requirements for 2014 received a reprieve due to a variety of vendor issues and other hang-ups. Most reported Stage 1 meaningful use objectives and measures for 2014 and will move forward with Stage 2 in 2015. Meaningful use reporting in 2015 requires full-year participation for anyone beyond year one reporting. Providers who did not qualify for a hardship exemption or complete their meaningful use attestation for Stage 1 by October 1, 2014 will receive a 1 percent penalty on their MPFS reimbursements for 2015.

Q What Medicare Part B changes affect beneficiaries in 2015 from a cost perspective?

A The Medicare Part B premiums remain $104.90 for most beneficiaries. The Part B deductible also remains at $147.00. These beneficiary costs are unchanged from 2013 and 2014. REVIEW

Ms. McCune is vice president of the Corcoran Consulting Group. Contact her at DMcCune@corcoranccg.com.



SYMPTOMATIC VITREOMACULAR ADHESION (VMA)

SYMPTOMATIC VMA MAY LEAD TO VISUAL IMPAIRMENT FOR YOUR PATIENTS[1-3]

IDENTIFY | Recognize metamorphopsia as a key sign of symptomatic VMA and utilize OCT scans to confirm vitreomacular traction.

REFER | Because symptomatic VMA is a progressive condition that may lead to a loss of vision, your partnering retina specialist can determine if treatment is necessary.[1-3]

THE STEPS YOU TAKE TODAY MAY MAKE A DIFFERENCE FOR YOUR PATIENTS TOMORROW

ThromboGenics®

References: 1. Sonmez K, Capone A, Trese M, et al. Vitreomacular traction syndrome: impact of anatomical configuration on anatomical and visual outcomes. *Retina*. 2008;28:1207-1214. **2.** Hikichi T, Yoshida A, Trempe CL. Course of vitreomacular traction syndrome. *Am J Ophthalmol*. 1995;119(1):55-56. **3.** Stalmans P, Lescrauwaet B, Blot K. A retrospective cohort study in patients with diseases of the vitreomacular interface (ReCoVit). Poster presented at: The Association for Research in Vision and Ophthalmology (ARVO) 2014 Annual Meeting; May 4-8, 2014; Orlando, Florida.

FDA APPROVED

now...

IS THE TIME TO PREVENT INTRAOPERATIVE MIOSIS AND REDUCE POSTOPERATIVE OCULAR PAIN

OMIDRIA™ (phenylephrine and ketorolac injection) 1% / 0.3% is *the first and only FDA-approved treatment* that both[1]:

- **Preemptively inhibits intraoperative miosis**
- **Decreases postoperative ocular pain for 10 to 12 hours**

OMIDRIA is preservative- and bisulfite-free[1]

OMIDRIA requires no change to routine operating procedures[1]

INDICATION AND USAGE

OMIDRIA is an α1-adrenergic receptor agonist and nonselective cyclooxygenase inhibitor indicated for:

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

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

CMS PASS-THROUGH STATUS EFFECTIVE JANUARY 1, 2015

OMIDRIA™ is reimbursed by the Centers for Medicare and Medicaid Services (CMS)

- OMIDRIA has been granted transitional pass-through payment status under the Medicare hospital outpatient prospective payment system (OPPS)
- Pass-through status allows for payment for OMIDRIA separate from the bundled Ambulatory Payment Classification (APC) payment

For more information about OMIDRIA, including how to order or to obtain reimbursement, contact 1-844-OMEROS1 (1-844-663-7671) or visit omidria.com.

IMPORTANT SAFETY INFORMATION

OMIDRIA must be diluted prior to intraocular use.

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

Systemic exposure of phenylephrine may cause elevations in blood pressure.

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

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

Use of OMIDRIA in children has not been established.

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

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Reference: 1. OMIDRIA [package insert]. Seattle, WA: Omeros Corporation; 2014.

OMIDRIA™
(phenylephrine and ketorolac injection) 1% / 0.3%

WIDE OPEN

OMEROS®

Topo-guided Ablation: Coming into Its Own

Christopher Kent, Senior Editor

The range of conditions that can be addressed with this technology continues to expand.

Topography-guided laser ablation has become increasingly popular outside the United States; now that it has limited Food and Drug Administration approval it may start to catch on in the United States as well. In the meantime, it has slowly evolved from a way to improve damaged corneas to a way to help treat issues such as keratoconus (especially in combination with cross-linking), to a tool for enhancing laser refractive surgery outcomes in hyperopic and even normal eyes.

Here, three surgeons with extensive experience using this technology share their latest thoughts about what topography-guided ablation is capable of, and the pros and cons of using it.

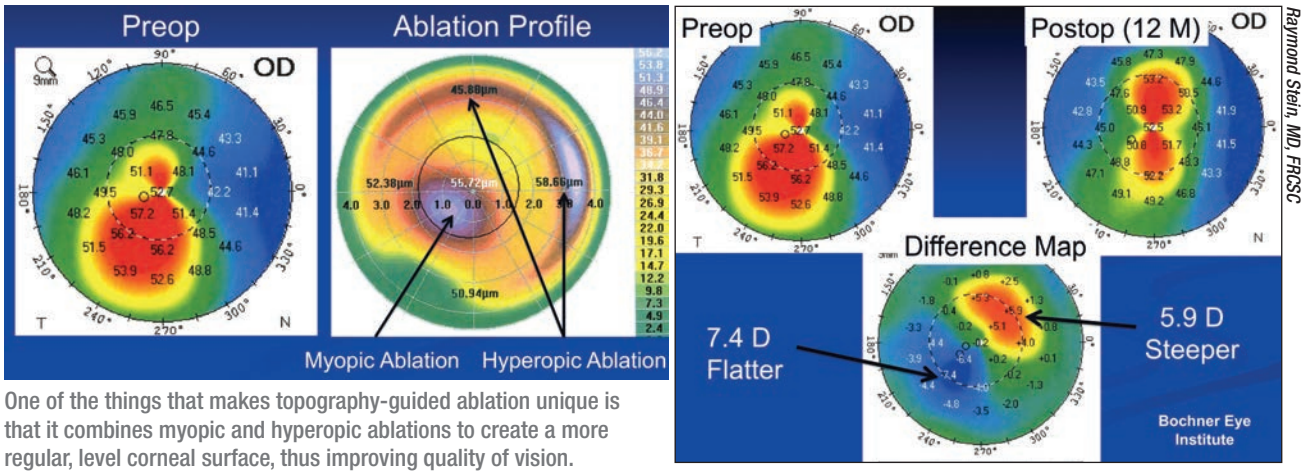
Expanding the Niche

A. John Kanellopoulos, MD, clinical professor of ophthalmology at New York University Medical School and medical director of the Laservision.gr Institute in Athens, Greece, has performed topography-guided procedures using the WaveLight platform since 2003, treating more than 4,000 cases. "We began by using it to treat irregular corneas such as those with decentered laser ablations and irregular pathology such as contact-lens-related ulcers, trauma and so forth," he says. "We moved on to using this technology to normalize some eyes with naturally occurring irregularities, such as keratoconus.

"Our experience has proven that topography-guided systems are a very reliable way to document most of the aberrations of the human eye and transfer them to treatment," he continues. "More than 90 percent of human visual aberrations are the result of irregularities in the cornea, and this is especially true in eyes that have had previous surgery or have acquired irregularities. Employing topography-guided treatment, these conditions can be addressed to the maximum, without the variability that wavefront-guided treatment—potentially the counterpart of topography-guided treatment—can offer."

"It's incredible to be able to take an irregular cornea and improve the patient's quality of vision," says Raymond Stein, MD, FRCSC, medical director of the Bochner Eye Institute in Toronto, and associate professor of ophthalmology at the University of Toronto. "We've been using this technology for about seven years, but in the past three years, combined with cross-linking, it's become our treatment of choice. I'd say we do a topography-guided PRK to smooth the cornea in 90 percent of our cross-linking

This article has no commercial sponsorship.



Raymond Stein, MD, FRCSC

One of the things that makes topography-guided ablation unique is that it combines myopic and hyperopic ablations to create a more regular, level corneal surface, thus improving quality of vision.

patients. Basically, we flatten the steep areas of the cornea and steepen the flat areas, improving quality of vision. It's a fantastic treatment."

Dr. Kanellopoulos observes that topography-guided ablation is very common in many countries outside the United States and is considered time-tested. "Outside the U.S., in addition to the Nidek and the WaveLight platforms that have been FDA-approved, many laser platforms have topography-guided options," he points out. "Zeiss has a topography-guided option in its excimer laser; Schwind does as well; and another one is made by Ivis, an Italian manufacturer. Depending on the practitioner, I think refractive surgery centers use this technology in anywhere from 10 to 50 percent of their patients. Some centers use it purely for therapeutic purposes to treat irregular corneas and eyes with pathology, either after a laser procedure or after an accident, or eyes with naturally occurring irregularities. Some centers, like ours, view topography-guided treatment as a way to customize and further enhance laser vision correction.

"The FDA gave approval for topography-guided treatment using either the Alcon or Nidek systems in October 2013, but neither system is currently used in the U.S.," he adds. "Alcon is planning to roll out its use in 2015. But it should be noted that the FDA approval was for use in normal eyes. Obviously the main interest most surgeons have in employing topography-guided ablation is in abnormal eyes, and potentially in hyperopic eyes."

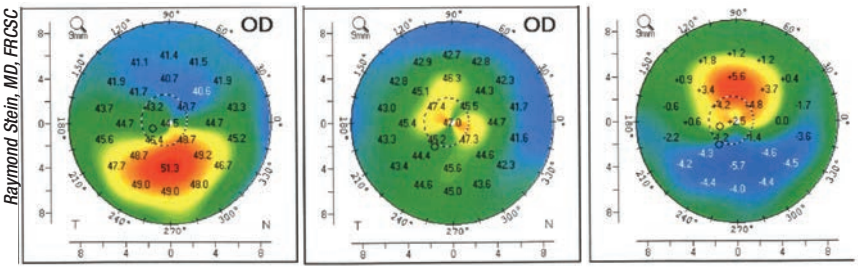
Using the Technology

One of the things that separates topography-guided ablation from standard ablations is the strategy it employs to level out the corneal surface. "With wavefront-guided ablation, typically the mountains would simply be flattened, and it would require a significant amount of flattening to equalize the whole cornea," explains Dr. Stein. "Topography-guided ablation elevates the valleys as well, so the mountains don't have to be flattened nearly as much. That means less tissue removal to achieve the goal of improving vision quality. We typically remove about 50 µm.

"For example," he continues, "the typical keratoconus patient has steepening inferotemporily, while the cornea is relatively flat superiorly. A topography-guided ablation does a partial myopic treatment over the cone to flatten that, and a partial hyperopic treatment above. *(See example, above.)* By ablating out in the periphery it actually steepens the superior cornea. It's a unique ablation profile.

"Over time we've learned that the best candidates for this type of treatment are corneas that have less than a 10-D difference between the steepest and flattest parts of the cornea," he adds. "In that situation we can flatten the steep areas by about 5 D and steepen the flat areas by about 5 D. That's about the maximum we can hope to achieve. We've had many patients who came in with less than a 10-D difference between the low and high parts of the cornea, and a reasonably thick cornea, who went from 20/200 best-corrected spectacle or soft-contact-lens acuity to 20/25 or 20/30 best-corrected. But if a patient has a 20-D difference between the steepest and flattest parts of the cornea, we can't hope to achieve the same degree of improvement in best-corrected spectacle visual acuity."

Dr. Stein describes a typical procedure in his practice. "The technician captures eight images using an equivalent of the Pentacam—WaveLight's Oculyzer—which are digitally transferred to the excimer laser," he says. "We do eight images because we want to maximize the data quality; more than eight would be too time-consuming. We review the data and eliminate the outliers; then we devise a treatment protocol. We schedule these patients on the same day we do laser vision correction patients. So if I'm in the OR I'll do PRK and LASIK cases; then I'll do a topography-guided PRK. After that, the patient will have



Raymond Stein, MD, FRCSC

Topography-guided ablation is being used to treat keratoconus, irregular astigmatism, corneal scars, ectasia and hyperopia, among other things. Above: Ectasia treated with topography-guided ablation. Left to right: Preop; one year postop; difference map.

cross-linking done by another member of our staff; that takes longer."

Placido Disc or Tomography?

Of course, there are several ways to evaluate the topography of a cornea. Surgeons say each method has some limitations. "Both placido disc-based topography-guided treatments and Pentacam-based topography-guided treatments have some intrinsic shortcomings," notes Dr. Kanellopoulos. "Placido disc relies mainly on a cornea having an adequate tear film, while the Pentacam relies on a cornea being clear and translucent. As a result, their effectiveness depends on the pathology. For instance, a corneal scar would be better treated with a placido-disc-based topography-guided treatment because that technology is not affected by the clouding of the cornea. On the other hand, if a patient has a less-than-optimal tear film or a very irregular cornea, Pentacam-guided treatment may be the best way to go. Unfortunately, it appears that users in the United States will not have the Pentacam-driven option, even though it's available in many platforms, because that would entail a separate FDA approval process. That does not seem feasible in the near future."

Dr. Kanellopoulos says that one advantage of placido disc technology is that it's currently available in the Alcon platform with cyclorotation adjustment. "As you might imagine, this can be a pivotal part of getting excellent results, especially when treating irregular corneas or corneas with high astigmatism," he says. "That's true even if tomography might be slightly better than placido disc, if that particular patient happens to have significant cyclorotation. Even 2 degrees of cyclorotation becomes extremely significant in topography-guided treatments of irregular corneas or corneas with high astigmatism or angle kappa, because every 2 degrees of cyclorotation reduces the astigmatic efficacy by 8 percent, which is astounding."

Dr. Kanellopoulos says that today he prefers to use both topography and tomography. "I like to compare both options, and also compare them to the standard ablation profile for that refractive error, as well as the results of very thorough slit-lamp biomicroscopy," he explains. "I may also compare their readings to an objective measure such as the Cassini's multicolor LED reflection topography and an epithelial map obtained by anterior segment OCT. This gives me a lot of input regarding whether the treatments are different, and if so, how. That information then helps me to determine which of the two will be better for the patient." Dr. Kanellopoulos notes that he and his colleagues have reported extensively on this in the past two years at the major annual meetings and published several papers on it.

Issues Slowing Adoption

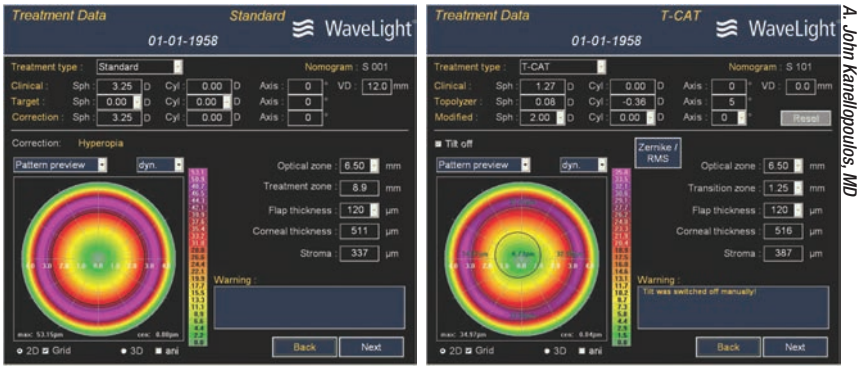
Despite the widespread availability of topography-guided ablation outside the United States, its use is nowhere near that of standard laser procedures. "The problem is not the technology," says Simon P. Holland, MD, clinical professor of ophthalmology at the University of British Columbia in Vancouver. (Dr. Holland has used topography-guided ablation at the Pacific Laser Eye Centre in Vancouver, working with David T. C. Lin, MD, since 2004.). "The current lasers are generally excellent, and the results we're getting are very good. However, the number of patients who would clearly benefit from it is relatively small. The market is mainly patients who've had difficulty, such as ectasia, post-keratoplasty irregular astigmatism, previous injuries or corneal scars.

"The other indication, which keeps us busiest, is keratoconus," he continues. "That's really opened up in the past few years because we now have cross-linking, and we've found that it's safe to take a limited amount of tissue, providing that the cornea is subsequently cross-linked to maintain its strength. We've done about 650 eyes using two different machines in the past six years since cross-linking became available to us, and about two-thirds of those were keratoconus. There's a great need for this type of procedure in these patients, but again, the number of patients in this situation is relatively small compared to the overall population of people needing refractive treatment."

Dr. Holland says a second issue limiting the popularity of topography-guided ablation is the learning curve. "It's difficult to get started using this technique," he says. "Every case has to be customized. For example, if you're doing transepithelial ablation, the variable thickness of the epithelium has to be taken into consideration. So it's very hard to translate one treatment onto another patient. That means you can't use the technology right out of the box and expect to get great results—you

really have to build up your experience and look at your data. Eventually you learn what's most likely to produce a good result in each case."

Dr. Stein agrees. "I think you have to do at least 50 cases to become really adept," he says. "The patients should do reasonably well in those first 50 cases, but they'll do even better after the first 50. Once the surgeon has the experience, treatment decisions can be made pretty quickly."



A. John Kanellopoulos, MD

Ablation profiles for correcting hyperopic astigmatism. Left: centered on pupillary center. Right: adjusted by topography to compensate for angle kappa and center on line of vision.

Addressing Different Conditions

Surgeons note that there are a number of indications for which topography-guided treatment is an excellent option, including irregular corneas from focal scars, keratoconus, pellucid marginal degeneration and ectasia following laser vision correction.

• ***Keratoconus***. Dr. Stein says this is the number one indication for topography-guided ablation in his practice. "Cross-linking is successful in stopping the disease from progressing in close to 98 percent of these patients," he notes. "But patients want us to take it one step further—they want an improvement in their quality of vision so they won't need a rigid gas permeable contact lens in order to see. That's what combining topography-guided ablation with cross-linking can offer them. In a high percentage of patients we can eliminate the need for RGP lenses, allowing patients to wear glasses or soft contact lenses. This is really a huge advance in our ability to help these patients."

Dr. Stein agrees, noting that he introduced cross-linking into Canada about seven years ago. "The first four years, we simply did cross-linking for the patients with keratoconus, ectasia and pellucid marginal degeneration," he says. "Today, in 90 percent of these cases, we do topography-guided PRK in addition to the cross-linking."

• ***Hyperopia***. Hyperopes often achieve better outcomes when treated with a topography-guided refractive procedure. "In my opinion, topography-guided ablation is the equivalent of a successful treatment in hyperopes," says Dr. Kanellopoulos. "For many years we've advocated using topography-guided ablation in all hyperopic eyes because they tend to have significant angle kappa. Topography-guided ablation treats on the cornea apex by default; that's usually the position of the visual axis."

Dr. Stein agrees. "We do a high percentage of our hyperopic PRK and LASIK using topography-guided procedures, and we're getting better refractive outcomes," he says. "I think you're going to see a lot more of this down the road."

• ***Post-LASIK and PRK problems***. Dr. Stein notes that topography-guided ablations are excellent for treating complications following LASIK or PRK, such as irregular astigmatism or a small optical zone. "With topography-guided PRK we can enlarge the optical zone and give patients better quality of vision," he says.

• ***Post-radial keratotomy.*** "A lot of RK patients who were done 20 years ago are now undergoing cataract surgery, and a lot of these corneas are somewhat irregular," Dr. Stein points out. "If a surgeon performed an eight-incision RK but made some incisions deeper than others, for example, that would probably induce some irregular astigmatism. With topography-guided PRK we can try to smooth out the irregular cornea before the cataract surgery. We're doing this on quite a few patients now, and I see this as a significant application down the road."

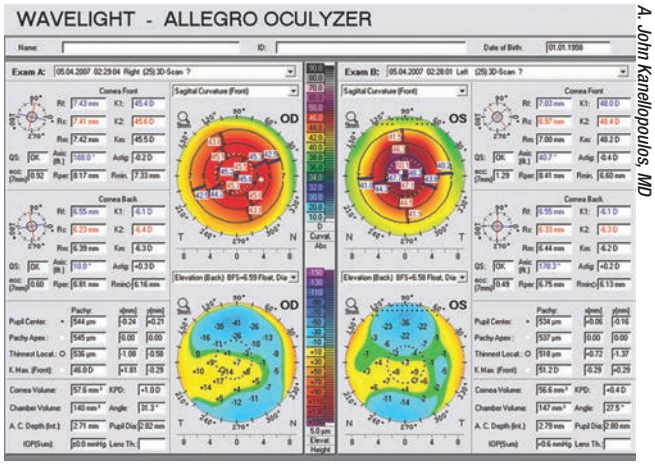
• ***Unhappy 20/20 patients.*** "We've had some fascinating cases—people who have 20/20 vision and complain that they can't see well," notes Dr. Holland. "When we image them we find that there's a subtle area with inferior steepening that's generating aberrations. Often these are patients whose vision could be corrected by wearing a rigid lens, but they are intolerant. I understand that few surgeons want to treat a 20/20 eye, but we have done some cases like this and the results have been promising."

• ***Arcuate astigmatic incisions.*** Another source of corneal irregularity that Dr. Stein has encountered is arcuate incisions made years ago to correct astigmatism. "If you make an arcuate cut to treat astigmatism—as many surgeons did in the past—that's more central and not the proper depth, you can induce irregular astigmatism. That's another application for topography-guided PRK."

Improving Normal Vision

"Another intrinsic advantage of topography-guided became clear with the recent FDA study conducted by Alcon," says Dr. Kanellopoulos. "Even as a seasoned topography-guided sur-

geon, I have learned a lot from that data. We've always known that topography-guided treatment is better for irregular and hyperopic eyes, but the FDA data has shown that even virgin eyes can benefit from this. A very large percentage of normal eyes in that study gained lines of vision. This probably has to do with subtle corneal irregularities that normal eyes have. These subtle irregularities are addressed by topography-guided ablation. This appears to enhance visual function.



A patient with regular myopia treated in the left eye with a standard laser protocol and in the other with a topography-guided laser. The topography-guided treatment produced a better visual outcome.

A. John Kanellopoulos, MD

"We've seen very clear examples of this in our practice," he continues. "One patient with 6 D of regular myopia was treated in the left eye with standard laser and in the right eye with topography-guided laser. *(See above.)* Postop, both her wavefront and visual function were better in the topography-guided eye. In the postop topometric indices you can clearly see that the topography-guided eye has a much lower index of high decentration and index of surface variance than the standard treatment eye, which may explain the better visual outcome."

Dr. Kanellopoulos says that this has led him to do all of his cases, including the routine ones, using topography-guided treatment. "I see a significant advantage in the fact that it can further normalize even apparently healthy corneas, offering better visual acuity and an increase in lines of vision," he says.

Dr. Holland agrees, particularly when eyes have a little bit of irregular astigmatism. "When we look at our routine PRK and LASIK cases today, we ask whether the corneal aberrations are consistent with the patient's refraction," he says. "If they are, we consider the possibility that the patient would benefit from correcting that slight degree of irregularity with a limited topography-guided treatment."

Managing Altered Refraction

One of the concerns with topography-guided ablation is that while smoothing the cornea it may alter the refraction, potentially leading to a refractive surprise.

"Practice has proven that when you treat virgin eyes with topography-guided ablation there's really no significant care or extra nomogram that one needs to employ," says Dr. Kanellopoulos. "However, when you employ topography-guided ablation in irregular eyes, it can significantly change the spherical refractive error; you may end up with some residual hyperopia or myopia. In my opinion this is not a significant issue because the procedure is employed in these eyes mainly to improve best-corrected visual acuity; one should expect that a second refining procedure to address the refractive error may be necessary."

Along these lines, Dr. Stein points out that they sometimes end up reducing the quality of a keratoconus patient's uncorrected acuity in order to improve his best-corrected acuity. "That's a very important point that patients need to understand," he says. "We discuss that in depth with them. They may come in with an uncorrected acuity of 20/50 and a best-corrected acuity of 20/40. By smoothing the cornea and doing cross-linking we may reduce their uncorrected acuity to 20/80, but we improve their best-corrected acuity to 20/25, so they get much better quality of spectacle- or contact-lens-corrected vision. This is not typical with LASIK or PRK. There, the patients want the best uncorrected visual acuity; that's why they come in. But in this case, we want to halt the progression, and second, improve their best-corrected acuity."

Dr. Kanellopoulos says that a common mistake made by surgeons just starting to use topography-guided ablation is overmanipulating the Q-value, which reflects the asphericity of the cornea. "In order to improve Q-value the laser will perform a hyperopic-type correction that will induce myopia," he explains. "This is a general rule. For example, if we try to convert the Q-value in an eye that's between -0.1 and -0.5, this will induce 0.5 to 0.75 D of myopia. A seasoned topography-guided surgeon will anticipate this. But for a novice topography-guided surgeon, this may be a refractive surprise. Generally, more complicated cases with an extremely irregular ablation pattern are more likely to create a significant refractive change."

Dr. Kanellopoulos notes that most topography-guided surgeons are aware of the issue. "Experienced users of topography-guided ablation have acquired the ability to predict that refractive shift and adjust the treatment accordingly, to preempt the anticipated refractive error," he adds. "We call this 'topography neutralization.' This, of course, is a cookbook approach by the surgeon; it helps to reduce the number of potential retreatments that are required in these patients."

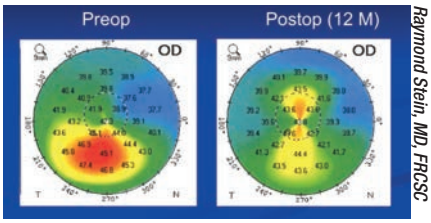
Offsetting the Change

Some surgeons have developed nomograms to address this potential refractive change by compensating during the procedure; others prefer to wait.

"The topography-guided technique we've used the most, which was pioneered by my partner, David Lin, MD, is the customized topographic neutralization technique, or Custom TNT," says Dr. Holland. "Using this protocol we first try to improve the topography; then we add the astigmatism correction; then we add the spherical correction. This approach allows us to compensate for the refractive effects of the surface smoothing. For instance, when treating most keratoconus, you're trying to flatten the steep part, but you have to compensate for that by steepening the periphery. That creates a peripheral trench that gives you a hyperopic effect, which then induces myopia. So, you have to compensate for that by treating for additional myopia; if you don't, the patient will end up myopic."

Dr. Stein says he generally doesn't try to correct the spherical error when performing the topography-guided ablation. "We generally save that for a separate procedure," he says. "The final refractive error is not totally predictable, so our main goal is to improve BCVA."

Dr. Stein adds that if the patient has a significant refractive error, he wouldn't do LASIK to correct it later. "LASIK would weaken the cornea because of the flap," he notes. "If the prescription was a nominal one, and the patient has a reasonable corneal thickness, then we might consider a PRK at a later time. But you have to be very careful about removing more tissue and weakening the cornea. Also after cross-linking, if we do PRK down the road, the results are not as predictable. However, in patients who have a significant refractive error and really want an improvement in uncorrected acuity, we have the option of a toric implantable contact lens such as Visian—if the patient is a candidate for an ICL—once the refraction is stable. That might eliminate the patient's need for contact lenses or glasses."



Raymond Stein, MD, FRCSC

An example of keratoconus treated with topography-guided PRK and cross-linking.

Topo-guided vs. Wavefront

"The difference between topography-guided ablation and wavefront ablation strategies is very simple," says Dr. Kanellopoulos. "Wavefront-guided ablation works by reducing the corneal tissue to a lower level. It removes a lot of tissue in order to make the cornea more spherical, based on the flattest part of the cornea. In contrast, topography-guided uses a bimodal treatment; it aims to shave off the peaks of corneal curvature and steepen flatter areas indirectly by ablating around them. This bimodal approach gives topography-guided ablation a tremendous advantage, in my opinion. It ablates much less tissue than wavefront-guided ablation—in some instances one-third as much tissue.

"Another significant difference between these types of treatment is that topography-guided treatment is almost always possible, even in very irregular eyes," he continues. "In contrast, wavefront-guided treatment becomes very challenging or impossible in eyes with high refractive error or significant irregularity."

Is one of them better for treating irregular astigmatism? "My experience has been that if it's a small irregularity and mild astigmatism in a cornea with a lot of tissue, then wavefront-guided and topography-guided may be equivalent," Dr. Kanellopoulos says. "But in cases where it's really important to correct the irregularity, such as cases needing higher astigmatic correction and not having the tissue reserves that you would want in order to treat with wavefront-guided, topography-guided becomes the only option. In addition, we have clearly shown that topography-guided collagen cross-linking coupled with a topography-guided excimer ablation can maximize the refractive change in the cornea while reducing even further the amount of tissue you need to ablate."

Dr. Kanellopoulos notes that he also finds it much easier to understand and predict the changes that will be produced by topography-guided treatments. "Wavefront is an approach that has a lot of theory in it that I can't necessarily grasp by looking at objective data," he points out. "And again, the human wavefront is a dynamic entity; it's very difficult to capture reproducible wavefront maps. Furthermore, if there is variability in the wavefront maps it's very difficult to decide which is the representative wavefront map that should be used for treatment in that patient."

Dr. Holland agrees, noting that another advantage is being able to decide whether or not to treat crystalline lens-related aberrations in older patients. "You may or may not want to treat those, depending on the age of the patient," he says. "I think that accounts for the popularity of wavefront-optimized rather than wavefront-guided treatments."

Dr. Stein adds that the number of data points on which the treatment is based is far higher with topography-guided ablation. "With a very sophisticated wavefront unit you might collect 1,000 data points," he says. "With the topography unit we capture more than 20,000 data points. There's less potential for error because we're capturing

more information on which to base the ablation."

Given that wavefront and topography measure different things, what about combining the two measurements to guide ablation? Dr. Kanellopoulos says the WaveLight research team has been working on this approach. "This is a very exciting new entity called ray tracing," he says. "It's been reported in the literature, showing astounding accuracy in determining refractive error, and has all the benefits that topography-guided treatment can give in terms of quality of vision. So there is a significant advantage to combining them.

"Actually," he adds, "many seasoned topography-guided anterior segment surgeons do this inadvertently by comparing the wavefront guided treatment plan to the topography-guided treatment plan and then making adjustments to the topography-guided treatment plan based on the former. However, this would be perfected if the two data sets could be combined through common software. We're hoping that the future will bring this to fruition in a one-box diagnostic that could then give the clinician a precalculated ablation pattern combining the advantages of both of these very valuable techniques."

When You're Starting Out

Dr. Stein offers some suggestions for surgeons just starting to offer this type of procedure. "First, don't pick corneas that are too thin or have any significant scarring," he says. "Second, make sure your technicians are capable of capturing relatively consistent maps. Third, make sure the cornea is not too dry or wet when the imaging is done. Fourth, make sure the treatment is about 50 µm or less, unless the cornea is unusually thick.

"Finally, if you're just getting involved with this technology, spend some time with a surgeon who has experience—experience that involves many different types of eye conditions," he adds. " Every type of corneal problem you may encounter will be a little different, whether it's radial keratotomy, a decentered ablation, irregular arcuate cuts, ectatic eyes or keratoconus patients. No article or textbook you can read will give you the experience you need to become good at this."

"As with any new procedure, you should underpromise and overdeliver," says Dr. Holland. "Patient expectations are high, so it's probably best to start off by telling patients that they may need a second treatment. In fact, we used to do topography-guided treatments in two separate steps. We'd explain to the patient that we were going to first regularize the cornea and improve the topography; then, after everything settled down—which could take as long as a year—the patient would come back in for the refractive treatment. Today we use the TNT procedure *[described earlier]*, where we modify the topography and do the refractive treatment in one sitting. But if you're just starting out, separating the two parts would be the safer way to go. At the very least, you need to warn the patient that you can only do a limited refractive treatment with this technology; you don't want to be too aggressive when you start.

"In addition, it's helpful to begin by treating astigmatic patients such as post-keratoplasty, rather than more complex cases," he says. "And it's important to remember that it takes a long time for vision to stabilize after the treatment. Do not retreat too early. Epithelial remodeling can take three to six months, and if you do cross-linking as well, then you're talking about a year. A keratoconus patient, in particular, can take a long time to stabilize. If necessary, fit the patient with soft contact lenses during this time, and make sure to follow his progress closely."

Looking to the Future

Dr. Holland admits that topographic treatment needs to become simpler and easier to do, but he believes that will happen over time. "It's taking a long time because we're starting with the most difficult cases—the therapeutics," he explains. "Then we're working backwards. For now, the real value of this type of procedure lies with the therapeutic cases. The regular cases don't really need it, and it's hard to bring in new technology and use it on patients you know would get a good result without it. But eventually we'll take the positive aspects of the new treatment and apply it to the general population. Over time we'll work out the best ways to use it in healthier eyes.

"In the meantime, using this approach is definitely worthwhile, in our hands," he says. "We've gotten some dramatic results—and only a few disappointing ones—with ectasia, post-keratoplasty and keratoconus patients. In our ectasia group, for example, about one-third of our patients gain two or more lines of BCVA. About a third of them end up 20/40 uncorrected or better. It's a huge result for these patients who are being handicapped by the severe irregular astigmatism that they get. The extra effort it takes to do these treatments is definitely worthwhile."

"I have to say that topography-guided ablation, especially when it's combined with cross-linking, is a remarkable procedure," adds Dr. Stein. "We're able to take patients who are not functioning well and improve their best corrected visual acuity. It's one of the most enjoyable parts of my practice." REVIEW

Dr. Kanellopoulos is a consultant for WaveLight, Alcon, iOptics and Avedro. Drs. Stein and Holland have no financial ties to products or companies mentioned.

The Solution to Every Case.

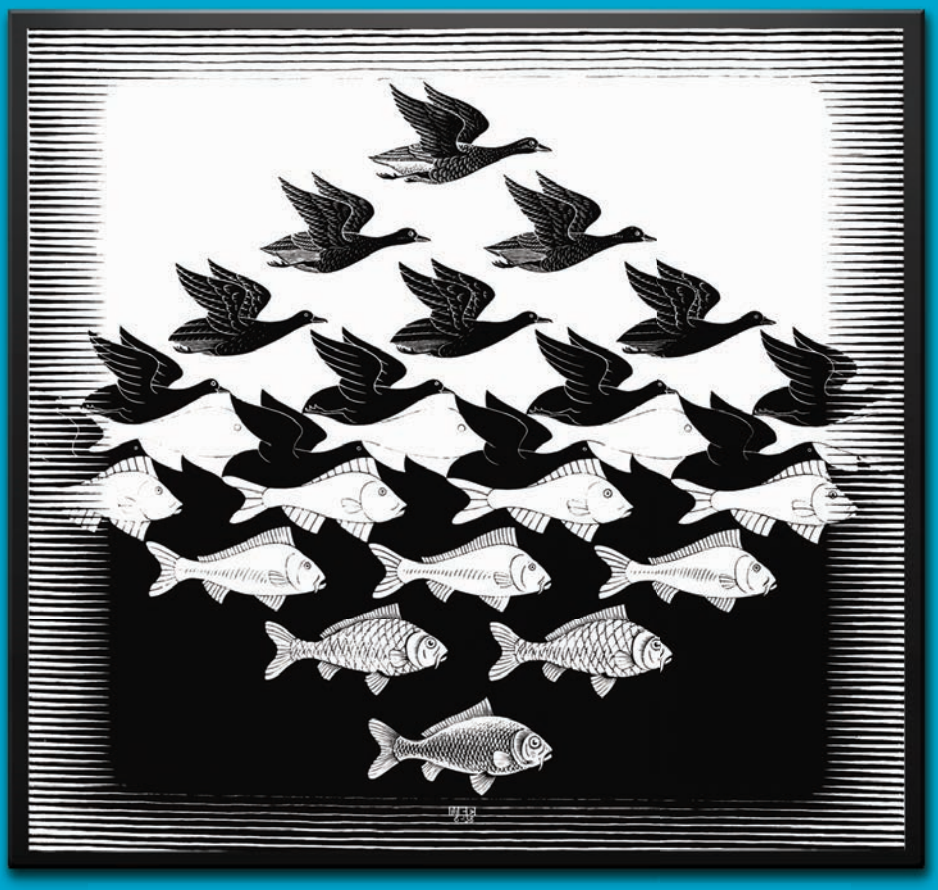
Follow the clues and find the world's finest surgical microscope designed for ophthalmology. Our key piece of evidence: our new C.Red® that emits an even brighter and more stable red reflex.

Add extreme depth perception. Super stable, surgeon friendly mechanics. Precise optics. And that's our case.

Now prove it to yourself. Call 800-787-5426 to learn more from Haag-Streit.

800.787.5426
haag-streit-usa.com

HAAG-STREIT USA



Indication and Usage
Diabetic Macular Edema
OZURDEX® (dexamethasone intravitreal implant) is a corticosteroid indicated for the treatment of diabetic macular edema.

Dosage and Administration
FOR OPHTHALMIC INTRAVITREAL INJECTION.
The intravitreal injection procedure should be carried out under controlled aseptic conditions. Following the intravitreal injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.

IMPORTANT SAFETY INFORMATION
Contraindications
Ocular or Periocular Infections: OZURDEX® (dexamethasone intravitreal implant) is contraindicated in patients with active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.

Glaucoma: OZURDEX® is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.

Torn or Ruptured Posterior Lens Capsule: OZURDEX® is contraindicated in patients whose posterior lens capsule is torn or ruptured because of the risk of migration into the anterior chamber. Laser posterior capsulotomy in pseudophakic patients is not a contraindication for OZURDEX® use.

Hypersensitivity: OZURDEX® is contraindicated in patients with known hypersensitivity to any components of this product.

Warnings and Precautions
Intravitreal Injection-related Effects: Intravitreal injections, including those with OZURDEX®, have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored regularly following the injection.

Steroid-related Effects: Use of corticosteroids including OZURDEX® may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.

Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

Adverse Reactions
Ocular adverse reactions reported by greater than or equal to 1% of patients in the two combined 3-year clinical trials following injection of OZURDEX® for diabetic macular edema include: cataract (68%), conjunctival hemorrhage (23%), visual acuity reduced (9%), conjunctivitis (6%), vitreous floaters (5%), conjunctival edema (5%), dry eye (5%), vitreous

UPDATED DME INDICATION

SEE DME Differently.

- **The pathophysiology**
  — An **inflammatory cascade** plays a key role[1-5]
- **The therapeutic targets**
  — Suppress multiple **inflammatory cytokines**[6]
- **The clinical results**
  — Achieve clinically significant **3-line gains** in BCVA[6,*]

Now for use in the general DME population

IMPORTANT SAFETY INFORMATION (continued)
Adverse Reactions (continued)
detachment (4%), vitreous opacities (3%), retinal aneurysm (3%), foreign body sensation (2%), corneal erosion (2%), keratitis (2%), anterior chamber inflammation (2%), retinal tear (2%), eyelid ptosis (2%). Non-ocular adverse reactions reported by greater than or equal to 5% of patients include: hypertension (13%) and bronchitis (5%).

Increased Intraocular Pressure: IOP elevation greater than or equal to 10 mm Hg from baseline at any visit was seen in 28% of OZURDEX® (dexamethasone intravitreal implant) patients versus 4% of sham patients. 42% of the patients who received OZURDEX® (dexamethasone intravitreal implant) were subsequently treated with IOP-lowering medications during the study versus 10% of sham patients.

The increase in mean IOP was seen with each treatment cycle, and the mean IOP generally returned to baseline between treatment cycles (at the end of the 6-month period).

Cataracts and Cataract Surgery: The incidence of cataract development in patients who had a phakic study eye was higher in the OZURDEX® group (68%) compared with Sham (21%). The median time of cataract being reported as an adverse event was approximately 15 months in the OZURDEX® (dexamethasone intravitreal implant) group and 12 months in the Sham group. Among these patients, 61% of OZURDEX® subjects versus 8% of sham-controlled subjects underwent cataract surgery, generally between Month 18 and Month 39 (Median Month 21 for OZURDEX® group and 20 for Sham) of the studies.

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

*Best-corrected visual acuity.

Ozurdex®
(dexamethasone intravitreal implant) 0.7 mg

1. Jain A, Varshney N, Smith C. The evolving treatment options for diabetic macular edema. *Int J Inflam.* 2013;2013:689276. **2.** Bhagat N, Grigorian RA, Tutela A, Zarbin MA. Diabetic macular edema: pathogenesis and treatment. *Surv Ophthalmol.* 2009;54(1):1-32. **3.** Ehrlich R, Harris A, Ciulla TA, Kheradiya N, Winston DM, Wirostko B. Diabetic macular oedema: physical, physiological and molecular factors contribute to this pathological process. *Acta Ophthalmol.* 2010;88(3):279-291. **4.** Scholl S, Kirchhof J, Augustin AJ. Pathophysiology of macular edema. *Ophthalmologica.* 2010;224(suppl 1):8-15. **5.** Zhang W, Liu H, Al-Shabrawey M, Caldwell RW, Caldwell RB. Inflammation and diabetic retinal microvascular complications. *J Cardiovasc Dis Res.* 2011;2(2):96-103. **6.** OZURDEX® Prescribing Information.

ALLERGAN Retina

www.Ozurdex.com APC52TE14 143433

OZURDEX®

(dexamethasone intravitreal implant) 0.7 mg

Brief Summary—Please see the OZURDEX® package insert for full Prescribing Information.

INDICATIONS AND USAGE

Retinal Vein Occlusion: OZURDEX® (dexamethasone intravitreal implant) is a corticosteroid indicated for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

Posterior Segment Uveitis: OZURDEX® is indicated for the treatment of non-infectious uveitis affecting the posterior segment of the eye.

Diabetic Macular Edema

OZURDEX® is indicated for the treatment of diabetic macular edema.

CONTRAINDICATIONS

Ocular or Periocular Infections: OZURDEX® (dexamethasone intravitreal implant) is contraindicated in patients with active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.

Glaucoma: OZURDEX® is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.

Torn or Ruptured Posterior Lens Capsule: OZURDEX® is contraindicated in patients whose posterior lens capsule is torn or ruptured because of the risk of migration into the anterior chamber. Laser posterior capsulotomy in pseudophakic patients is not a contraindication for OZURDEX® use.

Hypersensitivity: OZURDEX® is contraindicated in patients with known hypersensitivity to any components of this product *[see Adverse Reactions]*.

WARNINGS AND PRECAUTIONS

Intravitreal Injection-related Effects: Intravitreal injections, including those with OZURDEX®, have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments.

Patients should be monitored regularly following the injection *[see Patient Counseling Information]*.

Steroid-related Effects: Use of corticosteroids including OZURDEX® may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses *[see Adverse Reactions]*.

Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

ADVERSE REACTIONS

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

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

Retinal Vein Occlusion and Posterior Segment Uveitis

The following information is based on the combined clinical trial results from 3 initial, randomized, 6-month, sham-controlled studies (2 for retinal vein occlusion and 1 for posterior segment uveitis):

Adverse Reactions Reported by Greater than 2% of Patients

MedDRA Term	OZURDEX® N=497 (%)	Sham N=498 (%)
Intraocular pressure increased	125 (25%)	10 (2%)
Conjunctival hemorrhage	108 (22%)	79 (16%)
Eye pain	40 (8%)	26 (5%)
Conjunctival hyperemia	33 (7%)	27 (5%)
Ocular hypertension	23 (5%)	3 (1%)
Cataract	24 (5%)	10 (2%)
Vitreous detachment	12 (2%)	8 (2%)
Headache	19 (4%)	12 (2%)

Increased IOP with OZURDEX® peaked at approximately week 8. During the initial treatment period, 1% (3/421) of the patients who received OZURDEX® required surgical procedures for management of elevated IOP.

Following a second injection of OZURDEX® (dexamethasone intravitreal implant) in cases where a second injection was indicated, the overall incidence of cataracts was higher after 1 year.

Diabetic Macular Edema

The following information is based on the combined clinical trial results from 2 randomized, 3-year, sham-controlled studies in patients with diabetic macular edema. Discontinuation rates due to the adverse reactions listed in the table below were 3% in the OZURDEX® group and 1% in the Sham group. The most common ocular (study eye) and non-ocular adverse reactions are as follows:

Ocular Adverse Reactions Reported by ≥ 1% of Patients and Non-ocular Adverse Reactions Reported by ≥ 5% of Patients

MedDRA Term	OZURDEX® N=324 (%)	Sham N=328 (%)
Ocular		
Cataract[1]	166/243[2] (68%)	49/230 (21%)
Conjunctival hemorrhage	73 (23%)	44 (13%)
Visual acuity reduced	28 (9%)	13 (4%)
Conjunctivitis	19 (6%)	8 (2%)
Vitreous floaters	16 (5%)	6 (2%)
Conjunctival edema	15 (5%)	4 (1%)
Dry eye	15 (5%)	7 (2%)
Vitreous detachment	14 (4%)	8 (2%)
Vitreous opacities	11 (3%)	3 (1%)
Retinal aneurysm	10 (3%)	5 (2%)
Foreign body sensation	7 (2%)	4 (1%)
Corneal erosion	7 (2%)	3 (1%)
Keratitis	6 (2%)	3 (1%)
Anterior Chamber Inflammation	6 (2%)	0 (0%)
Retinal tear	5 (2%)	2 (1%)
Eyelid ptosis	5 (2%)	2 (1%)
Non-ocular		
Hypertension	41 (13%)	21 (6%)
Bronchitis	15 (5%)	8 (2%)

[1] Includes cataract, cataract nuclear, cataract subcapsular, lenticular opacities in patients who were phakic at baseline. Among these patients, 61% of OZURDEX® subjects vs. 8% of sham-controlled subjects underwent cataract surgery.

[2] 243 of the 324 OZURDEX® subjects were phakic at baseline; 230 of 328 sham-controlled subjects were phakic at baseline.

Increased Intraocular Pressure

Summary of Elevated IOP Related Adverse Reactions

	Treatment: N (%)	
IOP	**OZURDEX® N=324**	**Sham N=328**
IOP elevation ≥10 mm Hg from Baseline at any visit	91 (28%)	13 (4%)
≥30 mm Hg IOP at any visit	50 (15%)	5 (2%)
Any IOP lowering medication	136 (42%)	32 (10%)
Any surgical intervention for elevated IOP*	4 (1.2%)	1 (0.3%)

* OZURDEX®: 1 surgical trabeculectomy for steroid-induced IOP increase, 1 surgical trabeculectomy for iris neovascularization,1 laser iridotomy, 1 surgical iridectomy
Sham: 1 laser iridotomy

Cataracts and Cataract Surgery

At baseline, 243 of the 324 OZURDEX® subjects were phakic; 230 of 328 sham-controlled subjects were phakic. The incidence of cataract development in patients who had a phakic study eye was higher in the OZURDEX® group (68%) compared with Sham (21%). The median time of cataract being reported as an adverse event was approximately 15 months in the OZURDEX® group and 12 months in the Sham group. Among these patients, 61% of OZURDEX® subjects vs. 8% of sham-controlled subjects underwent cataract surgery, generally between Month 18 and Month 39 (Median Month 21 for OZURDEX® group and 20 for Sham) of the studies.

The increase in mean IOP was seen with each treatment cycle, and the mean IOP generally returned to baseline between treatment cycles (at the end of the 6 month period).

USE IN SPECIFIC POPULATIONS

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies with OZURDEX® in pregnant women. Animal reproduction studies using topical ocular administration of dexamethasone were conducted in mice and rabbits. Cleft palate and embryofetal death in mice and malformations of the intestines and kidneys in rabbits were observed. OZURDEX® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

Topical ocular administration of 0.15% dexamethasone (0.375 mg/kg/day) on gestational days 10 to 13 produced embryofetal lethality and a high incidence of cleft palate in mice. A dose of 0.375 mg/kg/day in the mouse is approximately 3 times an OZURDEX® injection in humans (0.7 mg dexamethasone) on a mg/m2 basis. In rabbits, topical ocular administration of 0.1% dexamethasone throughout organogenesis (0.13 mg/kg/day, on gestational day 6 followed by 0.20 mg/kg/day on gestational days 7-18) produced intestinal anomalies, intestinal aplasia, gastroschisis and hypoplastic kidneys. A dose of 0.13 mg/kg/day in the rabbit is approximately 4 times an OZURDEX® injection in humans (0.7 mg dexamethasone) on a mg/m2 basis.

Nursing Mothers: Systemically administered corticosteroids are present in human milk and can suppress growth and interfere with endogenous corticosteroid production. The systemic concentration of dexamethasone following intravitreal treatment with OZURDEX® is low. It is not known whether intravitreal treatment with OZURDEX® could result in sufficient systemic absorption to produce detectable quantities in human milk. Exercise caution when OZURDEX® is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of OZURDEX® in pediatric patients have not been established.

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies in animals have been conducted to determine whether OZURDEX® (dexamethasone intravitreal implant) has the potential for carcinogenesis.

Although no adequate studies have been conducted to determine the mutagenic potential of OZURDEX®, dexamethasone has been shown to have no mutagenic effects in bacterial and mammalian cells *in vitro* or in the *in vivo* mouse micronucleus test. Adequate fertility studies have not been conducted in animals.

PATIENT COUNSELING INFORMATION

Steroid-related Effects

Advise patients that a cataract may occur after repeated treatment with OZURDEX®. If this occurs, advise patients that their vision will decrease, and they will need an operation to remove the cataract and restore their vision.

Advise patients that they may develop increased intraocular pressure with OZURDEX® treatment, and the increased IOP will need to be managed with eye drops, and, rarely, with surgery.

Intravitreal Injection-related Effects

Advise patients that in the days following intravitreal injection of OZURDEX®, patients are at risk for potential complications including in particular, but not limited to, the development of endophthalmitis or elevated intraocular pressure.

When to Seek Physician Advice

Advise patients that if the eye becomes red, sensitive to light, painful, or develops a change in vision, they should seek immediate care from an ophthalmologist.

Driving and Using Machines

Inform patients that they may experience temporary visual blurring after receiving an intravitreal injection. Advise patients not to drive or use machines until this has been resolved.

Bringing LASIK Back into Focus

Walter Bethke, Managing Editor

Steps you can take inside and outside your practice to help boost your LASIK volume.

For several years now, following a significant decrease in the 2008 to 2009 time period, LASIK volumes have been flat, leaving surgeons casting about for new ways to reach patients and boost their practices' LASIK conversion rates. Though experts agree the 2008 economic recession has had a lot to do with stagnant LASIK volumes, they also say there are still some steps you can take both inside and outside of your practice that can help capture more LASIK candidates as the overall economy recovers. Here's a look at how you can reach today's candidates.

Who Wants LASIK?

Surgeons and refractive surgery marketing experts say that the LASIK market has changed since the procedure's inception. Surgeons now have to keep their eyes on a new demographic, even if its constituents aren't clamoring for LASIK right now.

Though 35- to 42-year-old patients are still the most common group that gets LASIK, industry experts say it's time to address millennials. "The 22- to 28-year-old age group is the fastest-growing and largest group of potential LASIK customers in the country," says Mike Malley, of CRM Marketing in Houston, which designs refractive marketing strategies for 35 practices. "They have the same distribution of refractive error as any other group, meaning more than half of them are potential LASIK candidates. So the question becomes, 'Are they having LASIK?' And the answer right now is they're not. Some of our college and post-college focus group studies have told us that millennials are aware of LASIK and would like to have it done, but it's just not on the top of their to-do lists. These individuals are out of college and saddled with education loans, and are primarily in a car-buying mode and possibly thinking about getting married. In their minds, LASIK is a distant seventh or eighth in importance. Even so, they are candidates, and the likelihood of them having it done is fairly strong—but it will take two or three years."

LASIK Promotion

As the patient demographics have changed over the years, so too has the best way to reach them, say experts. As a result, you may have to retool your marketing message.

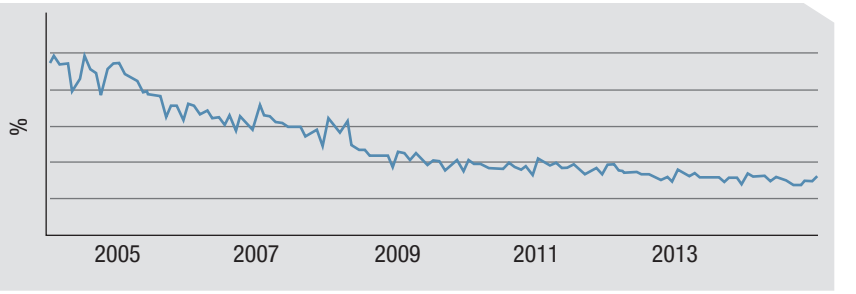
- ***External marketing.*** "Though the millennials are aware of LASIK and would like to have it, they're simply not having it done," says Mr. Malley. "So, the core group actually having

LASIK right now is the person in the 33-to-43 age group, split evenly between male and female, who has both the money to afford LASIK and frustration with their vision. They have a desire to make a change and are making it. We're actually seeing conversion in clinics increase because people coming in want to have it. They're doing their research on-line and coming in and having it done."

The act of reaching potential patients, even in lean times, through both traditional and new media, is what Eye-to-Eye Consulting's Cory Pickett, based in Midland, Texas, calls "filling the funnel." "Even if you get patients to come to your office to inquire about LASIK, you'll lose some by them simply not showing up, you'll lose some because they turn out not to be good candidates, and you'll lose others because they don't have the financial means to afford the procedure," Mr. Pickett says. "If your funnel is big, though, you'll eventually pick up your share of patients for LASIK. But if you just restrict yourself to a small portion of the population, then the return on your marketing dollars won't be as successful."

"Because of the differences between millennials and older patients, we have to have a bi-level marketing strategy now," Mr. Malley says. "For the 33-to-43 age bracket, you need a message to the effect of, 'If you're frustrated with or intolerant of contact lenses, or even your reading glasses, here's why our clinic is the answer.' But, at the same time, you have to influence the millennials with campaigns on websites such as Instagram, Twitter and Pandora, the last being a non-traditional radio approach. Millennials are more influenced by educational information than they are by purchasing offers. For example, to influence them, you're better off saying something like, 'Visit our site to download the latest report that shows LASIK is safer and more affordable than contact lenses in the long term,' rather than, 'Save $500 on LASIK.' They're not so much in a purchasing mode right now as they are in a fact-finding one."

Interest in "LASIK" on Google



Houston refractive business consultant Michael Malley says a decline in interest in LASIK is one more challenge surgeons need to overcome. Specifically, he refers to this graph from Google Analytics which shows that, since 2005, there's been a decrease of almost 70 percent in searches for LASIK-related information using the term "LASIK" on Google.

• ***Internal marketing.*** Experts say you can also harness one of your greatest assets: your current patients who already feel comfortable with you. "A lot of the practices we work with offer both LASIK and cataract surgery," says Mr. Malley. "And often their cataract practice is bigger than their LASIK one. What many don't realize is they can market LASIK to the cataract population internally—but with a message aimed at their children and grandchildren. Also, if you happen to have a contact lens practice, offer every one of those patients a LASIK pricing offer limited just to your practice's current patients."

Handling the Call

Advertising, promotion and word of mouth may get your phone to ring, but how your practice handles that call could be the difference between an opportunity to speak to that patient in-person or having him go elsewhere.

Mr. Pickett says it's worth making sure the person who answers your phone has the time, information and demeanor necessary to get a patient interested in seeing you. "Trying to have your front-desk person answer the phone and discuss LASIK while also check-in patients is the wrong way to go," he says. "However, it still happens all the time. For instance, one practice I work with had noticed their LASIK appointments were limited despite a good number of calls. They gave me permission to call their number several times as if I were a patient. Over several calls, I experienced having my call blown off, having someone take a message and then never call me back, being put on hold for 10 minutes, having the person on the other end become evasive when I asked a question and, finally, having the person be overly pushy."

Mr. Pickett says if you think your staff might be mishandling calls, or overburdened by handling LASIK prospects on the phone throughout the day, it might be worth looking into commissioning a call center.

"You give the call center all the information on LASIK that you would want given to prospective patients, and they'll input it into software that operators can use to answer patients' questions," Mr. Pickett explains. "When the person asks a question, the operator clicks on it on their computer screen and can phrase the answer the way you want it phrased. They'll even have operators with accents specific to the part of the country where your practice is located; if you're in Texas,

for example, the operator will have a slight drawl. The patient doesn't know that the person answering the phone is in a different part of the country, just that the call is being handled professionally. If a patient has a very specific question that only applies to him and the operator can't answer it, he can put the patient on hold and buzz your office to have someone speak to him."

Mr. Pickett says that, if your staff isn't great on the phone, a call center can often be worth its fee. "The payment for this service is usually based on the number of calls, but it can be $1,500 to $2,000 per month," Mr. Pickett says. "The cost depends also on the kind of coverage. Some only do it for evenings and weekends, while some take calls seven days a week. Though the cost usually equates to one LASIK patient per month, after working with them for around 10 years, I've found them to be worth more in terms of what they give you in return."

Procedures and Prices

The experts on the refractive frontlines say it helps to diversify your offerings to give patients options. There are also two approaches to pricing LASIK, each with pros and cons.

• ***Procedure variety.*** Mr. Pickett says he encourages the practices he works with to offer as many surgical options as possible, as long as the surgeon is comfortable doing them. "It can help to have a physician in your practice who implants phakic IOLs," he says. "That opens that up as an option so you're not losing the phakic IOL patients. Just the other day, one practice I work with had to refer out two women who weren't LASIK candidates but were candidates for phakic lenses. Granted, if you don't have a lot of high myopes in your patient population you may not have a lot of experience with phakic lenses, but I've found that most of the practices I work with have most, if not all, of the refractive surgeries available. For instance, when the presbyopic corneal inlays become available to us, every practice is going to want to offer them because almost every patient over 40 will be a candidate. In a similar vein, we did a large campaign for a practice's presbyopia-correcting IOL services, and it wound up generating a lot of LASIK business because patients didn't realize we couldn't correct astigmatism with just the lenses."

Overland Park, Kan., surgeon Dan Durrie says refractive surgeons either need to cultivate people skills or hire someone who already has them.

Mobile, Ala., ophthalmologist Richard Duffey, who not only performs LASIK and cataract surgeries but has also tracked surgeons' practice patterns for years under the auspices of the American Academy of Ophthalmology and the American Society of Cataract and Refractive Surgery, says LASIK and refractive cataract surgery are becoming increasingly intertwined. "I think that continuing to stay active in LVC has enhanced my premium IOL and refractive cataract surgery practice," he says. "I fall back on the technology of LVC—both LASIK and PRK—to fine-tune the less-than-perfect results that we occasionally get with premium lenses and femtosecond cataract surgery."

• ***Tiered pricing.*** Tiered pricing involves having a low price for LASIK based on a low refraction, no astigmatism and minimal follow-up, and then having one or more tiers above that as the cases become more complex. Experts say tiered pricing and one-price-fits-all approaches have advantages and disadvantages.

"When a patient calls about LASIK, eight times out of 10 his initial inquiry consists of, 'How much is LASIK at your practice?' " says Mr. Malley. "He usually doesn't ask about the doctor's reputation, the technology or the results. So, if your response is, 'Our fees start as low as $995 per eye, and when you come in we'll determine what your final price will be,' you've done the perfect thing. We feel the clinic is a better place to discuss pricing than over the airwaves."

Mr. Pickett says tiered pricing makes sense because patients have a consumer's mindset. "When they buy a new truck, they want to be able to choose the leather seats, bigger engine and/or bigger wheels," he says. "This is opposed to going into the dealer and finding there's only one model there that has all the options on it and is expensive. They like to feel if they choose to pay some more, they get some more. So, have options in your practice, such as maybe a base price with add-on options for the patient that lets you raise your price without costing you a lot. I've seen this be very effective. One tip to be successful with this is not to have a huge range, such as $299 to $2,999. Instead, offer something where there are a small number of specific plans. For instance, have one plan with a specific amount of follow-up care and duration of the enhancement period, followed by a plan with a longer amount of both, et cetera. Patients will usually choose the option with more value. For instance, we did a test in one refractive practice where we offered either microkeratome or femtosecond LASIK, with the former being $1,000 less. In one year, only one patient chose the cheaper microkeratome procedure."

Surgeons counter, though, that if you've got an established reputation in your community, offering a single

price cuts through potentially confusing options while still bringing in patients. "I used to use tiered pricing, and used it successfully," says Dr. Duffey. "But when one of my younger partners came in, he thought it was too confusing for him to use to start his practice. So, we looked at the average of what we charge for LASIK, and for each of our other procedures, and set each procedure's price at its average. I've found that it's easier now, and there's little question in anyone's mind. I used to believe that I could have a low-end price there and get patients to our weekly practice seminar or into the clinic. Once they saw our quality, consistency and equipment, I reasoned, they'd choose us, even though we might have a higher price for their particular case. However, now that we've been in the community so long, the public knows that we have the best quality and what we stand for."

• ***Credit plans.*** Options for paying for a refractive procedure can sometimes help get someone off the fence and over to the LASIK side. "I think financing options can help a great deal," says Mr. Pickett. "CareCredit, which has been the main one out there, and a newer one, Alphaeon, both have plans set up for vision procedures. There may be practices out there that are hesitant to offer the financing because they don't want to pay the financing charge to the company. But if money is the barrier that's stopping a patient from having the procedure, I think you're doing yourself a disservice by not offering financing. If you don't offer financing, you're limiting yourself, especially in markets where the local economy may be down and patients don't have $4,000 in disposable income to pay for LASIK outright, but they can afford $150 per month. In our experience, the practices that are offering financing are seeing 40 to 50 percent of patients finance it, and that's OK. Again, it's about filling the funnel. By offering financing, you're giving yourself a bigger funnel to work with."

Food for Thought

In addition to the strategies outlined above, experts say there are other areas of your practice you can focus on to enhance your LASIK volume.

• ***Patient counselors.*** Though some practices may not use a counselor, experts say having the right person can pay dividends in terms of conversion rates. "Marketing can get people interested in calling you on the phone, but you also have to focus on meeting the patient's needs and moving him through a process many practices don't like to acknowledge: the sales process," says Dan Durrie, MD, of Overland Park, Kan. "This is where a lot of practices are weak, with either the surgeon or the counselor not having the skills needed to understand the patient's needs and how to transition him from someone who's interested to someone who's comfortable both having the procedure done immediately and having it done at your practice. It takes a particular type of person to do this. Other industries know that this type of employee is trained differently and hired differently. He's not just one of your techs who's been really good so you promoted him to counselor. He has to be skilled at reading people and alleviating fears. He must also be adept at identifying who the alpha person in the room is if the patient brought someone with him. For instance, the counselor must know if he should be addressing the mother of the patient. These are skills we as physicians aren't taught, but which are pretty much essential in this field."

• ***Patient education.*** Mr. Pickett says this is where you can really separate your practice from the competition. "This is something I love to do because when I'm talking to a patient and explaining the surgery, I'm banking on none of the competitor practices doing it the way I'm doing it," he says. "Most of these patients will visit more than one practice, and sometimes yours is the first they visit, so you want to make a positive impression on them. You want them to say, 'These people know what they're doing; this is where I want to have my LASIK.' "

Making use of technology can boost the education process, too. "Companies like Eyemaginations and Patient Education Concepts have software that can educate patients in ways that are light years beyond our old flip charts and eye models," Mr. Pickett says. "And these approaches can often be customized to each patient. You can even have presentations in which you come in at the end and discuss your different LVC plans."

• ***"New and improved."*** Though it may be asking a lot of surgeons to purchase equipment during a flat LASIK period, Mr. Malley says the excitement that surrounds the announcement of anything new can actually bring some patients out of the woodwork. "The ray of hope we saw this past year was the LASIK practices who have experienced the most growth out of all the practices we serve—not the highest volume but the fastest rate of growth—were those who introduced the newest LASIK technology," Mr. Malley says. "Their volume increased by 10 to 20 percent. There appears to be a group of patients who are waiting for the next generation of technology designed to possibly make LASIK 'safer, faster, better or with improved outcomes.' I'm not sure how large this group is, but they're out there."

Mr. Pickett says that, in the end, there is no one solution to decreased LASIK volume, but rather a string of incremental improvements. "All of these steps you take add up," he says. "If each measure you take generates one to five patients per month, then before you know it you've got 20 extra patients and you've had a successful month." REVIEW

LASIK: Thin Flaps, Thin Volumes

Walter Bethke, Managing Editor

Refractive surgeons' views on technique and technology.

In the early days of LASIK, surgeons reached a consensus that they'd like to leave a residual stromal bed thickness of at least 300 µm after surgery, and the flaps they made were on the thicker side, around 145 to 160 µm. However, the emergence of corneal ectasia as a postop complication, and the advent of newer ways to make thinner flaps, have driven down the average flap thickness to a point where a flap between 100 to 119 µm is by far the most popular on our refractive surgery survey, judging by the latest results. However, surgeons would probably like more opportunities to make flaps, as they report that their LASIK volumes remain flat.

Flap thicknesses and LASIK volume are two of the topics covered in this month's refractive surgery survey. The survey e-mail was opened by 1,733 of 11,600 subscribers to *Review*'s electronic mail service (14.9-percent open rate), and 70 surgeons responded. See how their approaches to refractive surgery align with yours.

The Shrinking Flap

As mentioned earlier, surgeons are extolling the virtues of thin flaps, with 73 percent of them saying they prefer to make flaps that are between 100 and 119 µm thick, an increase from last year's 59 percent. Sixteen percent prefer flaps to be 120 to 130 µm. Six percent employ flaps thicker than 150 µm, 4 percent use flaps less than 100 µm and 2 percent prefer flaps between 131 and 149 µm thick.

Sixty-eight percent of the surgeons use a femtosecond laser to create their flaps, with the rest preferring a blade.

As for why surgeons like the relatively thin flap size of 100 to 119 µm, many think it's a good compromise between the extremes of thickness. Paul Kuck, MD, of LaCrosse, Wis., says this kind of flap works best for him. "A flap of 110 µm is safe enough to prevent tears and avoid too thin a flap if there is a variable cut," he says. "I still may go thinner, though: I just upgraded to an Alcon FS200 femtosecond laser."

A surgeon from Austin, Texas, thinks this thickness of flap gives the best of both worlds. "It's thick enough to be stable on lifting," he says, "but thin enough to allow completion of most cases with a flap plus ablation total that takes less than 40 percent of corneal thickness." George Walters, MD, of Port Arthur, Texas, says that flaps in this range "leave enough tissue for most ablations and are easier to handle than thinner flaps." Jeffrey Whitman, MD, of Dallas also thinks these flaps go easy on the corneal surface. "They have less of an effect on the corneal

nerves and dry eye," he says. "Also, I keep the flap to a smaller diameter."

Preferred Procedures

Though it will take another a year or two more to declare it a trend, the percentage of surgeons who say they prefer to use wavefront-optimized LASIK for most of their cases increased to 33 percent from 13 percent on last year's survey. A third say they prefer to use custom LASIK. Thirteen percent like PRK and 12 percent prefer conventional LASIK for most of their cases. Four percent do epi-LASIK on most patients, and 2 percent each say they mostly do CK, LASEK or Staar Visian implantation.

Monthly LASIK volumes reported on the survey remain somewhat flat, and hover around their 2014 levels (a comparison graph of the past three years appears below). Sixty-eight percent of surgeons say they perform 20 or fewer cases per month. Eight percent, however, say they do more than 100 cases per month, which is up slightly from last year's 6 percent. The average price surgeons charge for LASIK increased compared to last year, climbing to $3,395 from $2,452. For PRK, surgeons charge an average of $3,389 this year, versus $2,404 last year.

Feelings on Phakics

Thirty-six percent of the surgeons say that phakic IOLs are an option they reach for in select patients, but this doesn't mean these lenses don't have shortcomings.

William Trattler, MD, of Miami gets good results with the Visian ICL. "I love the ICL," he says. "But I wish it had a fenestration so we could eliminate the need to create a peripheral iridotomy." A surgeon from Philadelphia agrees, and voices a gripe many phakic lens surgeons have, namely that toric phakic lenses have yet to be approved in the United States. "I use the ICL," he says. "The benefits are that it uses a small incision and the eye is quick-healing. The drawbacks are difficult sizing, no astigmatism option and the need for YAG PIs."

A surgeon from Oklahoma also bemoans the approval process that is keeping a toric option out of his reach. "I don't like the slow approvals from the FDA," he says. "We should have gotten approval for a toric phakic lens in the United States. We should also have gotten approval for a fenestrated lens to stop having to perform PIs. Also, these lenses should be preloaded."

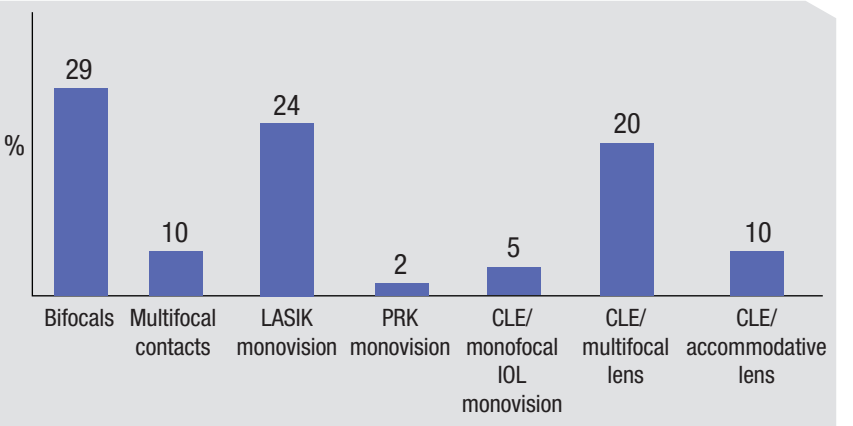
However, not everyone is a fan of phakic lenses, and some foresee problems down the road. A surgeon from Utah dislikes them as an option, saying, "The rate of debilitating glare and cataract formation are way under-reported. They all eventually have to be removed if the patient lives long enough and forms cataracts."

Tough Cases

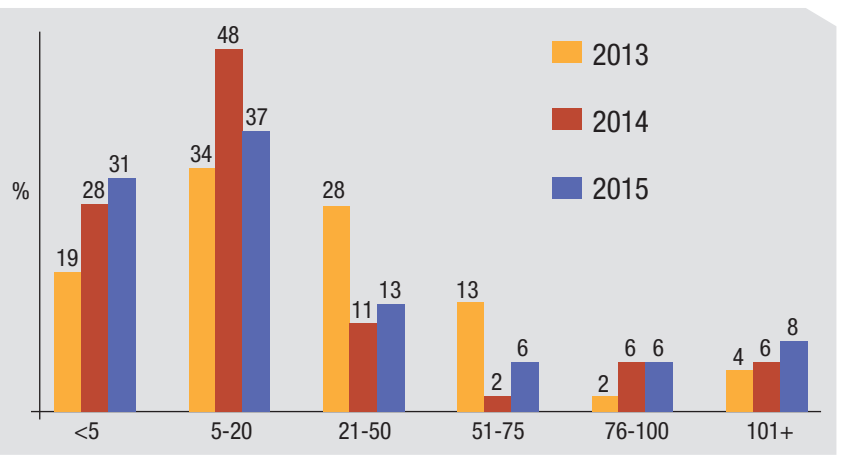
Surgeons say they alter their approach to certain patients, depending on the level of correction that's needed and, sometimes, patient age.

For a high (-11 D) myope, most of the surgeons, 75 percent, say they think a phakic IOL is best. Kurt Andreason, MD, director of the Wright Patterson Air Force Base's Warfighter Refractive Eye Surgery Center in

Best Procedure for a 45-year-old Hyperopic Presbyope



Average LASIK Monthly Case Volume by Survey Year



Ohio, says a phakic intraocular lens is usually a good method because other ones fall short in such patients. "The residual stromal bed is usually insufficient for this refraction," he says. "PRK with mitomycin-C is a consideration, but there is plenty of room for a phakic IOL in this situation, without much corneal effect." A physician from Oklahoma says he'll consider the patient's age. "If the patient age is under 45, I'll use an ICL," he says. "If it's over 45, I'll use CLE/IOL implantation. I choose these options for quality of vision and ease of healing without regression."

A challenging patient presentation that surgeons weighed in on is the 45-year-old hyperopic presbyope, whose situation doesn't lend itself to a clear-cut solution. On the survey, 29 percent of the surgeons avoid surgery altogether for this patient, saying that a pair of bifocals is best. Twenty-four percent like monovision LASIK and 20 percent prefer CLE/IOL. Multifocal contact lenses and CLE/accommodative IOL implantation each were chosen by 10 percent of the respondents. A surgeon from Utah chose the bifocal route: "With surgery in this type of patient, there's a high percentage of dry eyes afterward, particularly in females," he says. "It depends on how bad the hyperopia is. The surgeon should wait until cataracts begin to form before doing multifocal IOLs."

Future Plans

Surgeons have also been keeping an eye on the refractive surgery pipeline, and have opinions about which burgeoning technology piques their interest the most. The most popular new technologies are corneal inlays/onlays (38 percent) and corneal cross-linking (22 percent). The other popular options were small-incision lenticule extraction (18 percent) and a new accommodative lens (18 percent).

Dr. Andreason is in the group that's most looking forward to onlays. "This technology and its results seem promising," he says. "LASIK surgeons can do it safely, it is reversible and many patients will be motivated to try it if long-term results continue to be successful." George Walters, MD, of Port Arthur, Texas, feels similarly, saying, "This technology would benefit more patients and increase LASIK volume."

Wisconsin's Dr. Kuck is one of the 22 percent looking forward to the approval of corneal cross-linking. "It benefits keratoconus patients and decreases the risk of ectasia in patients with thin but 'Pentacam-normal' corneas," he says. An ophthalmologist from California agrees, and says that she is eagerly awaiting cross-linking because of its versatility, saying, "Cross-linking has lots of applications." REVIEW

OUR SCIENCE. YOUR ART. THEIR VISION.

NOW APPROVED FOR DIABETIC MACULAR EDEMA (DME)

As Demonstrated in 2 Pivotal, Phase 3 Trials in Patients With DME Evaluating Mean Change in BCVA* at 52 Weeks vs Baseline[1]

EYLEA® (aflibercept) Injection Offers Extended Dosing in DME—2-mg Every 8 Weeks Following 5 Initial Monthly Doses[1]

Initial Dosing	Follow-Up Dosing
5 Initial 2-mg Injections Monthly (Every 4 Weeks)	2-mg Every 2 Months (Every 8 Weeks)

Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.

*BCVA = best-corrected visual acuity, as measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letters.

IMPORTANT SAFETY INFORMATION FOR EYLEA® (aflibercept) INJECTION

- EYLEA® (aflibercept) Injection is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.
- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following use of intravitreal VEGF inhibitors, including EYLEA, defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies during the first year was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.
- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

IMPORTANT PRESCRIBING INFORMATION FOR EYLEA® (aflibercept) INJECTION

EYLEA® (aflibercept) Injection is indicated for the treatment of patients with

- Neovascular (Wet) Age-related Macular Degeneration (AMD): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.
- Macular Edema following Retinal Vein Occlusion (RVO): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly).
- Diabetic Macular Edema (DME): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections, followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.

For more information, visit www.EYLEA.com.

Reference: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. October 2014.

Please see brief summary of full Prescribing Information on the following page.

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

TARGETED SCIENCE

REGENERON

10/2014
LEA-0624

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

For complete details, see Full Prescribing Information.

1 INDICATIONS AND USAGE

EYLEA® (aflibercept) Injection is indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), and Diabetic Macular Edema (DME).

2 DOSAGE AND ADMINISTRATION

2.1 Important Injection Instructions. For ophthalmic intravitreal injection. EYLEA must only be administered by a qualified physician.

2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD). The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.

2.3 Macular Edema Following Retinal Vein Occlusion (RVO). The recommended dose for EYLEA is (0.05 mL or 50 microliters) administered by intravitreal injection once every 4 weeks (monthly).

2.4 Diabetic Macular Edema (DME). The recommended dose for EYLEA is (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.

2.5 Preparation for Administration. EYLEA should be inspected visually prior to administration. If particulates, cloudiness, or discoloration are visible, the vial must not be used. Using aseptic technique, the intravitreal injection should be performed with a 30-gauge x ½-inch injection needle. For complete preparation for administration instructions, see full prescribing information.

2.6 Injection Procedure. The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include surgical hand disinfection and the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a topical broad–spectrum microbicide should be given prior to the injection.

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

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

Each vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter, and injection needles should be changed before EYLEA is administered to the other eye.

After injection, any unused product must be discarded.

3 DOSAGE FORMS AND STRENGTHS

Single-use, glass vial designed to provide 0.05 mL of 40 mg/mL solution (2 mg) for intravitreal injection.

4 CONTRAINDICATIONS

EYLEA is contraindicated in patients with

- Ocular or periocular infections
- Active intraocular inflammation
- Known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as severe intraocular inflammation

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments. Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments (*see Adverse Reactions*). Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately (*see Dosage and Administration and Patient Counseling Information*).

5.2 Increase in Intraocular Pressure. Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA (*see Adverse Reactions*). Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular edothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately (*see Dosage and Administration*).

5.3 Thromboembolic Events. There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies during the first year was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in the *Warnings and Precautions* section of the labeling:

- Endophthalmitis and retinal detachments
- Increased intraocular pressure
- Thromboembolic events

6.1 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 other clinical trials of the same or another drug and may not reflect the rates observed in practice.

A total of 2711 patients treated with EYLEA constituted the safety population in seven phase 3 studies. Among those, 2110 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, active-controlled clinical studies (VIEW1 and VIEW2) for 12 months.

Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

Adverse Reactions	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%
Eye pain	9%	9%
Cataract	7%	7%
Vitreous detachment	6%	6%
Vitreous floaters	6%	7%
Intraocular pressure increased	5%	7%
Conjunctival hyperemia	4%	8%
Corneal erosion	4%	5%
Detachment of the retinal pigment epithelium	3%	3%
Injection site pain	3%	3%
Foreign body sensation in eyes	3%	4%
Lacrimation increased	3%	1%
Vision blurred	2%	2%
Intraocular inflammation	2%	3%
Retinal pigment epithelium tear	2%	1%
Injection site hemorrhage	1%	2%
Eyelid edema	1%	2%
Corneal edema	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, and endophthalmitis.

Macular Edema Following Retinal Vein Occlusion (RVO). The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following BRVO in one clinical study (VIBRANT).

Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies

Adverse Reactions	CRVO		BRVO	
	EYLEA (N=218)	Control (N=142)	EYLEA (N=91)	Control (N=92)
Eye pain	13%	5%	4%	5%
Conjunctival hemorrhage	12%	11%	20%	4%
Intraocular pressure increased	8%	6%	2%	0%
Corneal epithelium defect	5%	4%	2%	0%
Vitreous floaters	5%	1%	1%	0%
Ocular hyperemia	5%	3%	2%	2%
Foreign body sensation in eyes	3%	5%	3%	0%
Vitreous detachment	3%	4%	2%	0%
Lacrimation increased	3%	4%	3%	0%
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

Diabetic Macular Edema (DME). The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) for 52 weeks.

Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

Adverse Reactions	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%
Eye pain	9%	6%
Cataract	8%	9%
Vitreous floaters	6%	3%
Corneal erosion	5%	3%
Intraocular pressure increased	5%	3%
Conjunctival hyperemia	5%	6%
Vitreous detachment	3%	3%
Foreign body sensation in eyes	3%	3%
Lacrimation increased	3%	2%
Vision blurred	2%	2%
Intraocular inflammation	2%	<1%
Injection site pain	2%	<1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, eyelid edema, corneal edema, retinal detachment, injection site hemorrhage, and retinal tear.

6.2 Immunogenicity. As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.

In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-52 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy. Pregnancy Category C. Aflibercept produced embryo-fetal toxicity when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days at subcutaneous doses ≥0.1 mg per kg. Adverse embryo-fetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was less than 0.1 mg per kg. Administration of the lowest dose assessed in rabbits (0.1 mg per kg) resulted in systemic exposure (AUC) that was approximately 10 times the systemic exposure observed in humans after an intravitreal dose of 2 mg.

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

8.3 Nursing Mothers. It is unknown whether aflibercept is excreted in human milk. Because many drugs are excreted in human milk, a risk to the breastfed child cannot be excluded. EYLEA is not recommended during breastfeeding. A decision must be made whether to discontinue nursing or to discontinue treatment with EYLEA, taking into account the importance of the drug to the mother.

8.4 Pediatric Use. The safety and effectiveness of EYLEA in pediatric patients have not been established.

8.5 Geriatric Use. In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

17 PATIENT COUNSELING INFORMATION

In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist (*see Warnings and Precautions*). Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations (*see Adverse Reactions*). Advise patients not to drive or use machinery until visual function has recovered sufficiently.

REGENERON

Manufactured by:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

U.S. License Number 1760

Issue Date: October 2014
Initial U.S. Approval: 2011

Regeneron U.S. Patents 7,306,799; 7,531,173; 7,608,261; 7,070,959; 7,374,757; 7,374,758, and other pending patents

LEA-0618

The Future of Presbyopia Correction

Michelle Stephenson, Contributing Editor

Corneal inlays, scleral implants and excimer and femtosecond laser procedures are under investigation.

New options for presbyopia correction are currently under investigation that may soon offer younger patients alternatives to refractive lens exchange.

Michael Gordon, MD, in private practice in La Jolla, Calif., points out that approved and available treatments today are not ideal. "Today, we have poor attempts at doing presbyLASIK, particularly in the United States, because we are limited in how we use lasers," he says. "We have presbyopia-correcting intraocular lenses, which are good but not perfect because we really don't have any true accommodating IOLs. We have monovision with LASIK and monovision with IOLs, which is tried-and-true and has been around for a long time in many forms. I think it works very well, but it's not the ultimate answer because a little bit of stereopsis and distance vision are lost."

Understanding Presbyopia

Daniel Durrie, MD, in private practice with Durrie Vision in Overland Park, Kan., says ophthalmologists are changing the way they talk to patients about correcting presbyopia. "It has made it a lot simpler to come up with the best solution for each patient," he says.

Dr. Durrie notes that presbyopia is part of dysfunctional lens syndrome, which has three stages. Stage 1 typically starts around 43 years of age and goes until the early 50s. During this time, the lens loses its ability to focus. In stage 2, which occurs during the 50s and 60s, the lens turns yellow and hazy. During this time, patients begin to experience night vision problems and need more light to read. The third stage, which typically doesn't occur until the 70s, is true cataract formation.

"When we are evaluating someone who is having difficulty with reading glasses and bifocals, we really want to find out where he is in the stages of dysfunctional lens syndrome, and that helps us in coming up with a treatment," Dr. Durrie says. "If it is obvious that someone is in late stage 2 or early stage 3, we are going to lean towards lens replacement surgery, because anything we do on the cornea isn't really going to benefit them for very long. This discussion also lets patients know that presbyopia is a progressive condition. It is going to require lens replacement at some point in time. That has helped us look at the procedures of today as well as the procedures that are coming in the future and how we are going to fit them into practice."

This article has no commercial sponsorship.

Corneal Inlays

Several corneal inlays are under investigation, and each has a different principle of action. According to Dr. Durrie, one advantage of corneal inlays is that they have a tendency to provide near vision in the non-dominant eye and provide better distance vision than blended or monovision. "I think that's a step up and will be a premium product for people who are presbyopic and don't yet need their lens replaced," he says. "The Kamra by AcuFocus is leading the way through [the Food and Drug Administration trial process]. It has already gone to panel and is in the process of labeling and end-stage discussions with the agency now."

Richard Lindstrom, MD, in private practice in Minneapolis, says the Kamra inlay uses small-diameter aperture optics or pinhole optics. "Just as you would use a pinhole to improve someone's vision in the office, this concept is used by this corneal implant or inside an IOL," Dr. Lindstrom says. "It's not a multifocal, and it's not accommodating. Instead, it generates an increased depth of focus. This concept is used in disposable cameras that can take pictures at every distance. You target slight myopia. That along with the pinhole creates hyperfocality, which is widely used in the disposable camera industry. These patients see well at all distances. Typically, the inlay is only implanted in the nondominant eye. It looks very promising."

Jay Pepose, MD, PhD, in private practice in Chesterfield, Mo., agrees. "The Kamra inlay is a neat concept because there is not as much disparity in uncorrected distance acuity between the two eyes as there is with full monovision, and there is not as much compromise in contrast sensitivity or stereopsis as there is with full monovision. Unlike LASIK, where permanent changes have been made to the eye, the inlay can be removed if the patient doesn't like it or can't adapt to it," Dr. Pepose says.

In June 2014, the FDA Ophthalmic Devices Advisory Panel concluded that the benefits of the Kamra inlay outweigh the risks for patients with presbyopia. The panel reviewed data on 508 patients implanted monocularly with the inlay in the U.S. IDE clinical trial. In September 2014, the Kamra inlay received the CE Mark approval in Europe. It is not FDA-approved.

A study with three years of follow-up supports the safety and efficacy of the Kamra corneal inlay to correct presbyopia.[1] This study included 32 naturally emmetropic presbyopic patients, and the corneal inlay was implanted in the non-dominant eye. Patients' mean uncorrected near visual acuity improved from J6 preoperatively to J1 at three years, and the mean uncorrected intermediate visual acuity improved from 20/40 to 20/25 at three years. Additionally, at three years, 97 percent of eyes had an uncorrected near visual acuity of J3 or better, and 91 percent had an uncorrected intermediate visual acuity of 20/32 or better. The mean uncorrected distance visual acuity was 20/20, with all eyes achieving 20/32 or better. Nine eyes lost one line of corrected distance visual acuity, one eye lost more than two lines, and three eyes gained one line.

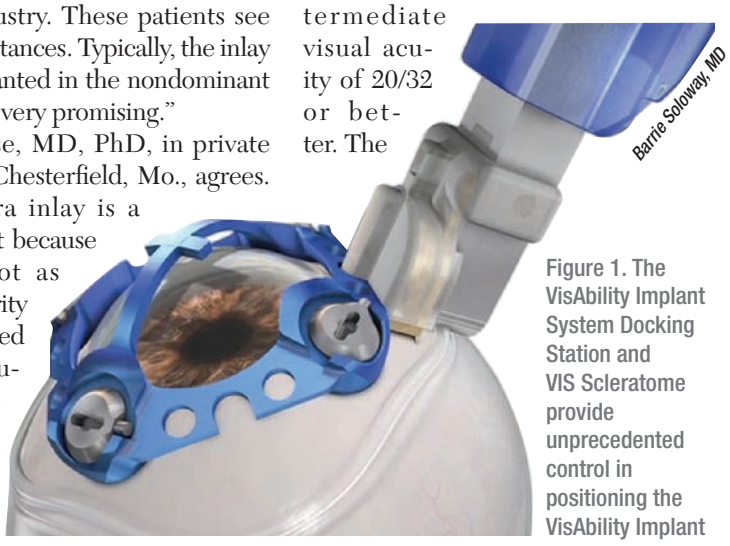


Figure 1. The VisAbility Implant System Docking Station and VIS Scleratome provide unprecedented control in positioning the VisAbility Implant

Another corneal inlay is the Flexivue Microlens (Presbia, Los Angeles). "This is a refractive inlay, meaning that the power can be changed because it is a different refractive index than the cornea," Dr. Gordon says. He is an investigator for this inlay and says that it is in the initial stages of the Phase III clinical trial. "The results are extremely good. It is considered 'smart' monovision because vision will change depending on pupil size both at near and far; however, it is still a form of monovision. The advantage is that it's an inlay that is very bioinert, so it can be removed or replaced as the patient ages, and a new power can be inserted."

A recent study evaluating the efficacy and safety of the Flexivue Microlens found that, 12 months after implantation, the inlay seems to be an effective method for the corneal compensation of presbyopia in emmetropic presbyopes between the ages of 45 and 60 years of age. The study included 47 patients.[2]

The Raindrop corneal inlay, formerly known as PresbyLens, by ReVision Optics (Lake Forest, Calif.) is also currently under investigation. It is a microscopic hydrogel inlay that creates a prolate-shaped cornea and is easily placed under a femtosecond laser flap.

Scleral Implants

Another alternative to correct presbyopia is the VisAbility scleral implant (Refocus Group, Dallas). "VisAbility uses four small implants placed in scleral tunnels, 4 mm posterior to the limbus," says Barrie Soloway, MD, director of vision correction surgery at the New York Eye and Ear Infirmary. "The VisAbility Implant System

uses a scleral approach to treat presbyopia that is fundamentally different from the optical or multifocal approach. The hypothesized mechanism of action of the VisAbility surgery is a retensioning of the posterior zonules, giving the ciliary muscles more efficiency in reshaping the lens in these presbyopic patients."

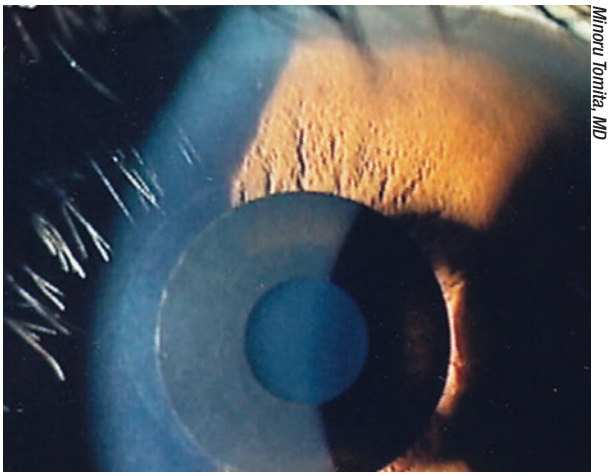
He notes that there are two advantages to this approach. First, surgery is well off the visual axis, so there are no changes in distance vision, such as problems with halos or glare, as might occur with most other approaches. "And, unlike bifocal laser or presbyopia-correcting IOLs, with VisAbility surgery, patients have a continuous range of focus from far through intermediate to near," Dr. Soloway adds.

He says that results of this surgery in a recently completed FDA clinical trial were promising, with 96 percent of patients seeing J3, 20/40 or better uncorrected at near monocularly, and all were better still binocularly. "During the course of the study, a number of radically new instruments, including a docking station, were developed, which marked a quantum leap improvement in the consistency and ease of the surgery," he says. "In Europe, where the CE-marked VisAbility Implant System is in use, surgeons report that their patients are having faster and better improvement in near and intermediate vision."

FDA IDE clinical trials are currently under way in the United States, and enrollment of 360 patients at a dozen sites should be completed this year.

Laser Procedures

Laser procedures are not ideal for treating presbyopia, mainly because the results are not reversible. "Once you've done it, you've removed tissue in a complex pattern, which can be impossible to undo, not to mention how to measure these eyes for their lens replacement when they need cataract surgery," Dr. Soloway explains.



Minoru Tomita, MD

Figure 2. The Kamra inlay.

He notes that most excimer and some femtosecond laser manufacturers are working on algorithms for multifocal corneal treatments with a lot of variability. "Some are working with a more plus center, while others are trying more plus in the periphery," Dr. Soloway says. "With either of these approaches, some patients experience glare and halos, and there can be a gap in focus in the intermediate distance range."

Monovision with an excimer laser is one option. A study conducted in Spain found that this procedure improved functional near vision in presbyopic patients.[3] However, although distance visual acuity was good, contrast sensitivity and stereoacuity diminished significantly. In this study, LASIK was performed with the Allegretto Wave Eye-Q 400-Hz laser. The dominant eye was corrected for distance vision, and the non-dominant eye was corrected for near vision by targeting -1.25 D of myopia. The study included 50 eyes of 25 patients with a mean age of 49.3 years ±4.5. Postoperatively, more than 90 percent of patients had a binocular uncorrected distance and near visual acuity of 0.0 logMAR or better. However, the contrast sensitivity function diminished, especially in the non-dominant eye and with binocular vision. All patients experienced significantly worse stereoacuity. Visual discrimination capacity declined in non-dominant eyes and under binocular conditions. No significant changes occurred in dominant eyes.

Another refractive surgery option is presbyLASIK. In a recent study of myopes and hyperopes, presbyLASIK using the MEL 80 platform induced significant changes in spherical aberration. This study concluded that presbyLASIK appears to offer an improved response over LASIK when correcting myopes due to an apparent increase in depth of focus resulting from changes in spherical aberration. Additionally, presbyLASIK provides a more consistent spherical aberration effect in hyperopes, independent of refractive change.[4]

Intraocular Lenses

For patients who have late stage 2 or stage 3 dysfunctional lens syndrome, lens replacement surgery is required. "In the United States, we are still limited to the big three: ReSTOR, Crystalens, and Tecnis multifocal," Dr. Pepose says. "I think we will likely see low add powers of the Tecnis multifocal available in the United States in 2015. Right now, the Tecnis lens is a +4 add on the posterior IOL surface, which has the near focal point optimized around 32 cm. The lower powers would move the point of focus farther out. For some people, that would afford a more comfortable reading distance for a book or computer. Fewer rings may mean fewer

(continued on page 71)


Corticosteroids for Diabetic Macular Edema

As diabetes becomes more common, a large unmet need has arisen for long-acting corticsteroid implants to treat the disorder.

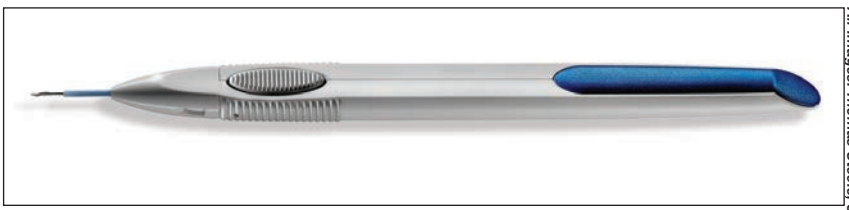
Thomas A. Ciulla, MD, Indianapolis

Diabetic macular edema is one of the leading causes of blindness in the industrialized world. Recently, both the dexamethasone implant *(See Figure 1; Ozurdex, Allergan)* and the fluocinolone implant *(See Figure 2; Iluvien, Alimera Sciences)* have been approved in the United States for the treatment of DME, heightening the interest in the use of long-acting corticosteroid implants for this disorder. There is a large unmet need for such treatments as diabetes becomes more common in an aging and increasingly obese population; the incidence of DME increases with the duration of diabetes, the severity of diabetic retinopathy, and with increasing levels of glycosylated hemoglobin. In fact, the Wisconsin Epidemiologic Study of Diabetic Retinopathy revealed that the 10-year rate of developing diabetic macular edema in the United States was 20.1 percent among type I diabetics, 25.4 percent among type II diabetics using insulin, and 13.9 percent for type II diabetics not using insulin.[1] Nearly half of those developing DME will lose two or more lines of visual acuity within two years.[2]

Pathophysiology of DME

Early in DR, there are changes in the structure and cellular composition of the microvasculature. Damage to the endothelial cells that are responsible for maintaining the blood-retinal barrier (BRB) leads to increased vascular permeability. In DME, breakdown of the inner BRB allows accumulation of extracellular fluid in the macula *(See Figure 3)*. Damage to pericytes that are essential cellular components for regulating capillary perfusion in the retina leads to altered retinal hemodynamics, including abnormal autoregulation of retinal blood flow.[3] The loss of retinal pericytes occurs early in DR and correlates with microaneurysm formation.[4,5] In individuals with diabetes, the capillary basement membrane thickens and increased extracellular matrix components are deposited, and these events may be contributing factors to the development of abnormal retinal hemodynamics, including the abnormal autoregulation of retinal blood flow. Many interrelated pathways are linked to the cellular damage from hyperglycemia and hypoxia affecting the BRB, including angiogenic growth factors and inflammatory cytokines. Corticosteroids modulate these pathways to exert a therapeutic effect in DME.

Vascular endothelial growth factor plays a key role in angiogenesis and vascular permeability.[6] There are at least nine different VEGF isoforms, due to alternative splicing that include VEGF-A, VEGF-B, VEGF-C, VEGF-D and VEGF-E. The actions of VEGF family members are mediated by the activation of tyrosine kinase receptors. VEGF receptors



All images: Thomas Steele, CRA

Figure 1. The Ozurdex dexamethasone implant inserter.

This article has no commercial sponsorship.

(VEGFR) can signal via the mitogen-activating protein kinase (MAPK) signaling pathway or through elevation in intracellular calcium concentration in endothelial cells forming the vessel walls. Activation of both pathways has been suggested to increase vascular permeability. VEGF-A is a critical regulator of ocular angiogenesis and vascular permeability. VEGF-A acts at VEGFR 1 and 2. VEGF mediates angiogenesis by promoting endothelial cell migration, proliferation and survival. VEGF also possesses inflammatory properties through its capacity to mediate microvascular permeability and increase adhesion of leukocytes, thus incorporating the inflammatory cascade, initiating early diabetic retinal leukocyte adhesion and aiding the development of diabetic vasculopathy.

Inflammation also plays an important role in diabetic retinopathy and diabetic macular edema. Leukostasis, adhesion molecules, prostaglandin up-regulation and retinal accumulation of macrophages occur in diabetes. Retinal leukostasis, in particular, may play a key role in the pathogenesis of DR. Leukocytes possess large cell volume, high cytoplasmic rigidity, a natural tendency to adhere to the vascular endothelium and a capacity to generate toxic superoxide radicals and proteolytic enzymes.[7-9] In diabetes, increased leukostasis affects retinal endothelial function, retinal perfusion, angiogenesis and vascular permeability. In patients with diabetes, leukocytes are also abnormal. They are less deformable; a higher proportion than usual are activated; and they appear to be involved in capillary nonperfusion, endothelial cell damage and vascular leakage in the retinal microcirculation. Numerous inflammatory mediators have been involved in diabetic retinopathy including tumor necrosis factor α (TNF-α), a pro-inflammatory cytokine and interleukin-6.

Pharmacotherapy of DME

Recently, intravitreal anti-VEGF agents, bevacizumab, ranubizumab and aflibercept have been used to treat DME. These three intravitreal agents bind VEGF, thereby decreasing angiogenesis and vascular permeability, causing regression of diabetic neovascularization and reduction in DME respectively. Several recent clinical trials suggest that anti-VEGF therapies are more effective than laser therapy.[10] However, anti-VEGF therapy requires repeated intravitreal injection, sometimes monthly or even indefinitely. Furthermore, anti-VEGF therapy is not effective in all patients, possibly because targeting VEGF does not suppress all the inflammatory cytokines involved in DME.

Corticosteroids can be utilized in sustained-released forms to treat DME. Corticosteroids inhibit macrophages that release angiogenic growth factors and down-regulate ICAM-1, which mediates leukocyte adhesion and transmigration; they have been noted to decrease major histocompatibility complex (MHC)-II expression in the subretina where AMD-associated neovessels form.[11-13] In addition to this anti-inflammatory mechanism, corticosteroids alter the composition of endothelial basal membrane by changing the local ratio of two laminin isoforms, suppressing basement membrane dissolution, and strengthening tight junctions to limit permeability and leakage that cause macular edema.[11,13]

Triamcinolone Acetonide

Triamcinolone acetonide has been studied in numerous clinical trials for diabetic macular edema as far back as the late 1990s.[14-21] More recently, the Diabetic Retinopathy Clinical Research Network (DRCR) has studied both posterior subTenon and intravitreal TA for DME. The DRCR protocol I represented a pivotal clinical trial assessing three different treatment schemes: intravitreal 0.5 mg ranibizumab plus prompt or deferred focal/grid laser; or 4 mg intravitreal TA combined with focal/grid laser compared with focal/grid laser alone.[22] At the two-year visit, compared with the sham + prompt laser group, the mean change from baseline in the VA letter score was 3.7 letters greater in the ranibizumab + prompt laser group; 5.8 letters greater in the ranibizumab + deferred laser group; and 1.5 letters worse in the TA + prompt laser group. When analysis was confined to the pseudophakic group of patients, TA

Figure 2. The Iluvien fluocinolone implant insertion device.

showed similar VA results to the ranibizumab, indicating that decreased acuity could be at least in part attributed to cataract formation. At the two-year visit, the percentages of eyes with central subfield thickness ≥250 µm were 59 percent in the sham + prompt laser group; 43 percent in the ranibizumab + prompt laser group; 42 percent in the ranibizumab + deferred laser group; and 52 percent in the TA + prompt laser group. These results show the potential of TA to serve as a less expensive, but comparable, therapy to anti-VEGF injections. However, anti-VEGF therapy has become first-line therapy in DME patients, especially those who are phakic, but intravitreal TA is often utilized in phakic patients who do not have access to ranibizumab.

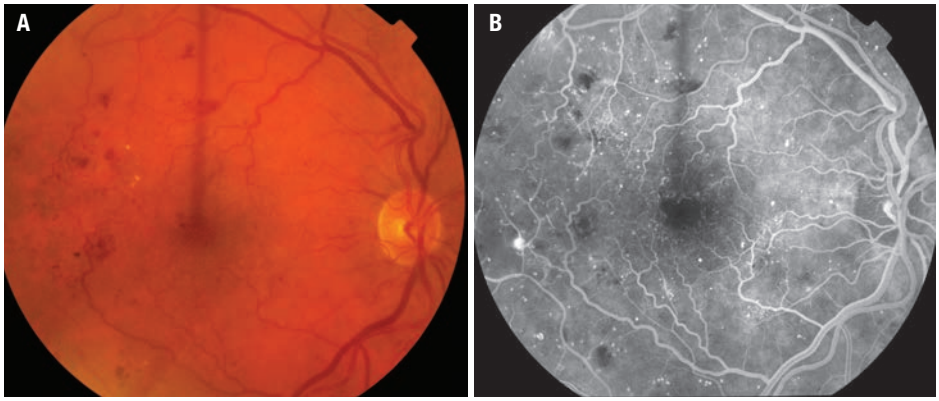


Figure 3. Color photograph (A) and mid- and late-phase fluorescein angiograms showing changes typical of diabetic macular edema. A small tuft of neovascularization elsewhere (NVE) is also evident.

Intravitreal TA has a half-life of 18.6 days and may persist at levels sufficient to exert clinical effect for up to three months.[23] Nevertheless, repeat injections are required, which can increase the risk of cataract and glaucoma. Instead of intermittent bolus therapy, it is thought that sustained release of a lower-dose corticosteroid may lead to greater efficacy with fewer complications of cataract or glaucoma. This has led to the development of the DEX and FA implants.

Dexamethasone Implant

In June 2009, the Food and Drug Administration approved a 0.7-mg DEX implant contained in a solid bioerodable polymer for the treatment of macular edema following retinal vein occlusion. It can exert a clinical effect for three to six months. In September 2010, the 0.7-mg implant was approved for treatment of non-infectious intermediate and posterior uveitis. In June 2014, it was approved for the use in DME in pseudophakic patients or those phakic patients scheduled for cataract surgery. In September 2014, approval was expanded for the use in general DME patients, both pseudophakic and phakic.

In a clinical trial known as the MEAD Study, 1,048 subjects with DME with best-corrected visual acuity 34 letters (20/200) to 68 letters (20/50), and center macula subfield thickness >300 µm were randomized in a 1:1:1 ratio to DEX implant 0.7 mg, DEX implant 0.35 mg or sham procedure and followed for three years.[24] Subjects were eligible for retreatment every six months based on predefined OCT criteria. The percentage of patients with ≥15-letter improvement in BCVA from baseline at study end was greater with DEX implant 0.7 mg (22.2 percent) and DEX implant 0.35 mg (18.4 percent) than sham (12 percent; $p \leq 0.018$). Mean average reduction in CRT from baseline was greater with DEX implant 0.7 mg (-111.6 µm) and DEX implant 0.35 mg (-107.9 µm) than sham (-41.9 µm; $p < 0.001$).

The DEX implant may be particularly well-suited for the treatment of DME in vitrectomized eyes; these eyes may more rapidly clear intermittently administered intravitreally injected drugs compared to nonvitrectomized eyes. A clinical trial known as the CHAMPLAIN study evaluated 55 patients with treatment-resistant DME and a history of previous pars plana vitrectomy. The study eyes received a single 0.7-mg DEX intravitreal implant and were followed for 26 weeks. These eyes showed statistically and clinically significant improvements in both visual acuity and vascular leakage from DME at 26 weeks. At week eight, 30.4 percent of patients had gained ≥10 letters in BCVA.[25]

Fluocinolone Acetonide Implant

The FA intravitreal implant is administered using a 25-ga. inserter, and it leads to sustained drug release for up to 36 months. Unlike the DEX implant, it is not bioerodable. In 2005, an FA intravitreal implant containing 0.59 mg FA was approved in the United States for the treatment of non-infectious uveitis. In a clinical trial known as the FAMOUS study, 37 patients with persistent DME despite prior focal/grid laser therapy were randomized 1:1 to receive an experimental intravitreal injection of a 0.2- or a 0.5-µg/day insert.[26] After administration of a 0.2-µg/day insert, the mean change from baseline in BCVA was 5.1, 2.7 and 1.3 letters at months three, six and 12, respectively. The mean change from baseline after administration of a 0.5 µg/day-insert was 7.5, 6.9 and 5.7 letters at months

three, six and 12, respectively. Aqueous humor sampling revealed sustained intraocular release of FA for greater than one year.

The Fluocinolone Acetonide for Diabetic Macular Edema (FAME) studies evaluated 953 eyes of patients with persistent DME after ≥one laser therapy treatments, randomized 1:2:2 for sham injection (n=185), low-dose FA insert (0.2 µg/day, n=375) or high-dose FA insert (0.5 µg/day, n=393).[27,28] At 36 months, 27.8 percent (high dose) and 28.7 percent (low dose) of implant-treated eyes versus 18.9 percent of sham eyes demonstrated an improvement of 15 or more letters (p=0.018). A subgroup analysis showed particular benefit among patients with DME for three or more years. Corticosteroid-related side effects were noted; up to 8.1 percent required incisional glaucoma surgery, and cataracts progressed in nearly all phakic eyes.

In September 2014, the FDA approved FA implant containing 0.19 mg fluocinolone for DME in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure. However, this previous course of corticosteroids was not specified. Clinicians could conceivably trial a topical corticosteroid, intravitreal bolus therapy with triamcinolone or DEX implant.

Complications

The exact mechanism of corticosteroid-induced secondary intraocular pressure rise is not known; however, one established contributory factor is increased outflow resistance within the trabecular meshwork.[29,30] In the FAME study, there was a greater need for surgical glaucoma intervention at the three-year point in patients receiving the FA injection group; 2.5 percent of the high-dose group, 1.3 percent of the low-dose group and 0 percent of the sham injection group required laser trabeculoplasty. Incisional glaucoma surgery was needed in 8.1 percent of the high-dose group, 4.8 percent of the low-dose group and 0.5 percent of the sham injection group.[27] In the MEAD study, ocular hypertension was usually controlled with medication or no therapy; only two patients (0.6 percent) in the DEX implant 0.7-mg group and one (0.3 percent) in the DEX implant 0.35-mg group required trabeculectomy.[24]

A meta-analysis by Weerawat Kiddee, MD, and colleagues found that 66 percent and 79 percent of individuals developed ocular hyptertension (OHT) following 0.59 and 2.1 mg FA implants respectively, and 11 percent and 15 percent of patients following 0.35 and 0.7 mg DEX implants, respectively. For patients with DME, 15.7 percent and 14.9 percent developed OHT following 0.35 mg and 0.7 mg DEX intravitreal implants. The analysis showed that prevalence of OHT was higher in FA implant groups than DEX implant groups. Pre-existing or family history of glaucoma seemed to have an increasing risk for OHT development after intravitreal corticosteroid application. However, various definitions for OHT limited accurate comparisons between studies.[31] As for the treatment of secondary corticosteroid-induced glaucoma, Dr. Kiddee and colleagues reported that therapy is similar to primary open-angle glaucoma. Elevated IOP was primarily treated with topical medication. Trabeculectomy was the most common surgical procedure for OHT.[31]

Ocular corticosteroid therapy is known to cause secondary cataract formation, a complication also associated with administration of systemic corticosteroids. The FAME study reported that cataract development rates were higher in those patients receiving FA inserts; they reported that 42.7 percent of the low-dose group, 51.7 percent of the high-dose group, and 9.7 percent of the sham injection group developed cataracts. These numbers represent 81.7 percent, 88.7 percent and 50.7 percent respectively of the patients in each group with phakic eyes at the start of the study.[27] In the MEAD study, rates of cataract formation in phakic eyes were 67.9 percent, 64.1 percent and 20.4 percent in the DEX implant 0.7 mg, DEX implant 0.35 mg and sham groups, respectively.[24]

In summary, although anti-VEGF therapy is becoming the treatment of choice for center-involved DME, the recently approved sustained-release low-dose DEX implant and FA implant add greatly to the treatment options. In particular, these implants will limit frequent intravitreal injection, often required with intravitreal anti-VEGF therapy. Corticosteroid implants may also limit the cost of repeated treatment with expensive anti-VEGF therapies such as ranibizumab or aflibercept and may minimize the risk of endophthalmitis, given the lower number of injections. While the FA implant lasts much longer than the DEX implant, potentially decreasing the visit and treatment burden on patients and their families, the FA implant appears to have a greater risk of ocular hypertension and cataract. However, these modalities have not been directly compared in a clinical trial.

There is insufficient evidence to draw more elaborate conclusions, especially to determine if multiple injections with the DEX implant lead to the same risks as the longer-lasting FA implant. As noted above, the FA implant's approval requires a prior treatment with a course of corticosteroids to rule out a clinically significant rise in intraocular pressure. However, this prior course of corticosteroids could conceivably be a topical corticosteroid, intravitreal bolus therapy with triamcinolone, or DEX implant.

There are no large randomized prospective clinical trials comparing sustained-release corticosteroid therapy to antiVEGF therapy as first-line therapy in center-involved DME, but DEX and FA implants could become early treatment for pseudophakic patients. For non-center-involved DME, laser treatment could remain first-line treatment, since the risks of laser photocoagulation are minimal in these cases, compared to the risks, discomfort and expense of intravitreal therapies. DEX or FA implants might be especially attractive as early therapies for center-involved DME in eyes that have undergone vitrectomy, since it is thought that anti-VEGF agents have shorter half-life, and presumable less efficacy in these cases.

For center-involved DME that is persistent despite periodic anti-VEGF therapy, the durable action of corticosteroid implants, especially the FA implant, facilitates combination therapy. In the future, patients could receive these implants as foundational therapy, and then receive additional treatment with laser or intravitreal anti-VEGF agents as combination therapy, which may conceivably provide some synergistic benefit. FA may be particularly attractive for this use in pseudophakic patients without significant risk of glaucoma, given its long duration of action.

Finally, corticosteroids implants may have a special role in the treatment of chronic DME. A recent study compared the efficacy of the FA implant in chronic (≥three years) versus non-chronic (<three years) DME in a preplanned subgroup analysis of the FAME study.[32] At month 36, the difference between FA implant and sham control in the percentage of subjects who gained 15 letters or more was significantly greater in 536 chronic DME subjects (34 percent vs. sham, 13.4 percent; $p<0.001$), compared to the 416 subjects with non-chronic DME (22.3 percent vs. sham, 27.8 percent; $p=0.275$). The differences could not be explained by baseline ocular characteristics, changes in anatomic features or differences in re-treatment or ancillary therapies. The authors speculate that early DME is driven primarily by VEGF, while chronic DME may driven more by inflammatory cytokines in addition to anatomic changes. The authors conclude that the FA implant may be an option for patients who do not respond to other therapy. This report may also partially account for the clinical observations of beneficial effect using the DEX implant when anti-VEGF agents have minimal effect. REVIEW

Dr. Ciulla is on the Retina Service at Midwest Eye Institute, 200 W. 103rd St. Indianapolis, IN 46290. Contact him at (317) 817 1822 or e-mail thomasciulla@gmail.com.

1. Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XV. The long-term incidence of macular edema. Ophthalmology 1995;102:7-16.
2. Ferris FL, 3rd, Patz A. Macular edema. A complication of diabetic retinopathy. Surv Ophthalmol 1984;28 Suppl:452-61.
3. Ciulla TA, Harris A, Latkany P, Piper HC, Arend O, Garzozi H, et al. Ocular perfusion abnormalities in diabetes. Acta Ophthalmol Scand 2002;80(5):468-77.
4. Ciulla TA, Amador AG, Zinman B. Diabetic retinopathy and diabetic macular edema: Pathophysiology, screening, and novel therapies. Diabetes Care 2003;26(9):2653-64.
5. Ehrlich R, Harris A, Ciulla TA, Kheradiya N, Winston DM, Wirostko B. Diabetic macular oedema: Physical, physiological and molecular factors contribute to this pathological process. Acta Ophthalmologica. 2010;88(3):279-91.
6. Miller JW, Le Couter J, Strauss EC, Ferrara N. Vascular endothelial growth factor a in intraocular vascular disease. Ophthalmology 2013;120:106-14.
7. Miyamoto K, Ogura Y. Pathogenetic potential of leukocytes in diabetic retinopathy. Semin Ophthalmol 1999;14(4):233-9.
8. Miyamoto K, Hiroshiba N, Tsujikawa A, Ogura Y. In vivo demonstration of increased leukocyte entrapment in retinal microcirculation of diabetic rats. Invest Ophthalmol Vis Sci 1998;39(11):2190-4.
9. Barouch FC, Miyamoto K, Allport JR, Fujita K, Bursell SE, Aiello LP, et al. Integrin-mediated neutrophil adhesion and retinal leukostasis in diabetes. Invest Ophthalmol Vis Sci 2000;41(5):1153-8.
10. Boyer DS, Hopkins JJ, Sorof J, Ehrlich JS. Anti-vascular endothelial growth factor therapy for diabetic macular edema. Therapeutic advances in endocrinology and metabolism. 2013;4(6):151-69.
11. Tokida Y, Aratani Y, Morita A, Kitagawa Y. Production of two variant laminin forms by endothelial cells and shift of their relative levels by angiostatic steroids. The J Biol Chem 1990;265(30):18123-9.
12. Ingber DE, Madri JA, Folkman J. A possible mechanism for inhibition of angiogenesis by angiostatic steroids: Induction of capillary basement membrane dissolution. Endocrinology 1986;119(4):1768-75.
13. Stokes CL, Weisz PB, Williams SK, Lauffenburger DA. Inhibition of microvascular endothelial cell migration by beta-cyclodextrin tetradecasulfate and hydrocortisone. Microvasc Res 1990;40(2):279-84.
14. Audren F, Erginay A, Haouchine B, Benosman R, Conrath J, Bergmann JF, et al. Intravitreal triamcinolone acetonide for diffuse diabetic macular oedema: 6-month results of a prospective controlled trial. Acta Ophthalmol Scand 2006;84(5):624-30.
15. Audren F, Lecleire-Collet A, Erginay A, Haouchine B, Benosman R, Bergmann JF, et al. Intravitreal triamcinolone acetonide for diffuse diabetic macular edema: Phase 2 trial comparing 4 mg vs 2 mg. Am J Ophthalmol 2006;142:794-99.
16. Jonas JB, Kamppeter BA, Harder B, Vossmerbaeumer U, Sauder G, Spandau UH. Intravitreal triamcinolone acetonide for diabetic macular edema: A prospective, randomized study. J Ocul Pharmacol Ther 2006;22(3):200-7.
17. Jonas JB, Kreissig I, Sofker A, Degenring RF. Intravitreal injection of triamcinolone for diffuse diabetic macular edema. Arch Ophthalmol 2003;121:57-61.
18. Jonas JB, Sofker A. Intraocular injection of crystalline cortisone as adjunctive treatment of diabetic macular edema. Am J Ophthalmol 2001;132:425-7.
19. Jonas JB, Spandau UH, Kamppeter BA, Vossmerbaeumer U, Harder B, Sauder G. Repeated intravitreal high-dosage injections of triamcinolone acetonide for diffuse diabetic macular edema. Ophthalmology 2006;113:800-4.
20. Martidis A, Duker JS, Greenberg PB, Rogers AH, Puliafito CA, Reichel E, et al. Intravitreal triamcinolone for refractory diabetic macular edema. Ophthalmology 2002;109:920-7.
21. Massin P, Audren F, Haouchine B, Erginay A, Bergmann JF, Benosman R, et al. Intravitreal triamcinolone acetonide for diabetic diffuse macular edema: Preliminary results of a prospective controlled trial. Ophthalmology 2004;111:218-24; discussion 24-5.
22. Elman MJ, Bressler NM, Qin H, Beck RW, Ferris FL, 3rd, Friedman SM, et al. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2011;118:609-14.
23. Beer PM, Bakri SJ, Singh RJ, Liu W, Peters GB, 3rd, Miller M. Intraocular concentration and pharmacokinetics of triamcinolone acetonide after a single intravitreal injection. Ophthalmology 2003;110:681-6.
24. Boyer DS, Yoon YH, Belfort R, Jr., Bandello F, Maturi RK, Augustin AJ, et al. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. Ophthalmology 2014;121:1904-14.
25. Boyer DS, Faber D, Gupta S, Patel SS, Tabandeh H, Li XY, et al. Dexamethasone intravitreal implant for treatment of diabetic macular edema in vitrectomized patients. Retina 2011;31:915-23.
26. Campochiaro PA, Hafiz G, Shah SM, Bloom S, Brown DM, Busquets M, et al. Sustained ocular delivery of fluocinolone acetonide by an intravitreal insert. Ophthalmology 2010;117:1393-9 e3.
27. Campochiaro PA, Brown DM, Pearson A, Chen S, Boyer D, Ruiz-Moreno J, et al. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. Ophthalmology 2012;119:2125-32.
28. Campochiaro PA, Brown DM, Pearson A, Ciulla T, Boyer D, Holz FG, et al. Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. Ophthalmology 2011;118:626-35 e2.
29. Tektas OY, Lutjen-Drecoll E. Structural changes of the trabecular meshwork in different kinds of glaucoma. Exp Eye Res 2009;88(4):769-75.
30. Wordinger RJ, Clark AF. Effects of glucocorticoids on the trabecular meshwork: Towards a better understanding of glaucoma. Prog Retin Eye Res 1999;18(5):629-67.
31. Kiddee W, Trope GE, Sheng L, Beltran-Agullo L, Smith M, Strungaru MH, et al. Intraocular pressure monitoring post intravitreal steroids: A systematic review. Surv Ophthalmo 2013;58(4):291-310.
32. Cunha-Vaz J, Ashton P, Iezzi R, Campochiaro P, Dugel PU, Holz FG, et al. Sustained delivery fluocinolone acetonide vitreous implants: Long-term benefit in patients with chronic diabetic macular edema. Ophthalmology 2014;121:1892-903.

***Richard Lindstrom**, MD*
Ophthalmologist and noted refractive and cataract surgeon.
Minnesota Eye Consultants

"Good lid and lash hygiene is not a sometime event. As a chronic Blepharitis sufferer, I use Avenova as part of my daily lid hygiene regimen. And I recommend Avenova to my patients."

NovaBay®

Avenova™

Daily lid and lash hygiene.

Neutrox™

(Pure Hypochlorous Acid) 0.01%

Hypochlorous Acid in Solution

- Kills organisms
- Neutralizes toxins from microorganisms
- Prevents biofilm formation

OPHTHALMOLOGIST AND OPTOMETRIST TESTED | RX ONLY

AVENOVA.COM | 1-800-890-0329

Putting Your Contacts to Work

Attempts to engineer contact lenses that also elute therapeutic drugs face hurdles in both the world of lenses and of drugs.

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

Well over half of all Americans use some sort of vision correction, and for about a quarter of these, the correction method of choice is the contact lens.[1] These are patients willing to adapt their lives to the routine of contact lens wear in exchange for the benefit of eliminating the need for eyeglasses. But what happens when contact lens wearers are faced with ophthalmic disorders such as glaucoma, allergy or dry eye? These conditions are typically treated with topical medications, often accompanied by an admonition to discontinue contact lens use, at least when applying drops, and often for many minutes afterward. This situation is a recipe for compliance failure, lens-use dropouts or any of the sequelae common to lens or medication misuse. As a possible solution to these problems, lens manufacturers and ophthalmic researchers have been experimenting with combining therapeutic agents with lenses. This month we'll take a look at how these efforts are progressing.

Initial Roadblocks

Most therapies for treating anterior-segment and ocular-surface diseases have traditionally involved the use of drops to deliver the drug. Topical drug delivery has significant advantages over other methods: It minimizes systemic exposure and systemic side effects; delivers drug precisely to the tissue of need; and reduces the potential for drug interactions. Despite these advantages, though, regulators have been reluctant to allow for concomitant contact lens use and topical delivery of drugs. One factor in these decisions is the perceived effects of preservatives such as benzalkonium chloride on the ocular surface, and the risk that if BAK-containing solutions are sequestered between the lens and the eye they might cause greater damage to cornea and conjunctiva. In addition, Phase II and Phase III studies of most topical agents are conducted on patients where contact lens use is typically excluded, leading to similar exclusions on package inserts. The approval process for lenses is separate, as they are classified as devices by the Food and Drug Administration, and concurrent use of topical medications is similarly excluded from this regulatory pathway.

Using a philosophy of, "If you can't beat them, join them," a number of studies have explored combining contact lenses with medications more commonly found in topical formulations as an alternative means of delivering drugs to the eye. The goal is to minimize the complications of lens use for these patients, while at the same time affording them a one-step method of addressing both medication needs and refraction correction. Providing therapeutic options to these patients is no small feat: There are an estimated 35 million contact lens users in the United States, and at least 125 million worldwide.[1] In order to provide this unique type of therapy, it's necessary to demonstrate that the drug-lens combinations are as safe and as effective as the drug alone. In addition, it must be established that the presence of the drug doesn't alter the vision-correction properties of the lenses. If these issues can be addressed successfully, then the drug-lens combination represents a real step forward for patients who use contacts for vision correction.

Drug-loading Strategies

Several different approaches have

This article has no commercial sponsorship.

been investigated for combining drugs and soft contact lenses.[2,3] These range from complex strategies such as the use of colloidal nanoparticles or molecular imprinting methods, to more straightforward methods such as including a drug in lens storage solutions. Each of these methods provides distinct advantages, so each may ideally be applicable for specific indications.

Colloidal nanoparticles are sub-micron-sized particles either coated with or encapsulating a drug's molecules. Two common forms are composed of either lipid spheres (liposomes) or colloidal gold or silver;[4-6] these are then dispersed into the contact lens matrix. Once the lenses are placed on the eye, the drug diffuses out of the contact lens matrix and away from the nanoparticle to enter the tear film. This packaging of drug in the colloidal particulate creates a two-step process that slows the diffusion of drug out of the lens and allows for a more sustained delivery of the drug to the corneal surface.

The idea of providing a nanoparticle vehicle for a drug within the matrix of the contact lens has been simplified in a methodology termed molecular imprinting.[7-9] This process involves modification of the contact lens material to create a template for the drug molecule within the hydrogel complex. Examples of this are lenses synthesized in the presence of varying concentrations of the non-steroidal anti-inflammatory, diclofenac. By modifying the ratio of a key hydrogel component to drug, the capacity of the lens for drug and the drug release kinetics from the contact lenses can be systematically varied.[10] Imprinted contact lenses allow for a significantly higher drug load than lenses loaded by simple diffusion in a drug solution, and so may be particularly useful in situations in which a higher dose of the drug is required for therapeutic efficacy.[8,9]

Examples of Drug-loaded Contact Lenses

Drug	Indication
econazole	antifungal[17]
cyclosporin A	dry eye[18]
dexamethasone	ocular inflammation[14]
latanoprost	glaucoma[16]
timolol	glaucoma[19]
ketotifen	allergic conjunctivitis[12,15]

One of the earliest and simplest methods of preparing drug-lens combinations is to simply equilibrate the lens in a physiological solution containing the drug. The hydrophilic matrix of soft contact lenses, which ranges from 30 to 80 percent water, can absorb the drug and then release it by simple diffusion when inserted into the eye. This process was demonstrated successfully in an early study using lenses loaded with pilocarpine as a treatment for acute closed-angle glaucoma;[11] after equilibration with 1% pilocarpine, a two-hour contact lens treatment reduced intraocular pressure by a mean of 46 percent, from 55.6 to 30 mm Hg. While the simplicity of this method of loading drug is expedient, it's limited by the rapid pharmacokinetics of diffusion, yielding a dose of, and exposure to, the therapeutic agent that is similar to topical application. A study comparing uptake and release of commonly used ocular pharmaceuticals in several soft contact formulations showed that the maximal lens uptake was drug-specific; for example, similar lenses could absorb 7 to 8 mg of cromolyn sodium but only 0.07 mg of dexamethasone sodium phosphate.[12] In addition, the rates of uptake and release were different with each drug. For most tested compounds, both uptake and release were rapid and complete in under an hour; the exception to this was the antihistamine ketotifen, which eluted more gradually over approximately five hours.

Loading strategies are likely to be influenced by the specific indications involved. While a drug-lens combination for glaucoma would benefit from the prolonged release provided by nanoparticles or imprinting, treatments for dry eye or allergy could benefit from diffusion-loaded lenses. Regardless of the loading strategy that's used, all drug-lens combinations face a common set of logistical hurdles before they reach the market.

Further Challenges

Despite what you might have read about the novelty of Google's lenses that measure blood pressure or glucose, efforts to bring multitasking to the contact lens realm have been around for decades, and are more nuanced than it might seem. In the case of the Google lenses, we know that the barrier function of the conjunctival vasculature can impact the exchange of solutes between tear film and general circulation, so hyperemia may alter measures of hyperglycemia. For combinations of lenses and therapeutics, there are still several hurdles to clear on the way to creating a viable drug-delivery device beyond just regulatory and safety issues. These include pharmacokinetic issues, lens material issues and drug stability concerns.

Ideally, when drug-loaded contact lenses are placed in the eye, the drug release should follow zero-order release kinetics, allowing a constant release of the drug to the corneal surface over a time frame of hours to days and, in select cases, weeks. This, however, is very difficult to achieve, and typically a more non-linear release of the drug from the lens is observed. There is an initial burst of the drug, leading to high levels of the drug in the eye, followed by a zero-order kinetics release. In addition to the undesirable high drug load initially, this non-linear release also leads to a quick

loss of the drug from the lens, shortening the duration of action and preventing sustained drug release to the eye. Loading nanoparticles and utilizing molecular imprinting have minimized the impact of the initial burst effect and increased the duration of drug release from the lens,[3,4] but this issue remains a major conundrum in the development of any drug-lens combination.

Another major concern is the potential loss of lens transparency, critical to visual function, in the course of the loading or storage process. This is a potential issue when surfactants are included in the formulation process of incorporating the drug in the lenses.[13] Opacity of the lens can be avoided by opting for drug-loaded nanoparticles, which can be preferentially loaded towards the periphery of the lens to minimize the impact on visual function. Loading contact lenses with drugs also can potentially diminish the oxygen permeability of the lens. This is of particular concern in long-term use, as it could lead to corneal edema and epithelial damage.[3]

In some cases, therapeutic benefit may be limited by the drug capacity of the lens, and this will be a function of the equilibrium solubility of the drug. This is of particular concern when working with hydrophobic drugs, as the hydrophilic matrix of soft contact lenses is not a receptive environment for hydrophobic drug molecules.[14] Attempts have been made to address this issue by encapsulating the hydrophobic molecules in either liposomes or nanoparticles. The use of molecular imprinting may also improve the delivery of hydrophobic drugs, but in such cases release of the drug is likely to be slowed, yielding a longer duration of exposure but a lower peak drug concentration in the tear film.

The Future of Combinations

The growing number of drug-lens combinations in clinical and pre-clinical development suggests that we are on the verge of a real breakthrough. For example, in pre-clinical studies with latanoprost-loaded lenses, encapsulation of the drug in a biodegradable film provides therapeutic levels of drug in the aqueous humor for at least a month.[15] This type of lens could be beneficial even for patients who don't require vision correction, because of the issues of compliance associated with the use of IOP-lowering agents.

Extended-wear contacts pre-loaded with slow-release drug formulations have the potential to improve compliance for patients with conditions like open-angle glaucoma, allergy or dry eye.

Several drug-lens combinations have reached the clinic, including a ketotifen-lens combination (Vistakon/Johnson&Johnson) for patients with allergic conjunctivitis (see, for example, NCT 00432757), and a combination product for lens wearers with dry eye containing the plant polysaccharide lubricant alginic acid (NCT 01918410). These combination products have the potential to provide allergy or dry-eye patients with a valuable option for vision correction, and would address two major causes of contact lens dropouts.

Other examples of drug-lens combinations in development are listed in the table on p. 57. Each provides a distinct advantage over current therapy, and allows for combining drug treatment with vision correction if needed. Simplifying treatments, especially when it means reducing the number of steps our patients must execute to receive appropriate therapy, is almost always a good thing. While the process of combining contact lenses with drugs has taken more time than we could have imagined, the end results—better compliance, better therapeutic outcomes and better vision—will be worth the effort. REVIEW

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

1. http://www.aao.org/newsroom/upload/Eye-Health-Statistics-April-2011.pdf Accessed 12/30/2014
2. Guzman-Aranguez A, Colligris B, Pintor J. Contact lenses: Promising devices for ocular drug delivery. J Ocul Pharm Ther 2013;29:2:189-99.
3. Gulsen D, Chauhan A. Ophthalmic drug delivery through contact lenses. Invest Ophthalmol Vis Sci 2004;45:7:2342-7.
4. Sung AY, Kim TH. Ophthalmic application of poly (HEMA)s containing nanoparticles and dimethylacrylamide. J. Nanosci. Nanotechnol 2012;12:7:5210-5.
5. Gulsen D, Li C-C, Chauhan A. Dispersion of DMPC Liposomes in Contact Lenses for Ophthalmic Drug Delivery. Curr Eye Res 2005;30:12:1071-80.
6. Garhwal R, Shady SF, Ellis EJ, et al. Sustained ocular delivery of ciprofloxacin using nanospheres and conventional contact lens materials. Invest Ophthalmol Vis Sci 2012;53:3:1341-52.
7. White CJ, Byrne ME. Molecularly imprinted therapeutic contact lenses. Expert Opin Drug Delivery 2010; 7:6:765-80.
8. Alvarez-Lorenzo C, Yañez F, Barreiro-Iglesias R, Concheiro A. Imprinted soft contact lenses as norfloxacin delivery systems. J Controlled Release 2006;113:3:236-44.
9. Hiratani H, Alvarez-Lorenzo C. Timolol uptake and release by imprinted soft contact lenses made of N, N-diethylacrylamide and methacrylic acid. J of Controlled Release 2002; 83:2:223-30.
10. Tieppo A, Pate KM, Byrne ME. In vitro controlled release of an anti-inflammatory from daily disposable therapeutic contact lenses under physiological ocular tear flow. Eur J Pharm Biopharm 2012;81:1:170-7.
11. Hillman JS. Management of acute glaucoma with pilocarpine-soaked hydrophilic lens. Brit J Ophthalmol 1974;58:7:674-9.
12. Karlgard CC, Wong NS, Jones LW, Moresoli C. In vitro uptake and release studies of ocular pharmaceutical agents by silicon-containing and p-HEMA hydrogel contact lens materials. International Journal of Pharmaceutics 257:2003:141–151.
13. Kapoor Y, Thomas JC, Tan G, John VT, Chauhan A. Surfactant-laden soft contact lenses for extended delivery of ophthalmic drugs. Biomaterials 2009; 30:5:867-78.
14. Kim J, Peng CC, Chauhan A. Extended release of dexamethasone from silicone-hydrogel contact lenses containing vitamin E. J of Controlled Release 2010;148:1:110-6.
15. Soluri A, Hui A, Jones L. Delivery of ketotifen fumarate by commercial contact lens materials. Optom Vis Sci 2012;89:8:1140-9.
16. Ciolino JB, Stefanescu CF, Ross AE, Salvador-Culla B, Cortez P, Ford EM, et al. In vivo performance of a drug-eluting contact lens to treat glaucoma for a month. Biomaterials 2014;35:1:432-9.
17. Ciolino JB, Hudson SP, Mobbs AN, et al. A prototype antifungal contact lens. Investigative ophthalmology & visual science 2011; 52:9:6286-91.
18. Peng CC, Chauhan A. Extended cyclosporine delivery by silicone-hydrogel contact lenses. Journal of Controlled Release. 2011;154:3:267-74.
19. Jung HJ, Abou-Jaoude M, Carbia BE, Plummer C, Chauhan A. Glaucoma therapy by extended release of timolol from nanoparticle loaded silicone-hydrogel contact lenses. Journal of Controlled Release 2013;165 :1:82-9.

Happily. Cinderella is in stable condition.

Reliance equipment is built to rhumba for decades. Our chairs and stands deliver a rare combination of artistry, ergonomics, and brutish durability for decades of use. Ready for a new dance partner? Call 800.787.5426, or visit haag-streit-usa.com.

800.787.5426
haag-streit-usa.com

RELIANCE INTERNATIONAL

How to Treat Persistent Fetal Vasculature

Successful treatment requires meticulous follow-up by pediatric ophthalmologists, and retina and contact lens specialists.

Nicholas C. Farber, MD, and Eric M. Shrier, DO, Brooklyn, N.Y.

Persistent fetal vasculature, previously known as persistent hyperplastic primary vitreous, is a spectrum of disease and can present with no clinical effects or with severe morbidity. This condition arises from failure of the hyaloid vasculature to undergo normal programmed involution.

During development, this fetal vasculature nourishes the developing lens and vitreous.[1] Any abnormalities along the involutional pathway produce the various manifestations of PFV. These are typically categorized as anterior, posterior or combined. Within the differential diagnosis of congenital leukocoria, PFV must be distinguished from retinoblastoma and retinopathy of prematurity, along with other potentially serious conditions. The posterior subtype has historically had very poor surgical outcomes and visual results.

PFV typically presents as a unilateral, idiopathic congenital malformation. Morton F. Goldberg, MD, in the 1997 Edward Jackson Memorial Lecture, introduced the term "persistent fetal vasculature" to replace "persistent hyperplastic primary vitreous," which he felt was a misnomer because of its failure to include all of the fetal intraocular vasculature, rather than just the post-lental vessels. PFV indicates that at least partial, and possibly total, persistence of this intraocular vasculature remains after birth.[2] Since the introduction of this broader and more inclusive definition, clinicians have been better able to stratify the disease entity and manage its various manifestations.

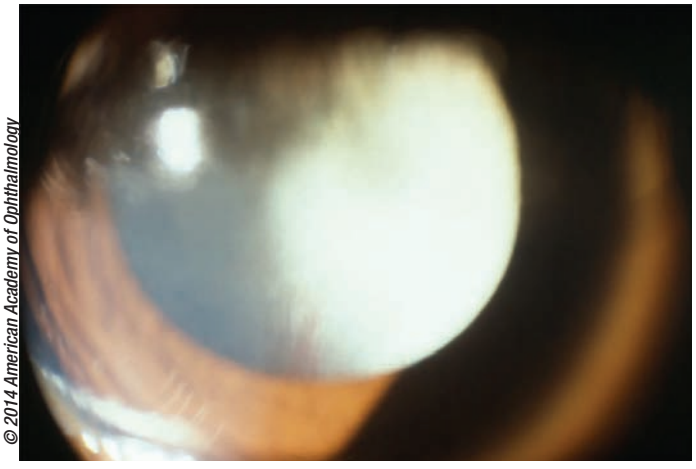


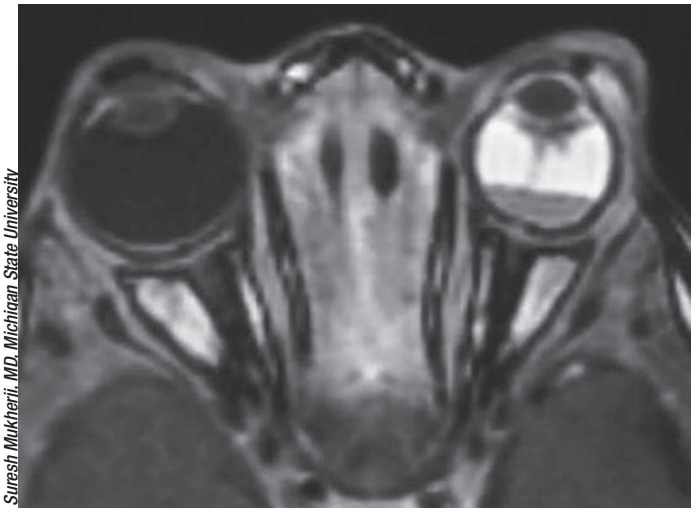
Figure 1. Persistent fetal vasculature presenting as leukocoria with a retrolental fibrovascular sheath.

Embryogenesis

The hyaloid vascular system begins to form in the fourth to fifth week of gestation when the hyaloid artery enters the optic cup inferiorly from the primitive dorsal ophthalmic artery, a branch of the internal carotid. It proceeds anteriorly and extends to the posterior pole of the lens. The vasa hyaloidea propria branches from the hyaloid artery into the vitreous cavity; in correlation, the tunica vasculosa lentis, a capillary network also branching from the hyaloid artery, covers the lens surface by the time the fetus is 8 to 9 mm in length.[3] The posterior aspect of this latter network connects to the choroidal vasculature through the

This article has no commercial sponsorship.

annular vessel at the anterior border of the fetal optic cup, forming the iridohyaloid vessels. These vessels extend radially alongside the equator of the lens.[2] The pupillary membrane is made up of anterior progression of the tunica vasculosa lentis. Along with fibrils and mesenchymal cells, this vasculature forms the primitive vitreous by two to three months gestation (40 to 60 mm in length). Of note, the hyaloid vasculature contains no veins. All drainage occurs through the choroidal vessels.



Suresh Mukherji, MD, Michigan State University

MRI of PFV manifestations including persistence of the hyaloid artery in Cloquet's canal, fibrovascular proliferation posterior to the lens and vitreous hemorrhage.

At this stage, the retinal vasculature development begins and coincides with the regression of the hyaloid. The secondary vitreous begins to form between the retina and posterior-most aspect of the primary vitreous. As the hyaloid system regresses, the avascular secondary vitreous expands towards the lens, pushing the vasa hyaloidea propria centrally towards the hyaloid artery. Tertiary vitreous formation encompasses formation of the zonules and regression of the iridohyaloid vessels. The fetal vascular regression is hypothesized to occur as a combination of apoptosis and macrophage activation, beginning with the smallest vessels and progressing to the largest. The final stage is occlusion of the hyaloid artery by the third trimester.[2,4] The mechanisms of persistence for these fetal characteristics are still unknown, but thought to be a combination of dysregulation of apoptosis through improper gene expression with irregular levels of VEGF, angiopoietin-2 and bFGF among others, as well as possible abnormal timing for normal expression of these genes and growth factors.[2,4] The nomenclature change from PHPV to PFV reflects the inclusion of pathology throughout this system: the vasculature, iris, lens, vitreous, retina, macula and optic nerve.[2]

Clinical Findings

Persistence of any of the fetal vasculature elements can be an isolated phenomenon, or can be found in combination; however, dividing the pathology into anterior, posterior or combined subtypes affords the clinician and patient therapeutic and diagnostic dichotomies. Dr. Adrian Hunt and colleagues defined the anterior subtype as the presence of a retrolental opacity, elongated ciliary processes or cataract. Posterior PFV included findings of an elevated vitreous membrane from the optic nerve, retinal fold or dysplasia, retinal detachment or optic nerve hypoplasia.[7]

Persistent fetal vasculature can also be seen in conjunction with other ocular abnormalities, including morning glory disc anomaly, Peter's anomaly, macular hypoplasia, microcornea and microphthalmos.[2] PFV is usually unilateral, and one case series by Zane F. Pollard, MD, and colleagues described 84 percent of his PFV patients with unilateral microphthalmos and only 2 percent with bilateral disease. PFV associated with systemic syndromes often is bilateral, but in this case series, those patients with bilateral disease had no further systemic findings.[5] Notable syndromes associated with PFV include: Norrie's disease, which presents with retinal dysplasia, optic nerve hypoplasia, deafness and mental retardation; trisomy 13 (Patau syndrome) with clinical findings including cleft lip or palate, polydactyly and heart defects; and the Walker-Warburg syndrome, which can present with hydrocephalus, agyria, retinal dysplasia and congenital retinal nonattachment.[2]

Dr. Pollard also found that 3 percent of full-term children have some clinically detectable remnants of the hyaloid system.[5] Most commonly, a persistent pupillary membrane can sometimes be observed on clinical exam as threadlike remnants of the anterior tunica vasculosa lentis. Occasionally described as pigmented "stars" on the anterior lens surface, this entity can also be seen causing pupil deformity and congenital ectropian or entropion uveae. If these vascular remnants are still perfused, spontaneous hyphema may occur. The most severe form of persistent pupillary membrane causes complete obscuration of the pupil with subsequent reduced vision and potential amblyopia.[2] During development, regression of the iridohyaloid vessels allows for growth of the zonular ligaments. With persistence of the iridohyaloid vasculature, the clinician may see superficial vessels in the iris stroma with possible hairpin loops near the pupillary sphincter. If,

subsequently, the zonules do not develop properly, lens subluxation may occur, typically away from the persistent vessel.[2] Persistent iridohyaloid arteries have also been associated with absence of the fovea and consequently, poor vision.[2] These abnormally persistent vessels can also be identified using fluorescein angiography. Elongated ciliary processes secondary to traction of the fibrovascular membrane are a common finding in anterior PFV, and were once thought to be pathognomonic.

A shallow anterior chamber can also be found and can even progress to fulminant angle-closure glaucoma. The etiology includes peripheral anterior synechiae, posterior synechiae and anterior displacement of the lens-iris diaphragm, all secondary to fibrovascular tissue in ectopic locations. In contrast to the more commonly found microphthalmos, children with this complication may present with normal-sized eyes or buphthalmos secondary to the congenital glaucoma. These eyes often begin small and then enlarge.

Persistence of posterior lental fibrovascular tissue can have various appearances within the greater spectrum of PFV. The most commonly recognized, a Mittendorf dot, presents as a small, paracentral retrolental opacity, easily seen with retinoscopy or slit-lamp biomicroscopy. This opacity represents the anterior terminus of the hyaloid artery. When seen with peripheral spoke-like vessels, this finding is often called a "brittle-star" configuration. In the most dramatic form, the entire posterior lens surface may be covered with fibrous tissue as thick as 1 mm.[2] This variant must be distinguished from retinoblastoma, complete retinal detachment, retinopathy of prematurity and Coats' disease, as the management of each entity is unique. In PFV, the vessels are usually regular and may be seen to anastomose. Invasion of the lens with the fibrovascular tissue may cause a lenticular hemorrhage if perfusion persists. Cataract formation can also widely vary from non-existent to partial or complete. Partial cataracts may also progress at any point in life. Persistence of the hyaloid artery may be seen within Cloquet's canal, connecting the optic nerve to the posterior lens with variable remaining perfusion.

Leukocoria is a common presentation for PFV and can result from a complete pupillary membrane, cataract formation, fibrovascular sheath attachment to the posterior lens capsule or a cloudy cornea secondary to glaucoma *(See Figure 1)*. Children may also first present with strabismus or amblyopia.

A common posterior sign of PFV is the Bergmeister's papilla emanating from the optic nerve. In isolation, this finding does not typically present visually significant sequelae; however, congenital non-attachment of the retina (also called tent-shaped retinal detachment), which is a more severe form of posterior PFV, has severe visual consequences. Traction is caused by adhesion of the fetal vasculature to the retina, with or without the presence of subretinal fluid. The "brittle-star" sign may be seen at the peak of the tent-shaped detachment and the surrounding spoke-like vessels can be seen well on fluorescein angiography.

Retinal non-attachment is most common in the inferotemporal quadrant, and epiretinal fibrovascular tissue is often found surrounding the area. Macular traction, degeneration and membrane formation may also be found and are often associated with severe visual morbidity. The optic nerve may also be hypoplastic or dysplastic.[2,5] Amblyopia may be a presenting symptom in PFV due to a severe but previously undiscovered isolated posterior abnormality without an obvious anterior component.

Diagnosis

The most common means for diagnosis is direct visualization of the persistent vascular remnant. Ultrasonography can be extremely useful to aid diagnosis, especially in the presence of a poor view to the posterior segment. B-scan ultrasonography can assist in ruling out masses and retinal detachments. In addition, CT with contrast will enhance the persistent fibrovascular tissue. Calcifications on B-scan or CT scan should alert the clinician to the possibility of retinoblastoma, as this is a frequent finding that indicates malignancy and is not typically found in PFV. CT scans on children, however, should only be ordered when absolutely necessary due to the possibility of increased malignancy risk.[10] MRI is superior in distinguishing soft tissue structures and morphology and does not carry the risk associated with radiation from CT *(See Figure 1)*.[5] Fluorescein angiography is another ancillary test that can delineate abnormal vasculature. For example, iridohyaloid vessels appear as radially oriented iris vessels with a hairpin turn around the pupil. Vessels forming a "brittle-star" can also fluoresce.[2,5]

Prognosis and Treatment

A wide range of treatments and potential outcomes exists for PFV because of the wide spectrum of presentation. Anterior PFV is most often treated with observation, lensectomy and glaucoma management, whether medical or surgical. Posterior PFV is usually associated with a poor visual outcome regardless of intervention due to retinal and optic nerve abnormalities.[7,8] Bilateral

(continued on page 77)

BEST HOSPITALS
U.S.News & WORLD REPORT
HONOR ROLL
2014-15

WE'RE CHANGING THE WAY

PATIENTS WITH VISION IMPAIRMENT ENVISION THEIR FUTURE

The Louis J. Fox Center for Vision Restoration of UPMC and the University of Pittsburgh—a joint program of the UPMC Eye Center and the McGowan Institute for Regenerative Medicine—is the first national, comprehensive, and multidisciplinary research and clinical program dedicated to ocular regenerative medicine. Our ophthalmologists and researchers focus on the discovery of new treatments for blindness and impairment through tissue regeneration, enhancement, transplantation, and technology. We're working hard to improve the quality of life for the millions of people affected by vision loss, so that we can all see a brighter future. Learn more at **UPMCPhysicianResources.com/Vision.**

UPMC LIFE CHANGING MEDICINE

UPMC is affiliated with the University of Pittsburgh School of Medicine.


Taking Control: Lifestyle Choices and Glaucoma

Patients often ask what they can do to help combat their disease—besides medications and surgery. Here are some options.

James C. Tsai, MD, MBA, New York

Today, more and more patients want to know about the potential relationships between lifestyle choices and their health. Patients are interested in this topic primarily for two reasons: They want to feel that they have some control over their disease; and alternative treatments have become a more accepted part of the physician-patient conversation. So it feels natural for a patient to ask: Are there things I can do that may help minimize my risk of losing vision, beyond drugs and surgery? How can I live my life in a way that will have the greatest positive impact on this disease?

When patients ask about this, I tell them that there are quite a few lifestyle choices that may impact the development and/or modify the progression of glaucoma for better or worse. Below, I have listed a number of pro and con factors you might wish to share with your patients, when appropriate. (Of course, elevated IOP is the major known risk factor for glaucoma, so that's the easiest issue to address; a number of the lifestyle choices listed below interact with the progression of glaucoma either by potentially raising or lowering IOP.)

Exercise and Glaucoma

If you want to decrease your IOP, aerobic exercise may help (although it's important to make sure that any patient with cardiac issues has this activity approved by his cardiologist). Some of the relevant data:

- One study found that in nonsmoking, healthy volunteers, aerobic exercise increased heart rate and systolic blood pressure while decreasing IOP and diastolic blood pressure.[1]
- A study of active college-age students found that dynamic resistance exercises lowered IOP.[2]
- A study of 20 young adult subjects found that IOP (as well as ocular pulse amplitude and axial length) decreased significantly after exercise ($p<0.0001$)[3]
- A study of 67 healthy patients under the age of 40 compared the impact of isometric and isokinetic exercises on IOP. Both types of exercise lowered IOP in direct proportion to exercise intensity, but the pressure-lowering effect of isokinetic exercise was more significant.[4]

The data is mixed regarding weightlifting. Some studies suggest that weightlifting may trigger the equivalent of the Valsalva maneuver, thereby raising IOP. On the other hand, the lifestyle consequences of exercise are generally positive, and weightlifting certainly is a form of exercise. (It's worth noting one of the big problems with research into these possible associations: Most of these studies were done in young, healthy subjects, not in glaucoma patients.)

It is difficult to arrive at a clear conclusion regarding related considerations such as body mass index and its relation to glaucoma. For example, published data shows a positive relationship between BMI and IOP, but an inverse relationship between BMI and glaucoma.[5,6]

Of course, lifestyle choices, including exercise, can also play an important role in cardiac health, and there's considerable evidence that cardiac health influences the development of glaucoma.[7-12] Among other things, altered ocular blood flow may be a major factor in the pathogenesis of glaucomatous optic neuropathy.

This article has no commercial sponsorship.

Activities & Habits

• ***Cigarette smoking.*** I believe a majority of physicians agree that smoking has few, if any, health-related benefits, and may cause serious harm. In terms of glaucoma, one meta-analysis concluded that smokers are at a significantly increased risk of developing open-angle glaucoma[13] but another study published in 2003 found no increased risk of glaucoma in smokers.[14] On the other hand, cigarette smoking has been linked to macular degeneration and cataract, and in some studies it has been associated with modest IOP elevation.[15]

• ***Practicing yoga.*** I have encountered a number of patients with worsening glaucoma who, when questioned, explained that in an attempt to improve their overall health they had taken up practicing yoga. Unfortunately, these yoga enthusiasts are likely to assume various degrees of body inversion—i.e., head-down positions including Sirasana (headstand posture). Being in these yoga positions for more than a few minutes can cause profound elevations in IOP (as much as a two-fold increase).[16]

Most people don't realize that head-down positions (in yoga or with other activities) are generally bad for their glaucoma—and doctors seldom think to ask whether their patients are practicing these activities.

• ***Playing high-resistance wind instruments.*** In 2000, Joel S. Schuman, MD, and colleagues reported that musicians who play high-resistance wind instruments such as trumpet and oboe appear to be at increased risk of glaucomatous damage.[17] The study found that IOP rose in proportion to the force of blowing, and total life hours of playing high-resistance wind instruments was significantly related to abnormal visual fields (p=0.03) and corrected pattern standard deviation scores (p=0.007). In fact, the latter increased by 0.011 units for every 1,000 hours of playing. (The authors of the study note that the resulting damage could be misdiagnosed as normal-tension glaucoma.)

©iStock.com/JobsonHealthcare

Although yoga is often considered a means to improve one's mental or physical health, head-down positions may cause a significant increase in intraocular pressure—not ideal for a glaucoma patient.

• ***Wearing tight neckties.*** Even in today's increasingly casual workplace, many men still wear neckties. Wearing them too tight can lead to prolonged periods of elevated IOP.[18]

Dietary Choices

• ***Omega fats in the diet.*** While many general health studies suggest that omega-3 fatty acids may be better for us than omega-6 fatty acids, at least one study suggests that this may not be the case in relation to glaucoma. It found that a high ratio of omega-3 to omega-6 fatty acids in our diet may be associated with an increased risk of POAG, especially high-tension POAG.[19] (A theory to explain a possible mechanism for this result has also been proposed.[20])

• ***Alcohol consumption.*** Some evidence suggests that drinking a modest amount of alcohol may lower IOP a small degree (i.e., 1 mm).[21,22] However, I don't want to encourage alcohol consumption since the evidence is not clear cut. So if asked, I usually just tell patients that alcohol doesn't have much effect on IOP. A majority of patients often believe the opposite; they think that consuming alcohol excessively may increase their IOP, and if they stop drinking alcohol their eye pressures will suddenly become much lower. This does not appear to be the case.

• ***Caffeine consumption.*** I tell my patients that a little coffee is fine; however, loading up on caffeinated coffee is not ideal for their glaucoma. Data from the Blue Mountains Eye Study showed that subjects with open-angle glaucoma who reported regular coffee drinking had significantly higher mean IOP than subjects who said they didn't drink coffee (p=0.03). However, the association between coffee consumption and elevated IOP was not found in those with ocular hypertension or no open-angle glaucoma at all.[23] In addition, Louis R. Pasquale, MD, and colleagues observed a positive association between heavier coffee consumption and increased risk of exfoliation glaucoma or becoming an exfoliation glaucoma suspect.[24] Given this data, I tell my glaucoma patients that it's probably not a good idea to routinely order a large double espresso.

• ***Magnesium.*** Several published papers have suggested that an adequate intake of dietary magnesium may be beneficial for patients with glaucoma; it appears that a deficiency interferes with a number of ocular processes.[9,25,26] However, the Rotterdam Study, using data from 3,502 participants, suggested that a high intake of magnesium may be associated with an increased risk of open-angle glaucoma.[27]

• ***Ginkgo biloba.*** The use of ginkgo biloba is very controversial. When I visited South Korea recently, I was told by a glaucoma specialist that up to three-quarters of patients with normal-pressure glaucoma may be prescribed this supplement in addition to their IOP-lowering medications. (That's anecdotal; I'm not aware of any reported data backing up that claim.) Nevertheless, studies have indeed found potential neuroprotection benefits from ginkgo;[28] possible effects on blood flow;[29] and short-term visual field improvements in patients with normal-tension glaucoma.[30]

In terms of other dietary factors, it's quite difficult to separate truth from fiction. Some papers have suggested that consumables that reduce oxidative stress may be protective. These may include dark chocolate, ubiquinone, melatonin, bilberries (because of their anthocyanosides) and tea, coffee and red wine (because of their polyphenolic flavonoids).[9,31] Antioxidants as a group have not shown a definitive risk impact on open-angle glaucoma.[32]

Other Health-related Issues

• ***Antihypertensive drugs at bedtime.*** Many elderly patients take antihypertensive drugs, but lowering blood pressure excessively at night can lead to a hypotensive crisis; blood pressure can dip too low to support ocular perfusion. If your glaucoma patient is taking this type of drug, he should talk to his internist to make sure he's not becoming too hypotensive at night.

• ***Sleep apnea.*** Studies have shown that moderate to severe obstructive sleep apnea is linked to increased risk of glaucoma development and progression.[33] If a patient is aware of snoring a lot at night and/or complains of being tired all the time, it's worth suggesting that the patient talk to his or her internist about this possibility.

A potential downside here is that one of the ways of addressing sleep apnea is to have the patient use a continuous positive airway pressure machine at night. While it is often an effective non-surgical treatment for sleep apnea, CPAP therapy was recently shown to increase IOP, especially at night,[34] so it's important to consider whether the benefits of CPAP therapy will be worth its potential downside.

One of the worst parts of having glaucoma is feeling that you're relatively powerless against it.

• ***Migraines.*** If one of your patients complains of migraine headaches, make sure the patient is discussing this issue with an internist/neurologist. Migraines can increase the risk of progression in patients who have normal-tension glaucoma.[35]

• ***Marijuana.*** While smoking marijuana has been demonstrated to lower IOP in both normal individuals and in those with glaucoma, its short duration of action (only three to four hours) and its deleterious mood-altering effects are less-widely appreciated, as noted in the American Glaucoma Society's position statement on this topic.[36] There is also the real possibility that marijuana's systemic effect of lowering blood pressure might prove deleterious to the optic nerve in glaucoma by compromising blood flow. Thus, the AGS position statement concludes, "Although marijuana can lower the intraocular pressure, its side effects and short duration of action, coupled with a lack of evidence that its use alters the course of glaucoma, preclude recommending this drug in any form for the treatment of glaucoma at the present time." (The position statement can also be viewed on the AGS website at http://www.americanglaucomasociety.net/professionals/policy_statements/marijuana_glaucoma.)

Empowering Your Patients

Given this information, when patients ask what they can do on their own to minimize their chances of losing vision from glaucoma, I advise them to: Do some aerobic exercise; limit cigarette smoking; try to eat a diet high in antioxidants and low in fat; avoid excessive caffeine; avoid head-down positions, especially if doing yoga; and consider taking a magnesium supplement (if they're not already taking one). I also ask whether they wear a necktie; play a wind instrument; take antihypertensive medications; have any symptoms that might indicate sleep apnea; or have a problem with migraines.

One of the worst parts of having a disease like glaucoma is feeling that you're relatively powerless against it. Giving our patients some knowledge about lifestyle factors like the ones outlined above can help empower them—and that can improve their quality of life immediately. REVIEW

Dr. Tsai is the Delafield-Rodgers Professor and chair of the Department of Ophthalmology at the Icahn School of Medicine at Mount Sinai. He also serves as president of the New York Eye and Ear Infirmary of Mount Sinai.

1. Schmidt KG, Mittag TW, Pavlovic S, Hessemer V. Influence of physical exercise and nifedipine on ocular pulse amplitude. Graefes Arch Clin Exp Ophthalmol 1996;234:8:527-32.
2. Chromiak JA, Abadie BR, Braswell RA, Koh YS, Chilek DR. Resistance training exercises acutely reduce intraocular pressure in physically active men and women. J Strength Cond Res 2003;17:4:715-20.
3. Read SA, Collins MJ. The short-term influence of exercise on axial length and intraocular pressure. Eye (Lond) 2011;25:6:767-74. doi: 10.1038/eye.2011.54.

4. Avunduk AM, Yilmaz B, Sahin N, Kapicioglu Z, Dayanir V. The comparison of intraocular pressure reductions after isometric and isokinetic exercises in normal individuals. Ophthalmologica 1999;213:5:290-4.
5. Mori K, Ando F, Nomura H, Sato Y, Shimokata H. Relationship between intraocular pressure and obesity in Japan. Int J Epid 2000;29:4:661-66.
6. Gasser P, Stümpfig D, Schötzau A, Ackermann-Liebrich U, Flammer J. Body mass index in glaucoma. J Glaucoma 1999;8:1:8-11.
7. Grieshaber MC, Flammer J. Blood flow in glaucoma. Curr Opin Ophthalmol 2005;16:79-83.
8. Feke GT, Pasquale LR. Retinal blood flow response to posture change in glaucoma patients compared with healthy subjects. Ophthalmology 2008;115:246-52.
9. Mozaffarieh M, Flammer J. A novel perspective on natural therapeutic approaches in glaucoma therapy. Expert Opin Emerg Drugs 2007;12:2:195–198. doi: 10.1517/14728214.12.2.195.
10. Liu Q, Ju WK, et al. Oxidative stress is an early event in hydrostatic pressure induced retinal ganglion cell damage. Invest Ophthalmol Vis Sci 2007;48:4580-89.
11. Leske MC, Wu SY, Hennis A, Honkanen R, Nemesure B, BESs Study Group. Risk factors for incident open-angle glaucoma: the Barbados Eye Studies. Ophthalmology 2008;115:1:85-93.
12. Leske MC, Heijl A, et al. Predictors of long-term progression in the early manifest glaucoma trial. Ophth 2007;114:1965-72.
13. Bonovas S, Filioussi K, et al. Epidemiological association between cigarette smoking and primary open-angle glaucoma. Arch Ophthalmol 2003;121:1762-68.
14. Kang JH, Pasquale LR, Rosner BA, Willett WC, Egan KM, Faberowski N, Hankinson SE. Prospective study of cigarette smoking and the risk of primary open-angle glaucoma. Arch Ophthalmol 2003;121:12:1762-8.
15. Pasquale LR, Kang JH. Lifestyle, nutrition, and glaucoma. J Glaucoma 2009;18:6:423-8.
16. Baskaran M, Raman K, Ramani KK, Roy J, Vijaya L, Badrinath SS. Intraocular pressure changes and ocular biometry during Sirsasana (headstand posture) in yoga practitioners. Ophthalmology 2006;113:8:1327-32. Epub 2006 Jun 27.
17. Schuman JS, Massicotte EC, Connolly S, Hertzmark E, Mukherji B, Kunen MZ. Increased intraocular pressure and visual field defects in high resistance wind instrument players. Ophthalmology 2000;107:1:127-33.
18. Teng C, Gurses-Ozden R, Liebmann JM, Tello C, Ritch R. Effect of a tight necktie on intraocular pressure. Br J Ophthalmol 2003;87:8:946-8.
19. Kang JH, Pasquale LR, Willett WC, Rosner BA, Egan KM, Faberowski N, Hankinson SE. Dietary fat consumption and primary open-angle glaucoma. Am J Clin Nutr 2004;79:5:755-64.
20. Desmettre T, Rouland JF. Hypothesis on the role of nutritional factors in ocular hypertension and glaucoma. [Article in French] J Fr Ophthalmol 2005;28:3:312-6.
21. Peczon JD, Grant WM. Sedatives, stimulants, and intraocular pressure in glaucoma. Arch Ophthalmol 1964;72:178-88.
22. Kang JH, Willett WC, Rosner BA, Hankinson SE, Pasquale LR. Prospective study of alcohol consumption and the risk of primary open-angle glaucoma. Ophthalmic Epidemiol 2007;14:3:141-7.
23. Chandrasekaran S, Rochtchina E, Mitchell P. Effects of caffeine on intraocular pressure: the Blue Mountains Eye Study. J Glaucoma 2005;14:6:504-7.
24. Pasquale LR, Wiggs JL, Willett WC, Kang JH. The relationship between caffeine and coffee consumption and exfoliation glaucoma or glaucoma suspect: A prospective study in two cohorts. Invest Ophthalmol Vis Sci 2012;53:6427-33.
25. Aydin B, Onol M, Hondur A, Kaya MG, Ozdemir H, Cengel A, Hasanreisoglu B. The effect of oral magnesium therapy on visual field and ocular blood flow in normotensive glaucoma. Eur J Ophthalmol 2010;20:1:131-5.
26. Gaspar AZ, Gasser P, Flammer J. The influence of magnesium on visual field and peripheral vasospasm in glaucoma. Ophthalmologica 1995;209:1:11-3.
27. Ramdas WD, Wolfs RC, Kiefte-de Jong JC, Hofman A, de Jong PT, Vingerling JR, Jansonius NM. Nutrient intake and risk of open-angle glaucoma: The Rotterdam Study. Eur J Epidemiol 2012;27:5:385-93. doi: 10.1007/s10654-012-9672-z.
28. Ahlemeyer B, Krieglstein J. Neuroprotective effects of Ginkgo biloba extract. Cell Mol Life Sci 2003;60:9:1779-92.
29. Wimpissinger B, Berisha F, Garhoefer G, Polak K, Schmetterer L. Influence of Ginkgo biloba on ocular blood flow. Acta Ophthalmol Scand 2007;85:4:445-9.
30. Quaranta L, Bettelli S, Uva MG, Semeraro F, Turano R, Gandolfo E. Effect of Ginkgo biloba extract on preexisting visual field damage in normal tension glaucoma. Ophthalmology 2003;110:2:359-62.
31. Mozaffarieh M, Fraenkl S, Konieczka K, Flammer J. Targeted preventive measures and advanced approaches in personalised treatment of glaucoma neuropathy. EPMA J 2010;1:2:229-35. doi: 10.1007/s13167-010-0018-1.
32. Kang JH, Pasquale LR, Willett W, Rosner B, Egan KM, Faberowski N, Hankinson SE. Antioxidant intake and primary open-angle glaucoma: A prospective study. Am J Epidemiol 2003;158:4:337-46.
33. Hashim SP, Al Mansouri FA, Farouk M, Al Hashemi AA, Singh R. Prevalence of glaucoma in patients with moderate to severe obstructive sleep apnea: ocular morbidity and outcomes in a 3 year follow-up study. Eye (Lond) 2014;28:11:1304-9. doi: 10.1038/eye.2014.195.
34. Kiekens S, De Groot V, Coeckelbergh T, et al. Continuous positive airway pressure therapy is associated with an increase in intraocular pressure in obstructive sleep apnea. Invest Ophthalmol Vis Sci 2008;49:934-40.
35. Drance S, Anderson DR, Schulzer M. Collaborative Normal-Tension Glaucoma Study Group. Risk factors for progression of visual field abnormalities in normal-tension glaucoma. Am J Ophthalmol 2001;131:699-708.
36. Jampel H. American glaucoma society position statement: Marijuana and the treatment of glaucoma. J Glaucoma 2010;19:75-6.

Sharpen Your LASIK Technique

Taking time to examine the patient carefully beforehand can help you respond to problems properly later on.

Arun C. Gulani, MD, MS, Jacksonville, Fla.

There's an old saying: "It's not how you start, it's how you finish." However, as far as LASIK is concerned, where you start has a great effect on where you finish. Taking time to plan the case, select proper patients, calculate tissue removal and identify potential pitfalls before they happen helps the surgery go smoothly. This is because, in a way, if you've taken the proper steps, then you've already planned for a good postop outcome. Here are my tips for smoother LASIK, after 20 years and thousands of cases.

Having used practically every laser technology in the world, I keep reiterating to visiting surgeons that technology is, of course, important, but it's the technique and proper refraction—a refractive surgeon must know how to refract—that determine consistently successful outcomes. I believe that by knowing your technology, honing your technique and envisioning success ahead of time, you can get closer to mastering refractive surgery.

Evaluating the Patient

Aside from the usual consideration of the patient's refractive error, there are a couple of other issues to address beforehand.

• ***Corneal surface status.*** For any LASIK surgeon, but especially the neophyte, preparing the surface ahead of time is very important. The ideal initial patient has no dry eye, anterior basement membrane disease, corneal scarring or previous corneal refractive surgery such as radial keratotomy.

With experience, though, you'll learn to correct some ocular surface problems. You can improve the patient's tear film through the use of cyclosporine A or lacrimal plugs. For patients with meibomian gland dysfunction, probing the gland orifices to clear them, or using a new treatment concept such as LipiFlow, can be useful for rehabilitating the cornea and ocular surface before surgery.

When you undertake the rehabilitation of the cornea, take your time. Monitor the patient for three to four weeks to look for signs of improvement that indicate that the patient can become a candidate. If the patient's condition stabilizes, you can do the LASIK at four to six weeks after initiating therapy. Of course, some cases may have associated systemic issues such as rheumatoid arthritis or Sjögren's syndrome. If this is the case, then the time needed to restore the surface may be longer, and you might wait a bit longer before doing surgery.

• ***Anticipate docking difficulties.*** The crucial step when using the femtosecond laser is docking. Catching red flags in the anatomy ahead of time can make this important step easier.

A small orbital fissure can pose problems when trying to dock the laser. The other important but usually overlooked aspect of anatomy is the conjunctiva. If the patient shows signs of excessive conjunctival tissue—conjunctivochalasis—you should anticipate problems with suction during laser docking. Conjunctivochalasis is particularly prevalent in older patients.

Performing the Procedure

There are certain steps you can take, and problem signs to watch for, as you proceed with the LASIK.

• ***Docking the femtosecond.*** For a patient with a small orbital aperture, it can be difficult to achieve a solid dock without some manipulation. In such a case, have the patient direct

This article has no commercial sponsorship.

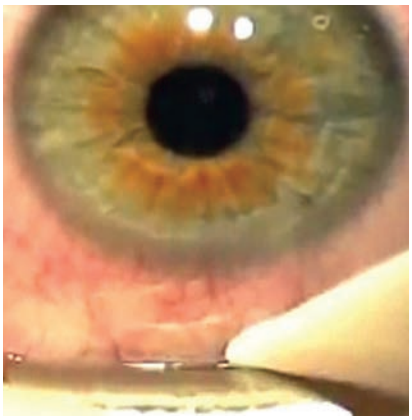
his eye toward the opposite side of his face. This can often give you the extra space you need to dock properly.

Earlier I discussed patients with conjunctivochalasis, which can make it difficult to achieve and maintain suction. In these cases, if your preop evaluation has prepared you, you can be ready to squeegee the conjunctiva down as you affix the suction ring. If you see a hemorrhage from the patient with conjunctivochalasis during docking, you can always re-dock after squeegeeing it out. In some extreme cases, I've performed amniotic membrane surgery to correct conjunctivochalasis in order to be able to perform laser vision surgery in the future.

One exercise that helped me was getting a feel for my equipment without a patient being there. Practice the docking maneuvers and note areas where you may have to troubleshoot. For example, in some cases of difficult docking, it's not the patient's anatomy that's at fault. Instead, a defective docking cone can cause an issue. However, if you're not familiar with your equipment, you might not catch this.

It also helps to narrate the care, performing what's known as vocal anesthesia. Make sure the patient is comfortable. Tell him to keep looking straight and not to move, and that he will feel some pressure. Then, approach the eye slowly. Don't surprise the patient with sudden jerky movements. Tell him he'll feel the suction, and make sure each step is nice and smooth. If you get the initial steps right, proper docking will almost happen as a matter of course.

• ***Making the flap cut.*** Once you've achieved a good dock and are proceeding with the femtosecond flap cut, monitor the eye to make sure everything is going smoothly. Make sure there are no cavitation bubbles blocking the beam or a break in suction occurring. Be vigilant that you're accomplishing the cut as planned. And, in instances where something appears to be going wrong, don't hesitate to abort the case. It's better to stop and have the option to continue later than hope that a disaster won't occur.



Squeegeeing with a Weck-Cel sponge can be helpful in cases of excess conjunctiva.

If you do have to abort the cut, you can often recut right there on the table, as long as a few conditions exist. If you haven't yet begun to cut, or the cornea is only minimally cut, stop. Then, squeegee the conjunctiva, relocate the flap hinge, set the laser for about 50 µm deeper and, if the corneal thickness is acceptable, proceed.

• ***Working with the flap.*** Before you try to lift the flap, first make sure that you've achieved a full cut. Don't just assume that you have a full cut and try to rip it open, which can lead to a tear. To make sure the cut is complete, I use an instrument I developed with Bausch + Lomb/ Storz that delineates the edge. Using the instrument, I go around the entire circumference of the flap to make sure it's a complete cut. I then go in close to the hinge and come out toward the outer edge of the flap in one smooth motion. Satisfied that it's separated from the bed, I can then lift the flap. My goal is as little manipulation as possible. The less manipulation, the better the patient outcome and flap alignment. More manipulation means more wrinkles, improper alignment, a longer surgical time and, ultimately, a poor result.

• ***After the ablation.*** When the ablation is done and the flap is back down, make sure it fits properly in the gutter and is equidistant from the sides in all areas. Also, use the high magnification level of your microscope to make sure there are no wrinkles. Again, try to do this quickly, with one sweep of your instrument, so you don't have to manipulate it too much.

I see the patient 20 minutes postop, then the next day and then at a week. The postop regimen consists of Prolensa and Zymaxid for two weeks and a corticosteroid, usually Durezol, tapered over three weeks.

A Note on Enhancements

Even though I like all the forms of LASIK, I'm a strong proponent for advanced surface ablation enhancements on previous LASIK corneas.

If it's a myopic ablation, PRK with 20 seconds of mitomycin-C works even better than a repeat LASIK because it actually ends up smoothing the LASIK flap. This is because in all LASIK flaps, if you remove the epithelium, you will notice some microstriae. That's just the nature of the LASIK flap. However, if you do a surface procedure for a myopic enhancement over the flap, it actually helps eliminate these microstriae, benefiting the quality of vision and even improving the optical zone.

If where you start truly has an impact on where you finish, then I hope that knowing your patient's preop refractive parameters, planning the procedure well, and staying abreast of how to troubleshoot your devices all allow you to finish strong with each of your LASIK surgeries. In the end, you won't have to hope for success because you've already planned for it. REVIEW

Suggested reading:
1. Gulani AC. Corneoplastique: Art of Vision Surgery. Ind J Ophthalmol 2014;62:3-11.
2. Gulani AC. Shaping the future and reshaping the past: The art of vision surgery. Chapter 98. In: Copeland RA, Afshari N, eds. Copeland and Afshari's Principles and Practice of Cornea. New Delhi, India: Jaypee Brothers Medical Publishers, 2013;2:1252-1273.

Prevalence and Risk Of DME in the USA

Results of a cross-sectional analysis of 1,038 participants in the 2005 to 2008 National Health and Nutrition Examination survey suggest that there is a greater burden of diabetic macular edema among non-Hispanic blacks, individuals with high levels of hemoglobin $A1_C$ and those with longer duration of diabetes.

Patients selected for this analysis were over 40 years of age, diagnosed with diabetes and had valid fundus photographs. Of the 1,038 participants, 55 had DME for an overall weighted prevalence of 3.8 percent (95 percent confidence interval, 2.7 percent to 4.9 percent) or approximately 746,000 persons in the United States population aged 40 years or older. Researchers identified no differences in the prevalence of DME by age or sex. Multivariable logistical regression analysis showed that the odds of having DME were higher for non-Hispanic blacks than for non-Hispanic whites (odds ratio, 2.64; 95 percent CI, 1.19 to 5.84; p=0.02). Elevated levels of glycosylated hemoglobin A1c (OR, 1.47; 95 percent CI, 1.26 to 1.71 for each one percent; p<0.001) and longer duration of diabetes (OR, 8.51; 95 percent CI, 3.7 to 19.54 for ≥10 vs. <10 years; p<0.001) were also associated with DME prevalence.

JAMA Ophthalmol 2014;132:1334-1340.
Varma R, Bressler N, Doan W, Gleeson M, et al.

Poor Bevacizumab Response Possible Sleep Apnea Indicator

A case-controlled prospective study from the University of Louisville in Kentucky indicates that patients with exudative age-related macular degeneration or diabetic macular edema who have poor response to anti-vascular growth factor therapy with bevacizumab have a significantly higher risk of obstructive sleep apnea compared with age-matched controls. Poor responders to bevacizumab should be screened to assess their risk for OSA.

Patients with AMD (n=103) were categorized into nonexudative (n=56; 54.37 percent) and exudative (n=47; 45.63 percent) groups. The DME group (n=77) included patients with nonproliferative diabetic retinopathy and cystoid macular edema (n=30; 37.66 percent). Patients were categorized based on the number of intravitreal injections of bevacizumab received. All groups were compared with age-matched controls and completed a screening questionnaire to assess the risk for OSA, the main outcome measure.

Within the exudative AMD group, 14 (29.79 percent) had poor response exudative AMD, as defined by persistent subretinal fluid on OCT after at least three anti-VEGF consecutive monthly injections, and were at significantly higher risk of OSA (p<0.05). Of the DME patients with cystoid macular edema, four (19 percent) received one injection, 18 (81.82 percent) received two or more consecutive injections and 16 (72.73 percent) received three or more consecutive injections. The risk for OSA increased significantly with the number of injections (p<0.05).

Retina 2014;34:2423-2430.
Nesmith B, Ihnen M, Schaal S.

Effects of Topical Diquafosol on Intraoperative Corneal Wetting

Four-week pretreatment with diquafosol 3.0% ophthalmic solution in cataract patients was effective in enhancing the intraoperative corneal surface wetting property, which suggests improved optical clarity during surgery.

After a two-week washout period, patients with senile cataract at the Miyake Eye Hospital in Nagoya, Japan, were randomly assigned to receive one drop of diquafosol 3.0% ophthalmic solution or artificial tears six times a day for four weeks prior to surgery. The main outcome measure, termed the corneal wetting property, was the time between when a clear image of the operating microscope light source appeared just after the corneal surface was irrigated with a balanced salt solution and the time at which that image began to blur.

The study enrolled 51 patients (76 eyes). The mean time to corneal wet-

ting was 50.1 seconds ±10.8 (standard deviation) in the diquafosol group and 45.3 ±9.2 seconds in the artificial tears group. The difference between the two groups was statistically significant ($p<0.029$).

J Cataract Refract Surg 2014; 40:1682-1688.
Miyake G, Ota I, Miyake K, Zako M, et al.

A Changing Pattern of Cataract Surgery Indications

A five-year trend in national data sets from the Netherlands, Sweden and Malaysia shows a decreasing visual threshold for cataract surgery as well as decreasing surgical complication rates and increasing visual outcomes regardless of the initial preoperative visual level. Cataract surgery on eyes with poor preoperative visual acuity was related to surgical complications and cataract surgery on eyes with excellent preoperative visual acuity was related to adverse visual results.

A multinational team of researchers analyzed preoperative, surgical and postoperative data of patients undergoing cataract extraction between 2008 and 2012 from two databases: the European Registry of Quality Outcomes for Cataract and Refractive Surgery, which contains complete data from the national cataract registries in the Netherlands and Sweden, and the Malaysian National Cataract Registry. The researchers' analysis examined preoperative and postoperative corrected distance visual acuity, preoperative ocular comorbidity in the surgery eye and capsule complications during surgery.

There were substantial differences in indication for surgery between the three national data sets. The percentage of eyes with a preop BCVA of 20/200 or worse varied from 7.1 percent to 72 percent. In all three data sets, the visual thresholds for cataract surgery decreased over time by 6 percent to 28 percent of the baseline values. The frequency of capsule complications varied between the three data sets, as well, from 1.1 percent to 3.7 percent in 2008 and from 0.6 percent to 2.7 percent in 2012. An increasing postop VA was also seen for all three data sets. A high frequency of capsule complication was related significantly to poor preop VA and a high frequency of decreased visual acuity after surgery was related significantly to excellent preop VA.

Ophthalmology 2015;122:31-38.
Lundström M, Henry Y, Salowi M, Barry P, et al.

Evaluation of Compounded Bevacizumab Prepared for IVI

Researchers at Weill Cornell Medical College found that intravitreal preparations of bevacizumab acquired from compounding pharmacies were negative for microbial contaminants and endotoxin, but had significant variations in protein concentrations. These variations appeared, in general, to be lower than in bevacizumab acquired directly from Genentech. The clinical implications of these variable protein levels remain uncertain.

The study, conducted at a university-based, good manufacturing practice facility and academic ophthalmology practice, was a prospective *in vitro* study of 21 syringes of compounded bevacizumab from 11 compounding pharmacies. Of these samples, 17 (81 percent) had lower protein concentrations (mean [standard deviation], 22.2 [4.9] mg/mL; range: 19.2 to 24.5 mg/mL) compared with bevacizumab acquired directly from Genentech (25 mg/mL; $p<0.05$). In three of the 10 compounding pharmacies where more than one sample was available, there were statistically significant differences in the protein concentration between samples from the same compounding pharmacy. No microbial contaminants or endotoxin were detected in any samples.

JAMA Ophthalmol 2015;133:32-39.
Yannuzzi N, Klufas M, Quach L, Beatty L, et al.

(continued from page 49)

photic phenomena."

On the more distant horizon, there are some other lenses like the FluidVision accommodating lens by PowerVision, which has fluid-filled haptics that actuate a central curvature change in the lens with accommodative effort. "In Europe, there is the AkkoLens, where two lenses are sliding across with different optical features (spherical refractive and cubic)," Dr. Pepose says. "One of the most exciting lenses that I saw in Europe this year is the lens by AMO called the Symfony, which is an extended depth of focus lens. It's a diffractive multifocal, and instead of having two foci, near and distance, it is spread out so that there is sort of a continuum of focal points. In order to offset the decrease in visual quality that you get by doing that, they offset the average corneal spherical aberration of the eye, and they also have offset chromatic aberration. This is a whole new class of lenses—extending depth of field lenses."

"If we could get a truly accommodating IOL that is safe and effective, that would be a panacea. In certain age groups, this would be an excellent avenue to correct presbyopia," Dr. Gordon adds. REVIEW

Dr. Durrie is a clinical investigator for AcuFocus. Dr. Gordon is an investigator and option holder for Presbia. Dr. Lindstrom has a financial interest in AcuFocus, AMO, Alcon and Bausch + Lomb. Dr. Pepose is a consultant for AcuFocus, AMO, Alcon and Bausch + Lomb. Dr. Soloway is the medical director of Refocus Group.

1. Seyeddain O, Hohensinn M, Riha W, et al. Small-aperture corneal inlay for the correction of presbyopia: 3-year follow-up. J Cataract Refract Surg 2012;38:35-45.
2. Limnopoulou AN, Bouzoukis DI, Kymionis GD, et al. Visual outcomes and safety of a refractive corneal inlay for presbyopia using femtosecond laser. J Refract Surg 2013;29:12-18.
3. Alarcon A, Anera RG, Villa C, Jimenez del Barco L, Gutierrez R. Visual quality after monovision correction by laser in situ keratomileusis in presbyopic patients. J Cataract Refract Surg 2011;37:1629-1635.
4. Gifford P, Kang P, Swarbrick H, Versace P. Changes to corneal aberrations and vision after Presbylasik refractive surgery using the MEL 80 platform. J Refract Surg 2014;30:598-603.

Equipment and Supplies / Practice For Sale

Products and Services

Practice For Sale

Merchandise Offered

Equipment and Supplies

Merchandise Offered

NEW

Lombart CS-5 Package

Quality, Style & Value

Package includes:

- The Lombart CS-5 Chair & Stand
- Topcon VT-10 Refractor
- Topcon SL-2G Slit Lamp
- Reichert LongLife Chart Projector with mount, slide & screen
- Upgrade to the Lombart CVS-PC for only $1500 or to the CVSi21 for only $2000 more
- Additional upgrades & configurations available.

$13,595

Or lease for $265/mo. for 60 months*

*Lease rate subject to credit approval, 1st payment is due at signing with 59 remaining rental payments of $265 and a $1.00 purchase option. Taxes, freight and installation additional. Hand Instruments optional. Subject to change without notice.

1-800-566-2278

Call 1-800-Lombart

Or Your Local Lombart Representative

Corporate Office - 5358 Robin Hood Road, Norfolk, VA 23513-2430
757-853-8888 | FAX 757-855-1232 | 800-566-2278
www.lombartinstrument.com
lombart@lombartinstrument.com

Sales and Service Centers Coast to Coast

ATLANTA • BALTIMORE/WASHINGTON D.C. • BOSTON • BOYNTON BEACH/MIAMI • BRADENTON • CHARLOTTE • CHICAGO • CINCINNATI • DALLAS • DENVER • DETROIT • GREENSBORO • HOUSTON
JACKSON • KANSAS CITY • KNOXVILLE • LOS ANGELES • MILWAUKEE • MINNEAPOLIS • NEW JERSEY/NEW YORK/PENNSYLVANIA • NORFOLK • PORTLAND • SAN ANTONIO • SAN DIEGO • SAN FRANCISCO

A young woman presents with tearing and eye pain along with blurred vision and a change in her appearance some months earlier.

Marta Melnyk, MD

Presentation

A 34-year-old female presented to Wills Eye Emergency Room complaining of worsening left eye pain and tearing. She noted a change in appearance that occurred nine months prior to presentation. She experienced mild left-eye pain and blurry vision that began six months prior. The symptoms progressed and patient sought medical care 1.5 months prior to the ER visit, but she was unable to obtain outpatient follow-up, and worsening pain ultimately brought her to the emergency room.

Medical History

Past medical history was significant for diabetes, hypertension, asthma and genital herpes, which were treated with lantus insulin 12 units once daily; amlodipine 10 mg once daily; valsartan 320 mg once daily; clonidine patch 0.1 mg applied weekly; albuterol inhaler when needed; and acyclovir 500 mg once daily. Her past surgical history included tonsillectomy, cholecystectomy, hysterectomy, tubal ligation and hernia repair. Family history was noncontributory. The patient was a current smoker, but denied alcohol or illicit drug use. She was allergic to latex.

Examination

The patient's visual acuity was 20/40 in the right eye with pinhole improvement to 20/25, and count fingers in the left eye with pinhole improvement to 20/400. There was a trace relative afferent pupillary defect on the left. Confrontational visual fields were full and intraocular pressure was 16 in both eyes. Ishihara color plates were full in both eyes (patient held the plates close to her face for left eye testing). Extraocular movements were full on the right. The left eye displayed only 40 percent supraduction and 90 percent abduction.

External exam revealed left-eye proptosis and hypoglobus. Hertel exophthalmometry was 14 mm on the right and 20 mm on the left. Resistance to retropulsion of the left orbit was noted. Further examination revealed left upper eyelid fullness and inferior superficial punctate keratopathy on the left cornea. The slit-lamp exam was otherwise unremarkable. Dilated fundus exam was normal. The patient underwent a CT scan *(See Figure 1)*.

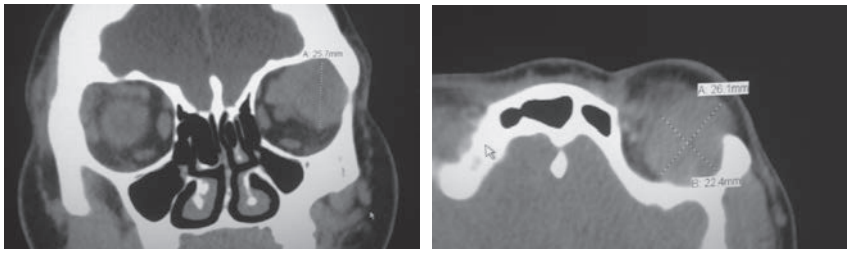


Figure 1. CT coronal and axial images displaying a well-circumscribed left lacrimal mass producing a mass effect on the globe and scalloping of the frontal bone.

What is your differential diagnosis? What further workup would you pursue? Please turn to p. 72

Diagnosis, Workup and Treatment

The patient's proptosis, hypoglobus and extraocular movement limitations suggested an orbital neoplastic, inflammatory or infectious process. The patient had decreased visual acuity and trace relative afferent pupillary defect, but normal color plates. This could suggest optic nerve involvement, but was more likely a result of mass effect on the globe. The patient underwent a CT scan *(See Figure 1)*, which revealed a lobulated heterogeneous mass arising from the left lacrimal gland 2.6 cm in maximal diameter. The lesion caused mild mass effect on the left globe and extraocular muscles, as well as mild scalloping of the frontal bone.

The patient's laboratory workup revealed mildly elevated ACE and anti-SSA levels, with normal ANA, ANCAs and anti-SSB. The patient initially underwent X-ray of the chest, which showed opacities in the right upper lobe. Elevated ACE and X-ray findings prompted further investigation into the possibility of sarcoidosis. The patient then underwent CT of the chest, which revealed opacities in the right upper lobe. These findings were consistent with an infectious or inflammatory process. There were no mediastinal or hilar lymphadenopathy or lung parenchymal changes to suggest sarcoidosis.

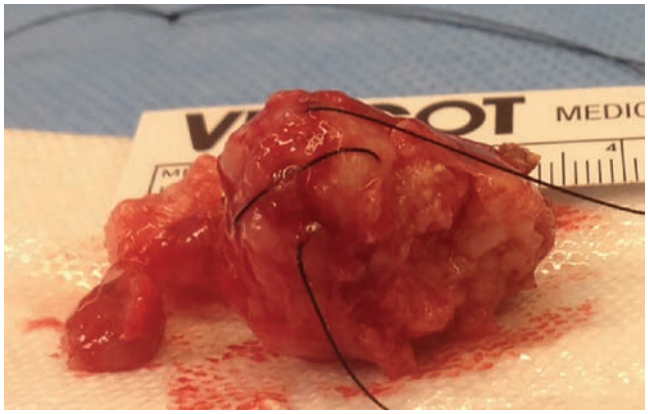


Figure 2. Pseudoencapsulated left lacrimal gland mass with surface bosselations.

The patient underwent anterior orbitotomy with an excisional biopsy of the left lacrimal gland mass. The pathology report described the mass as a pseudoencapsulated tumor with surface bosselations *(See Figure 2)*. Histopathology revealed a characteristic mix of epithelial ducts and mesenchymal components, and the patient was diagnosed with benign mixed tumor.

Discussion

Pleomorphic adenoma or benign mixed tumor (BMT) is the most common epithelial tumor of the lacrimal gland, comprising 50 percent of cases.[1] The main differential diagnostic consideration for BMT is adenoid cystic carcinoma (ACC), which is the most common malignant tumor of the lacrimal gland, accounting for 50 percent of malignant cases.[1] BMT usually presents as a slow-growing, painless, round mass that may cause accentuation of the lacrimal gland fossa, but does not cause bone destruction.[1-3] On the other hand, ACC classically presents as a rapidly growing painful mass that erodes the bone and infiltrates surrounding structures. ACC's predilection for perineural invasion is the cause for the severe pain associated with ACC.[1-3]

Our patient's presentation with significant pain and seemingly rapid progression over nine months raised an initial concern for a malignant neoplastic process, but the CT revealed scalloping of the frontal bone, rather than destruction.

The suspected preoperative diagnosis is critical in the management of lacrimal gland tumors as it can influence surgical planning. For example, complete excision without biopsy is recommended in the case of pleomorphic adenomas, while an incisional biopsy is recommended for most other lacrimal tumors prior to planning definitive treatment.[3] This recommendation is based on the results of Ramon L. Font, MD, and John W. Gamel, MD, who reviewed 136 cases of BMT and found that biopsy prior to excision had adverse influence upon the outcome with five-year recurrence rate of 32 percent, compared to 3 percent in cases that were initially completely removed.[4] Recurrence of BMT is particularly concerning because it has been associated with malignant transformation into malignant mixed tumor (MMT).[2] Drs. Font and Gamel's data has been questioned due to its retrospective nature and heterogeneous sources of cases. Another case series of 72 patients in a single center with longer follow-up showed a much lower rate of recurrence with only one case, which occurred in a patient who underwent biopsy prior to excision.[5] Some have questioned the absolute "no biopsy" rule in management of lacrimal gland pleomorphic adenoma since fine-needle aspiration biopsy is successfully used for diagnosis of pleomorphic adenomas in other salivary glands.[6]

The original algorithm for management of an unknown lacrimal

gland tumor published in 1979 relied heavily on clinical presentation to determine whether to pursue en bloc excision or incisional biopsy. It was recommended that painless tumors with symptoms for greater than 12 months are likely benign and should undergo complete excision, while painful tumors present for less than 12 months should undergo biopsy. Additionally, X-ray finding of bone destruction steered one toward malignant etiology and incisional biopsy.[3]

The advent of computer tomography has greatly improved our pre-biopsy diagnostic acumen and changed the original algorithm. In a case series of 63 orbital BMTs, only 69 percent had symptoms for greater than 12 months, 89 percent had no pain and 98 percent had benign imaging characteristics on CT.[7] Based on the specificity of CT in identifying benign tumors, the updated algorithm recommended completely excising tumors with benign CT findings, even if they present atypically for BMT with pain and short duration of symptoms.[7] The application of the updated algorithm in this case has been shown to be successful. REVIEW

The author would like to thank Jacqueline Carrasco, MD, of Wills Eye Oculoplastic and Orbital Surgery Service, for her time and assistance in preparing this case report.

1. Eagle RC. Eye Pathology. Philadelphia: Wolter Kulver/Lippincott Williams & Wilkins, 2011.
2. von Holstein SL, Coupland SE, Briscoe D, et al. Epithelial tumors of the lacrimal gland: A clinical, histopathological, surgical and oncological survey. Acta Ophthalmol 2013;91:195-206.
3. Wright JE, Steward WB, Krohel GB. Clinical presentation and management of lacrimal gland tumors. Br J Ophthalmol 1979;63(9):600-606.
4. Font RL, Gamel JW. Epithelial tumors of the lacrimal gland: An analysis of 265 cases. In: Jakobiec FA, ed. Ocular and Adnexal Tumors. Birmingham, AL: Aesclulapius Publishers Inc.; 1978:787-805.
5. Currie ZI, Rose GE. Long-term risk of recurrence after intact excision of Pleomorphic Adenomas of the Lacrimal Gland. Arch Ophthalmol 2007;125(12):1643-1646.
6. Lai T, Prabhakaran VC, Malhortra R, Selva D. Pleomorphic adenoma of the lacrimal gland: Is there a role for biopsy? Eye 2009;23:2-6.
7.Rose GE, Wright JE. Pleomorphic adenoma of the lacrimal gland. Br J Ophthalmol 1992;76,395-400.

(continued from page 62)

disease is also typically associated with a poor outcome due to the high prevalence of posterior component.[8] Dr. Hunt and colleagues found that eyes without posterior disease often trended toward vision of counting finger or better; this outcome was not statistically significant, however.[4] Despite the trend for poor visual outcome, it is possible to obtain useful vision, even with combined anterior and posterior PFV.[8] Age at diagnosis is a predictor of final visual outcome, with earlier detection and treatment leading to an increased likelihood of useful vision.[5] In one study, post-surgical patients who presented at a mean of 2.4 months achieved a final visual acuity of 20/200 or better, while those that presented at a mean of 4.3 months achieved 20/300 or worse.[7] Furthermore, those who received surgical intervention before 77 days of age tended to maintain useful remaining vision.[7]

In 1955, Algernon Reese, MD, described a two-stage surgical approach for PFV at his Jackson Memorial Lecture. His initial goal was to avoid enucleation, as opposed to visual rehabilitation, with the initial steps including lensectomy and removal of any retrolental membrane.[6] Previously, an open-sky technique was used in order to minimize hemorrhagic complications of these possibly perfused vessels; today's retinal surgical techniques, however, allow for single step, closed procedures. Progressive retinal detachment, which often occurs as fibrovascular tissue contracts and drags the peripheral retina, is an indication for surgical intervention in an effort to preserve the globe. Angle-closure glaucoma and persistent intraocular hemorrhage are also indications to consider surgery.[7] In an attempt to avoid peripheral fibrovascular tissue, some vitreoretinal surgeons advocate a translimbal or transpupillary approach rather than the traditional pars plana vitrectomy; however, similar complication rates have been reported with either approach.

Appropriate patient selection is essential for successful surgical management. Surgery should be avoided in patients with a poor visual prognosis, including severe optic nerve involvement or foveal hypoplasia. Refractive correction and amblyopia therapy are also important for visual rehabilitation, especially in unilateral cases; unfortunately, the density of amblyopia in these cases often makes compliance difficult. Even after surgery, vitreous hemorrhage, glaucoma and rhegmatogenous retinal detachments may recur.[8] These potential complications require lifelong monitoring and even in the most ideal situations, visual outcome may be disappointing. All in all, PFV requires meticulous care and follow-up and may involve pediatric ophthalmologists, vitreoretinal surgeons and contact lens specialists. REVIEW

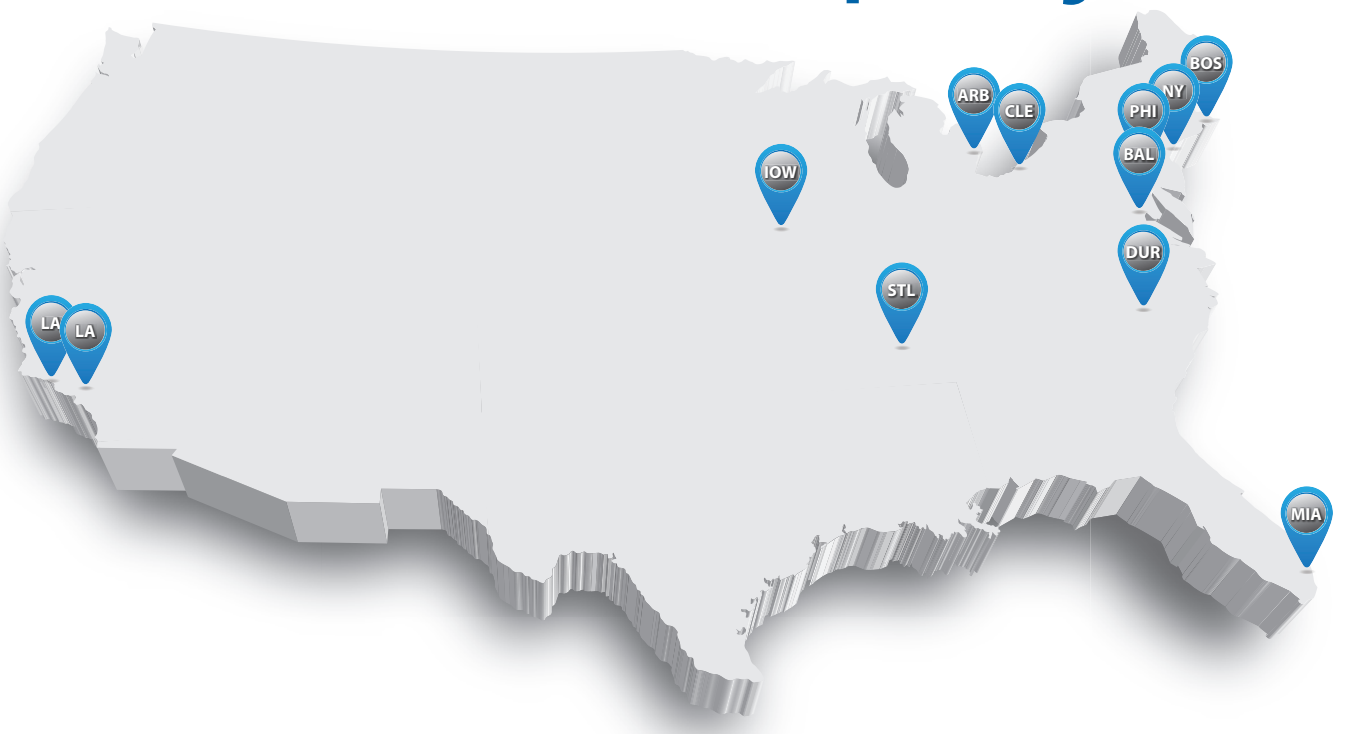
Dr. Farber is a second year resident at SUNY Downstate Medical Center and Dr. Shrier is a retina attending at SUNY Downstate Medical Center.

1. Mary-Sinclair M, et al. Varied manifestations of persistent hyperplastic primary vitreous with graded somatic mosaic deletion of a single gene. Molecular Vision 2014;20:215-230
2. Goldberg, MF. Persistent Fetal Vasculature (PFV): An Integrated Interpretation of Signs and Symptoms Associated with Persistent Hyperplastic Primary Vitreous (PHPV) LIV Edward Jackson Memorial Lecture. Am J Ophthal 1997;124:587-626.
3. Lambert SR, et al. Congenital Fibrovascular Pupillary Membranes: Clinical and Histopathologic Findings. Ophthalmology 2012;119:634-64.
4. Saint-Geniez M, D'Amore P. Development and Pathology of the Hyaloid, Choroidal, and Retinal Vasculature. Int J Dev Biol 2004;48:1045-1058.
5. Pollard Z. Persistent Hyperplastic Primary Vitreous: Diagnosis, Treatment and Results. Tr Am Ophth Soc 1997;95:487-549.
6. Reese A. Persistent Hyperplastic Primary Vitreous. The Jackson Memorial Lecture. Am J Ophthal 1955;40:317-331.
7. Hunt A, et al. Outcomes in persistent hyperplastic primary vitreous. Br J Ophthalmol 2005;89:859-863.
8. Alexandrakis G, et al. Visual Acuity Outcomes with and without Surgery in Patients with Persistent Fetal Vasculature. Ophthalmology 2000;107:1068-1072.
9. Dass A, Trese M. Surgical Results of Persistent Hyperplastic Primary Vitreous. Ophthalmology 1999;106:280-284.
10. Pearce M, et al. Radiation exposure from CT scan in childhood and subsequent risks of leukaemia and brain tumours: A retrospective cohort study. The Lancet 2012;380:499-505.

REVIEW Advertising Index

This advertiser index is published as a convenience and not as part of the advertising contract. Every care will be taken to index correctly. No allowance will be made for errors due to spelling, incorrect page number, or failure to insert.

Great Company



Where will you find Keeler's Vantage Plus? Easy...the top 12 ophthalmology centers in the US*.

Keeler Vantage Plus

- Intelligent Optics for superior views (US Patent: 8,132,915)
- HiMag™ Lens for detailed magnified views
- Convertible Illumination LED and Xenon
- Lightest Wireless System

Get a
Free Keeler Indirect
When You
Buy Any 3 Keeler Indirects,
& Trade-In Any 3 Indirects
through March 31, 2015

Learn more at www.keelerusa.com

Buy Online!
keelerusa.com

Keeler
OPTICS

*Top-ranked hospitals for ophthalmology – Source: U.S. News & World Report

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%

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

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

RESTASIS® twice a day, every day, helps patients experience increased tear production

Increased tear production was seen at 6 months.[1]

Indication and Usage

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

Important Safety Information

Contraindications

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

Warnings and Precautions

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

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

Adverse Reactions

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

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

Reference: 1. RESTASIS® Prescribing Information.

ALLERGAN

APC20AF14 141005