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REVIEW® of Ophthalmology
May 2016
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THE AGING PATIENT

The coming wave of elderly patients will necessitate many changes in the average ophthalmology practice.
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REVIEW NEWS
Volume XXIII • No. 5 • May 2016

USC Study: Chinese Americans Suffer Higher Wet AMD Rate

The University of Southern California Roski Eye Institute researchers and clinicians published the results of the National Eye Institute-funded Chinese American Eye Study, the largest ophthalmology study among those with Chinese ancestry living in the United States. The findings, published in *JAMA Ophthalmology*, point to critical interventions in the prevention and treatment of blinding eye diseases, such as age-related macular degeneration and diabetic retinopathy, among Chinese Americans.

Key findings of the CHES study point to a higher percentage (85 percent) of neovascular AMD than geographic atrophy AMD (15 percent). This is almost the opposite of what has been found in whites or other ethnic groups, who typically have the same percentage of AMD types or higher prevalence of dry AMD. The study also found the prevalence of AMD is higher among Chinese Americans as compared to the Chinese population living in urban/rural China, suggesting the influence of environmental or behavioral factors should be considered.

The other substantial finding in the study is the participants with diabetes (17.4 percent) were three times more likely than those without the disease to have significant visual impairment. This increase was found in the Chinese-American study participants with Type II diabetes who had cataracts or macular edema resulting in visual impairments. While 41 percent of these Chinese-American study participants had DR, this is a lower percentage than has been reported among Chinese people living in rural China (46 percent) and Latinos living in Los Angeles (48 percent). As well, Chinese Americans were found to have a lower reported rate of DR than Chinese residing in rural northern China, likely a result of their better access to diabetes screening and treatment.

Asian Americans are the fastest growing racial group in the United States, and Chinese Americans are the largest segment of this population, according to the latest U.S. Census. Rohit Varma, MD, MPH, interim dean of the Keck School of Medicine of USC and director of the USC Roski Eye Institute, was the study's principal investigator and one of the world's leading experts in population-based eye disease.

"This study sounds a clarion call for all eye care providers to be aware of the prevalence of wet AMD in those of Chinese ancestry and to provide the available treatments such as injections and laser therapies," said Dr. Varma. "And while not as prevalent as we see in the Latino community, we also need to be aware of addressing those Chinese Americans with diabetes to prevent DR and the onset of significant visual impairment."

Dr. Varma added that the treatments for wet AMD are aimed at blocking the growth of new abnormal blood vessels in the eye and are widely available as opposed to the lack of therapy options for dry AMD, a diagnosis that is typically treated through health lifestyle changes.

"The study gives us unprecedented insights into the burden of eye disorders among this fast growing racial group in the United States. The findings will help inform preventive screening strategies and guide healthcare resource planning," said Maryann Redford, DDS, MPH, a program director for Collaborative Clinical Research at the National Eye Institute.

The CHES study involved more than 4,500 Chinese Americans age 50 or older living in Monterey Park, Calif. Almost all (98 percent) of the study participants were first-generation immigrants. The participants underwent comprehensive eye exams and interviews to assess risk factors for AMD and DR, including lifestyle factors such as smoking and daily diet. Photographs of the inside of the eyes were taken to also detect signs of these eye diseases.

Researchers Devise 'Mini-Retinas'

Stem cell science has progressed so that researchers can now share recipes for making human retinas. The first protocols enabled the generation of retinal cells in laboratory plates and more recently as complex tissue in the form of tiny eye-like cups. Researchers in Germany now have another efficient way to make 3-D retina organoids, which mimic the organ's tissue organization, from mouse or human stem cells. Their version of "mini-retinas," pub-

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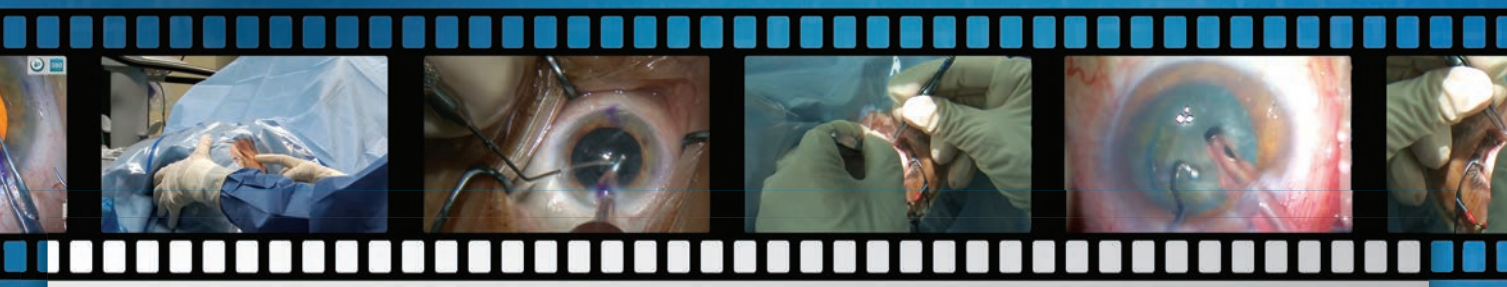

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Richard Mackool, MD, a world renowned anterior segment ophthalmic microsurgeon, has assembled a web-based video collection of surgical cases that encompass both routine and challenging cases, demonstrating both familiar and potentially unfamiliar surgical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

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

Learning Objectives:

After viewing the video, participants should be able to:

1. Outline the method of deepening a shallow anterior chamber prior to phacoemulsification by performing a pars plana vitrectomy.
2. Describe techniques that protect the corneal endothelium during phacoemulsification.

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

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lished online on March 31 by *Stem Cell Reports*, offers new perspectives on retina growth, injury and repair.

"The goal isn't just to make the closest thing next to a real retina, but also to possibly harness the flexibility of the system to create more diverse ways of studying retina tissue," says senior author Mike Karl of the German Center for Neurodegenerative Diseases. "We need to respect that each protocol is a new beast with different tastes, wrappings and purposes."

Stem cell technologies have the potential to develop therapies for the treatment of diseases such as age-related blindness, and as clinical researchers work to apply the cells into new therapies, stem cell biologists such as Dr. Karl have been working to understand the regeneration of neurons from lower vertebrates to humans, which can aid regenerative medicine in more indirect ways.

For example, the 3-D retinal organoids developed in Dr. Karl's lab (an effort led by first author Manuela Völkner) efficiently replicate the formation of the retina. This specifically includes the light-detecting cone cells, which now can be produced in high quantities in their mini-retinas. Cone photoreceptors, which are responsible for high acuity and color vision, are the most precious retinal cell type with regard to potential future cell replacement therapies in patients affected by retinal degeneration.

Dr. Karl and colleagues' comparative studies on pluripotent stem cell-derived human and mouse retina organoids and mouse retina *in vivo* support the power of the new organoid protocol. "Tissue heterogeneity is a major challenge in organoid systems, and here our work provides new insight, which will help to develop specific organoid-based models, specifically to reliably study retinal disease mechanisms," says Dr. Karl.

(continued on page 7)

Ophthalmic Product Development Insights

MaryJane Rafii, PhD, and Matthew Chapin • Ora Inc., Andover, Mass.

Choosing and Planning Your Exit Strategy

Across our prior columns, we have been exploring business and product development-related issues specifically revolving around entrepreneurs and start-up initiatives. In this installment, we will review considerations surrounding exit strategy for new entrepreneurs.

Your exit strategy impacts many aspects of your business plan and approach, and not taking this important fact into consideration will certainly impact your future options. It is not a matter of whether you will exit, but of when and how.

The exit strategy needs the consensus of partners and investors as well, which could be a rate-limiting step. You need everyone to agree on the best way forward—whether a sale, an acquisition, a license, partnerships or going it alone—and that it is in the interest of everyone who has put either money or sweat equity in the company. We have all big hopes and, in some cases, we have to make a realistic assessment of any exit opportunities being presented, balanced with the actual chances for a larger, but less likely, future potential exit.

Different People, Different Strategies

For example, if you suggest to your key partners or employees that you have no plans to exit the company in the near term, but then sell within two years of founding it, they are likely to be dissatisfied and could disrupt the sale. Or if you want to sell the business in five years but your operating partners want to own and manage it for the next 10, then you will have a problem.

The sooner you start planning your scenarios, the more rewarding the eventual exit is likely to be. Alas that is not a one-size-fits-all formula. The range of exit strategies includes taking the company public through an initial public offering; selling the company to a strategic partner; licensing of individual products; or another transaction like private equity. Acquisition is an attractive strategy to many entrepreneurs since another company purchases the business for either cash or stock, or a combination of both. The only issues are whether the acquiring company will retain the old management team and/or make substantial changes in the acquired company's operations and staff.

Different people start companies for different reasons, and that can influence their exit strategy. Initially everything looks great as the founder(s) own a 100 percent of the business. If they take on investment over time from VCs, angels or individuals, they usually give up a portion of the company or shares. Of course, those shareholders will have a say in any potential exit strategy. A word of caution: Choose them carefully, and ensure partners you will be taking on share overall strategic view for the company and timing of exit. As Eric Young,

general partner of Canaan Partners, a global venture capital firm that has invested in more than 250 companies in the past two decades said: "Some people want to change the world and that's why they start a company, and some people just don't want to work for anyone else."[1]

Nonetheless, a time will come when you have to make a decision to exit either because you need operating cash or because you have reached a point where you will have created enough value and enough buzz to be acquired. Or you may be faced with a situation to exit to return the invested capital, or a positive respectable double return, versus going the distance for larger returns however with higher risk.

Part of your decision will depend on whether or not you want to continue to manage your business. In an IPO this may not be an issue as you and your team generally play much the same roles before and after the transaction; however, in an acquisition, the acquiring company may replace you and your team with their own team or you may be playing the same roles but within a new structure. In such a case the old adage of having too many cooks in the kitchen may apply.

As a founder and business owner, I (MJR) can only testify that it is not an easy decision but one that has to be made when it is necessary. It is an excellent solution for companies like mine who were struggling with the fact that the funds that were necessary to move the programs forward were not raised in due time, or due to a lack of interest, or a bad market. So we all want a planned exit but it is not always planned ahead.

Common Scenarios

As we work with early-stage entrepreneurs and companies, we see a few common scenarios that arise in which the full amount of needed funding is not raised, or some other consideration alters the originally planned exit pathway:

1. The story was too long. Having a tight story is the key. Addressing this mainly to new entrepreneurs, we see many companies that have a slide deck that surpasses 30 or 40 slides and they get into too much detail for an introductory meeting. Have a different level of presentations for the introductory (many times non-confidential) versus the follow-up discussions held under a confidentiality agreement. Advice to readers: Ultimately, the point of your first meeting is not to close a deal but to get a second meeting.

2. The story is incomplete. Make sure the slide deck hits the key areas: product profile; how it fills an unmet need; market and product landscape; differentiating factors of the product; development plan; regulatory plan; budget; risks and how they're being addressed; operational plan (internal and leveraging external resources like contract research organizations); and a model to project sales.

On the clinical side you'll need: FDA-acceptable endpoints; what builds value and informs Phase III designs; competing trials (e.g., with orphan indications, how many trials of the same indication across competing products can the field take at once?); whether the proof of concept will be with non-FDA-acceptable endpoints, such as structural endpoints in some retinal diseases; how you'll build the story that informs decision making; and to make sure to accurately represent in your plan what is acceptable for Phase III. We frequently see initial slide decks talk about proof-of-concept endpoints that can be accepted for Phase III, when in fact they can't from a regulatory perspective. Have your facts straight and be direct about the proof-of-concept approach. Otherwise it may lose credibility. Of course,

you want the slide deck to tell a story and not have big holes in the thought process. We have seen times when an entrepreneur may be so excited about a particular aspect of the program that the combination of these critical elements is lost in the initial pitch.

3. Targeting the wrong investors. CEOs and founders believe in their companies and often think that everyone else should as well. Most successful investors already have a clear idea about what stage they want to invest in, the novelty of the opportunity and the type of deal presented. It's especially important to adapt, be clear and properly position the priorities of different paths if the technology is a platform play. For example, are you leading with front of the eye or back of the eye? An orphan or a mainstream indication? Are you leveraging repurposing of an existing drug versus pursuing a new chemical entity? The key advice to the new entrepreneur: Target the right audience.

4. Grant funding. Although this is one of the best ways to raise non-dilutive funding for your business, most of the time grant funding will not by itself by sufficient to fulfill the funding needs. Generally, it is best leveraged to get to the next steps of key work activities. However, we sometimes see entrepreneurs stuck in a process where emphasis on grants de-focuses from development of the business plan, fund raising and developing the exit plan. Advice to readers: Be mindful of time and resources spent on grant funding, and proper focus that the work to be funded will provide key data for future partners.

5. Not willing to change directions. There are times when your original idea will not stick. The smart entrepreneur is constantly able to adapt, evolve the business plan and be on the prowl for other opportunities to integrate and build out the pipeline portfolio. Advice to readers: Be quick to incorporate feedback, and if needed have a plan and time line for changing direction if the original one doesn't work.

This is certainly not a comprehensive list, but we hope it highlights some key items we encounter frequently. Keeping these issues in mind will help the new entrepreneur focus on what is going to drive decision-making and value inflection, and feed into the exit strategy. Your exit strategy affects various directions that you might choose to help your business grow. Not looking at your exit strategy during an early stage might lead you to limit your options for the future. Your basic decision will have two major components: how and when. Whichever strategy you choose and plan in advance will give you the time to do it right and maximize the return.

Dr. Rafii and Mr. Chapin are with the Corporate Development Group at Ora Inc. Ora provides a comprehensive range of full-service product development for developers, including entrepreneurs, start-ups, large pharma, and investors and buyers. Ora offers preclinical and clinical services; clinical-regulatory and product consulting; regulatory submissions integrated with asset, business partnering and financing support in ophthalmology. We welcome comments or questions related to this or other development topics. Please send correspondence to mchapin@oraclinical.com

1. www.inc.com/guides/2010

(continued from page 5)

"Even with our new additions to existing organoid systems, we have not yet reached that tipping point of robustness that we need for people without the expertise to grow these models," says Dr. Karl. "By working out the details, we also hope to help those who are not developmentally or stem cell-minded to just go and study what they want."

The Karl Lab's change to the mini-retina protocol involves cutting a retina organoid grown from stem cells into three pieces at an early stage of eye development. Each of these pieces, which look like little half moons, eventually grows into the full suite of cells found in the retina, thereby increasing the yield of retinal organoids up to fourfold compared to previous protocols. A trisection also spurs the surviving organoids to grow to reach sizes similar to uncut organoids. These mini-retinas swim around in the dish and because they're not attached to a surface, better reflect the structure of retinal tissue during development.

The next objective is to make his 3-D "mini-retinas" even more complex, perhaps by bringing in blood vessels, as well as to use the organoids to study regeneration and the function of different neural cell types—specifically, from the human retina.

Preventing Neuropathy in KPro Cases

Researchers from Massachusetts Eye and Ear/Harvard Medical School have identified inflammatory factors that cause optic neuropathy following implantation of a keratoprosthesis —similar to what glaucoma patients experience, without the rise of pressure in the eye—and have shown that blocking one of those factors, tumor necrosis factor alpha, successfully halts the development of optic nerve damage in a mouse model. Their findings, published online in *Investigative Ophthalmology and Visual Science*, shed light on the underlying process responsible for optic neuropathy in KPro patients and also suggest a new pathway for preventing optic nerve damage in patients who receive the KPro implant.

"We used a mouse model of the KPro to, first of all, identify the inflammatory factors that cause damage to the eye, and then we also quantified the amount of nerve cell death in the back of the eye that mediates the optic neuropathy, and, lastly, we looked at blocking these factors with antibodies," said Reza Dana, MD, MSc, MPH, director of the Cornea and Refractive Surgery Service at Massachusetts Eye and Ear and the Claes H. Dohlman Professor of Ophthalmology at Harvard Medical School. "We found that the KPro leads to high levels of TNFa, and that by blocking TNFa, we can prevent the nerve damage."

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

Chief Medical Editor
Mark H. Blecher, MD

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

Senior 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. — (845) 267-3065
E-mail:
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REVIEW News

With more than 1,000 KPro surgeries performed annually, and with new technologies being developed to increase the number of patients who may benefit, the KPro is a clear, plastic artificial cornea often used to replace diseased corneas in patients prone to rejecting biological tissues. The vast majority of KPro recipients report good vision initially, and then later experience a progression of optic neuropathy.

To better understand these responses in the eyes of KPro recipients, the researchers studied the effects of keratoprosthesis implantation in an animal model. They found that the mice can develop damage to the optic nerve despite normal pressure in the eye following KPro surgery and identified TNFa and IL-1 as inflammatory factors involved in this process, with high levels of TNFa mediating the damage to the optic nerve. The findings represent the first proof of concept regarding the role of TNFa as a result of keratoprosthesis surgery damaging the optic nerve.

"Now we have a much more mechanistic understanding of the mediator behind this clinical presentation," Dr. Dana said. "Future studies are needed to prove that TNFa blocking can be therapeutic in humans, but in the meantime, this new knowledge clarifies the pathway to cell death of the optic nerve following KPro surgery." REVIEW

ASCRS Forms Research Council

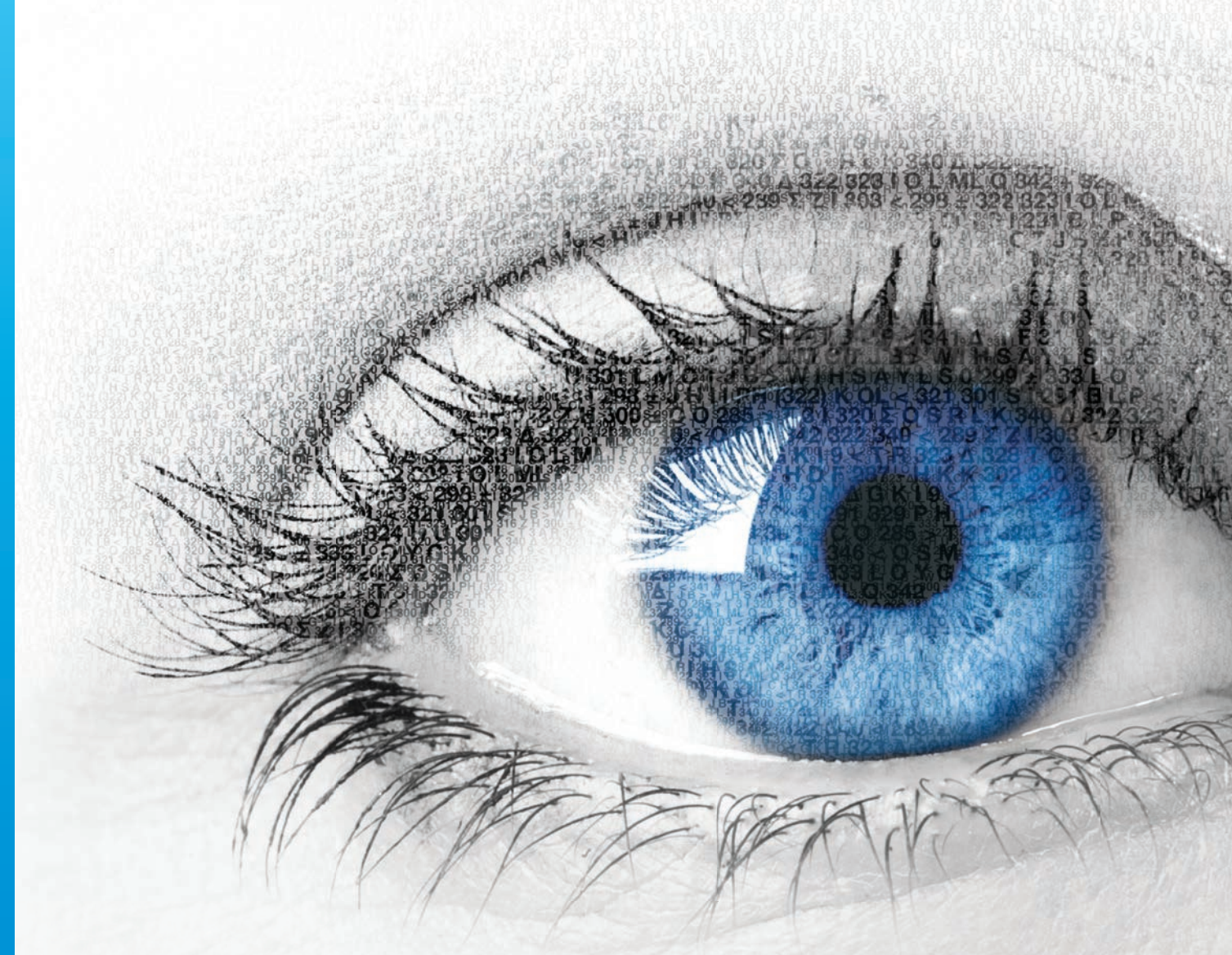
The American Society of Cataract and Refractive Surgery recently announced the formation of the ASCRS Research Council, an internal department that will collaborate with ASCRS members and partners on research trials aimed toward improving patient care and quality of life.

The Research Council will be chaired by Douglas Rhee, MD, chair of the Case Western Reserve Department of Ophthalmology and Visual Sciences. "We recognize that some of the really important questions in clinical medicine will need extensive collaboration to answer," said Dr. Rhee. "ASCRS is a leading organization in ophthalmology that is well-positioned to coordinate a multilateral effort between its academic and community membership and corporate and federal partners to investigate these immediately relevant clinical questions with scientific rigor."

The council's first study, which will examine the effects of enzymes/detergents on the anterior segment of the eye, is currently funded and underway. Led by Nick Mamalis, MD, director of the Intermountain Ocular Research Center in Salt Lake City, the study will explore whether enzymatic detergents used in cleaning ophthalmic surgical instruments can cause toxic anterior segment syndrome-like responses in a rabbit model. "Inspectors from the Centers for Medicare & Medicaid Services often require surgery centers or hospitals to strictly follow manufacturer's directions for use in the cleaning and sterilization of surgical instruments that specify the use of enzymes/detergents," said Dr. Mamalis, editor of the *Journal of Cataract & Refractive Surgery*. "We are very concerned that any residues of these materials on intraocular instruments may lead to TASS. It is important to study carefully the possible toxic effects of enzymes/detergents on the anterior segment of the eye in this animal model."

The ability to engage with nearly 9,000 ASCRS-member ophthalmologists in the United States and abroad offers the research council a substantial advantage in the design and undertaking of future studies. "With access to thousands of domestic and international members, we have the numbers and geographical distribution to explore meaningful questions in a way that will ultimately benefit the patient," said Kerry Solomon, MD, council member and incoming ASCRS president.

Study topics will be considered and vetted by the ASCRS Research Council, and all research will adhere to the strictest scientific rigor. "We understand the importance of proper study design, data collection and review," said Dr. Rhee. "Our goal is to produce relevant, useful data that can directly influence ophthalmic practice and patient care."



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

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

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

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100 Avenue of the Americas
New York, NY 10013

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See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2012

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FULL PRESCRIBING INFORMATION

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

2 DOSAGE AND ADMINISTRATION
Instill one drop of BEPREVE into the affected eye(s) twice a day (BID).

3 DOSAGE FORMS AND STRENGTHS
Topical ophthalmic solution containing bepotastine besilate 1.5%.

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

5 WARNINGS AND PRECAUTIONS
5.1 Contamination of Tip and Solution
To minimize contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use.

5.2 Contact Lens Use
Patients should be advised not to wear a contact lens if their eye is red. BEPREVE should not be used to treat contact lens-related irritation.

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

5.3 Topical Ophthalmic Use Only
BEPREVE is for topical ophthalmic use only.

6 ADVERSE REACTIONS
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 the clinical trials of another drug and may not reflect the rates observed in clinical practice.

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

6.2 Post Marketing Experience
Hypersensitivity reactions have been reported rarely during the post-marketing use of BEPREVE. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a casual relationship to drug exposure. The hypersensitivity reactions include itching, body rash, and swelling of lips, tongue and/or throat.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C: Teratogenicity studies have been performed in animals. Bepotastine besilate was not found to be teratogenic in rats during organogenesis and fetal development at oral doses up to 200 mg/kg/day (representing a systemic concentration approximately 3,300 times that anticipated for topical ocular use in humans), but did show some potential for causing skeletal abnormalities at 1,000 mg/kg/day. There were no teratogenic effects seen in rabbits at oral doses up to 500 mg/kg/day given during organogenesis and fetal development (>13,000 times the dose in humans on a mg/kg basis). Evidence of infertility was seen in rats given oral bepotastine besilate 1,000 mg/kg/day; however, no evidence of infertility was observed in rats given 200 mg/kg/day (approximately 3,300 times the topical ocular use in humans). The concentration of radio-labeled bepotastine besilate was similar in fetal liver and maternal blood plasma following a single 3 mg/kg oral dose. The concentration in other fetal tissues was one-third to one-tenth the concentration in maternal blood plasma.

An increase in stillborns and decreased growth and development were observed in pups born from rats given oral doses of 1,000 mg/kg/day during perinatal and lactation periods. There were no observed effects in rats treated with 100 mg/kg/day.

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

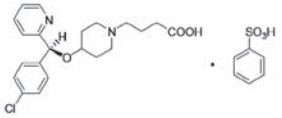
8.3 Nursing Mothers
Following a single 3 mg/kg oral dose of radiolabeled bepotastine besilate to nursing rats 11 days after delivery, the maximum concentration of radioactivity in milk was 0.40 mcg-eq/mL 1 hour after administration; at 48 hours after administration the concentration was below detection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

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

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

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

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



Bepotastine besilate is a white or pale yellowish crystalline powder. The molecular weight of bepotastine besilate is 547.06 daltons. BEPREVE® ophthalmic solution is supplied as a sterile, aqueous 1.5% solution, with a pH of 6.8.
The osmolality of BEPREVE (bepotastine besilate ophthalmic solution) 1.5% is approximately 290 mOsm/kg.
Each mL of BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% contains:
Active: Bepotastine besilate 15 mg (equivalent to 10.7 mg bepotastine)
Preservative: benzalkonium chloride 0.005%
Inactives: monobasic sodium phosphate dihydrate, sodium chloride, sodium hydroxide to adjust pH, and water for injection, USP.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Bepotastine is a topically active, direct H_1-receptor antagonist and an inhibitor of the release of histamine from mast cells.

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

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

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

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

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

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility
Long-term dietary studies in mice and rats were conducted to evaluate the carcinogenic potential of bepotastine besilate. Bepotastine besilate did not significantly induce neoplasms in mice receiving a nominal dose of up to 200 mg/kg/day for 21 months or rats receiving a nominal dose of up to 97 mg/kg/day for 24 months. These dose levels represent systemic exposures approximating 350 and 200 times that achieved with human topical ocular use. The no observable adverse effect levels for bepotastine besilate based on nominal dose levels in carcinogenicity tests were 18.7 to 19.9 mg/kg/day in mice and 9.6 to 9.8 mg/kg/day in rats (representing exposure margins of approximately 60 and 20 times the systemic exposure anticipated for topical ocular use in humans).

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

When oral bepotastine was administered to male and female rats at doses up to 1,000 mg/kg/day, there was a slight reduction in fertility index and surviving fetuses. Infertility was not seen in rats given 200 mg/kg/day oral bepotastine besilate (approximately 3,300 times the systemic concentration anticipated for topical ocular use in humans).

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING
BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% is supplied in a white low density polyethylene plastic squeeze bottle with a white controlled dropper tip and a white polypropylene cap in the following size:
5 mL (NDC 24208-629-02)
10 mL (NDC 24208-629-01)

STORAGE
Store at 15º – 25ºC (59º – 77ºF).

17 PATIENT COUNSELING INFORMATION
17.1 Topical Ophthalmic Use Only
For topical ophthalmic administration only.

17.2 Sterility of Dropper Tip
Patients should be advised to not touch dropper tip to any surface, as this may contaminate the contents.

17.3 Concomitant Use of Contact Lenses
Patients should be advised not to wear a contact lens if their eye is red. Patients should be advised that BEPREVE should not be used to treat contact lens-related irritation.

Patients should also be advised to remove contact lenses prior to instillation of BEPREVE. The preservative in BEPREVE, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of BEPREVE.

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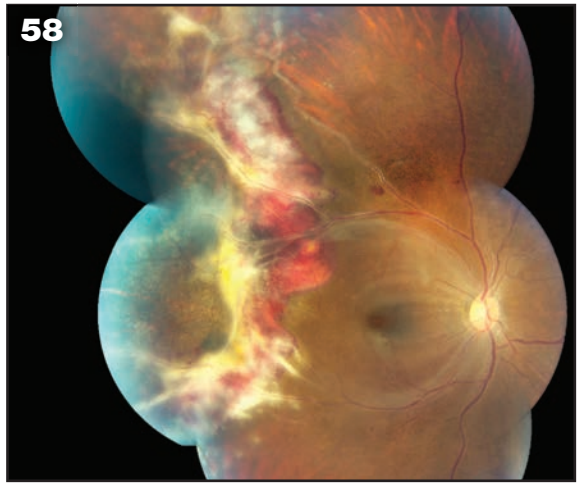
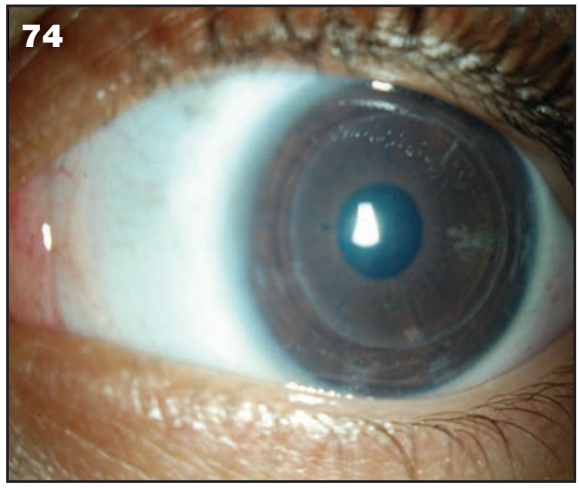
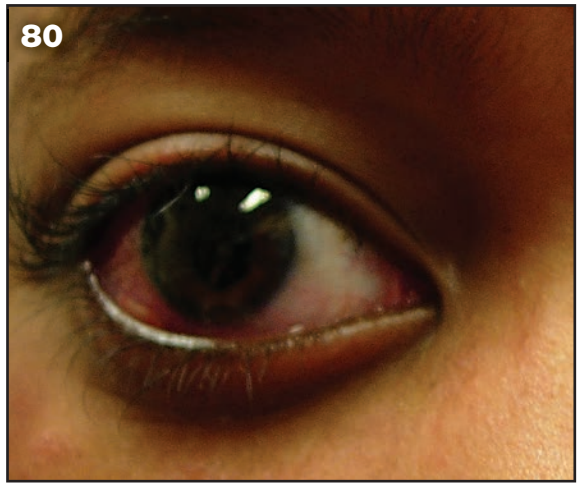
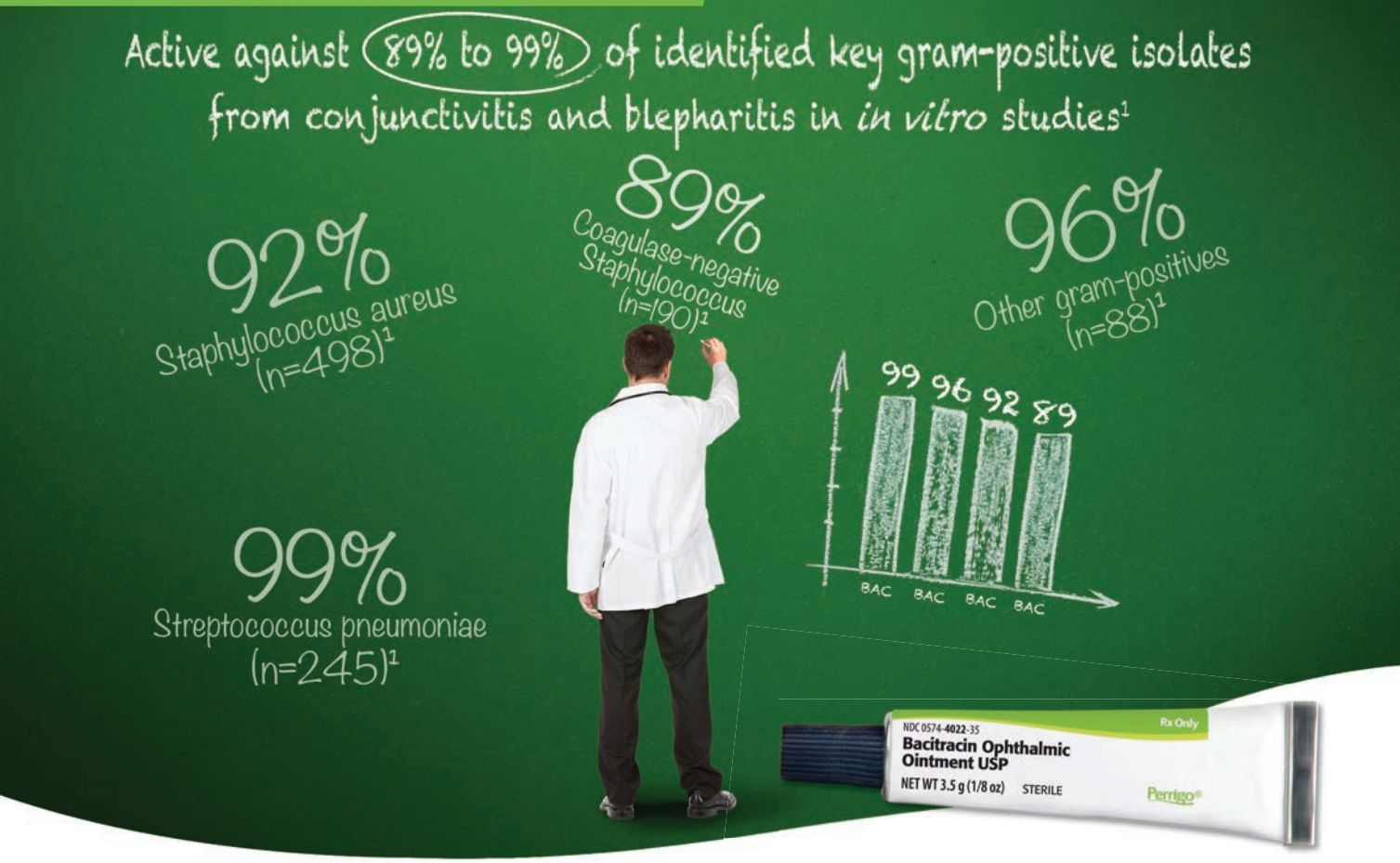






BACITRACIN OPHTHALMIC OINTMENT USP



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

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

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

Indication

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

Important Safety Information

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

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

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

Please see adjacent page for full prescribing information.

For a closer look, visit www.perrigobacitracin.com

BACITRACIN OPHTHALMIC OINTMENT USP

Perrigo® Specialty Pharmaceuticals

Bacitracin Ophthalmic Ointment USP

STERILE **Rx Only**

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

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

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

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

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

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

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

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

HOW SUPPLIED:

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

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

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

Manufactured For
Perrigo®
Minneapolis, MN 55427
0S400 RC J1 Rev 08-13 A

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

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Improving Topography-Guided Ablation

The advantages of this approach are now being pushed even further, thanks to new ideas and insights.

Christopher Kent, Senior Editor

All refractive surgeons would like to produce perfect outcomes, but hitting the target every time remains an elusive goal. The advent of topography-guided ablation has improved outcomes in many patients, but inaccuracies remain. Here, two surgeons describe new approaches to refining a planned ablation that promise to bring refractive outcomes closer to a perfect result than ever before—even when the eye is a challenging case.

The Epithelium Factor

Dan Z. Reinstein, MD, adjunct professor of ophthalmology at Columbia University Medical Center in New York City, and medical director at the London Vision Clinic in the U.K., notes that although the current Food and Drug Administration approval of topography-guided ablation in the United States only allows very limited use of the technology, many surgeons are anxious to use it to treat unhappy patients who have previously undergone refractive surgery. Dr. Reinstein points out that getting the best possible result in these patients can be complicated by the impact of epithelial masking, which evens out small irregularities. For that reason, he and his colleagues are working on performing ablations based on the stromal surface instead of the epithelial surface measured by corneal topography. The refractive results appear to be improved in some eyes.

"Topography-guided treatments work best for therapeutic treatment in cases of decentration and for enlarging small optical zones," says Dr. Reinstein.[1,2] "In general, topography-guided treatments work well for large-area, global irregularities—so-called regularly irregular astigmatism, which the pattern-recognition software in computerized topography can identify. They work less well for irregularly irregular astigmatism—rough or uneven curvature changes that show no recognizable pattern on topography—particularly very localized irregularities. This is due to the masking effect of the epithelium, which acts to compensate for irregularities on the stromal surface. The epithelial compensatory mechanism means that the true stromal surface irregularity is masked from front corneal surface topography. It is important to realize, therefore, that neither topography-guided ablation nor wavefront-guided ablation will ever be a complete solution, because they do not account for epithelial thickness changes. This has largely been ignored up to now, because until recently this data has only been available to a few researchers."

Dr. Reinstein explains that the degree of epithelial compensation present on the cornea is defined by the curvature gradient of the stromal surface.[3,4] "This explains why a topography-guided treatment works well for decentrations and small optical zones," he says. "The majority of those kinds of irregularities will be detectable by topography. This also explains why topography-guided treatments don't work in cases where the irregularity is localized (i.e., the curvature gradient is very high), and in some cases can actually make the situation worse: The epithelium will have compensated for the majority of the irregularity, hiding it from front-surface corneal topography. In these cases, a trans-epithelial phototherapeutic keratectomy procedure is much more effective, as it uses the epithelial thickness profile as a natural masking

This article has no commercial sponsorship.

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IMPORTANT SAFETY INFORMATION

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

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

Systemic exposure of phenylephrine may cause elevations in blood pressure.

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

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

Use of OMIDRIA in children has not been established.

INDICATIONS AND USAGE

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

References: 1. OMIDRIA [package insert]. Seattle, WA: Omeros Corporation; 2015. **2.** Hovanesian JA, Sheppard JD, Trattler WB, et al. Intracameral phenylephrine and ketorolac during cataract surgery to maintain intraoperative mydriasis and reduce postoperative ocular pain: integrated results from 2 pivotal phase 3 studies. *J Cataract Refract Surg.* 2015;41(10):2060-2068.

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Visit www.omidria.com

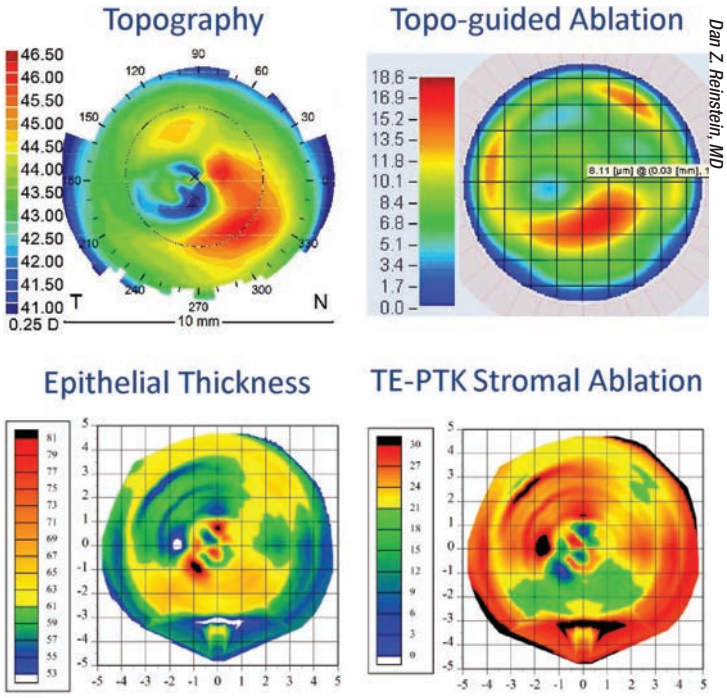
OMEROS

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

agent to focus the ablation onto the peaks in the stroma."[5,6]

Dr. Reinstein notes that surgeons are limited by the manufacturer regarding which topographer they can use to gather the data, but he says it's always important to obtain a corneal tomography scan to map the back surface of the cornea and corneal pachymetry profile. "It's also vital that an epithelial thickness map be obtained in order to appreciate the topography of the stromal surface," he says. "Epithelial thickness maps can be obtained using OCT or VHF digital ultrasound."

Dr. Reinstein says his group recently described the first case where the ablation profile was calculated based on the stromal surface topography.[7] "Paola Vinciguerra, MD, and colleagues are also working in this area using their custom phototherapeutic keratectomy approach, where they treat based on topography scans after removing the epithelium," he notes.[8] "If there are irregularities on the front corneal surface, the irregularities on the stromal surface will always be more severe due to epithelial masking—and it's the stromal surface that we actually need to regularize."



Basing an ablation on the stroma can make a significant difference in the outcome. In this example a patient had an injury to the right eye resulting in a central scar. The front surface topography (top left) is irregular; the topography-guided ablation profile (top right—not including any refractive error correction) indicates that the majority of the ablation should be done in an inferior zone. However, the epithelial thickness map (bottom left) shows that the epithelial thickness is also extremely irregular, as it is partially compensating for the irregularities on the stromal surface; the epithelium varies from 53 to 82 µm (a range of 29 µm) within a 1-mm zone centrally. The map of the predicted stromal tissue removal for a trans-epithelial PTK treatment (bottom right) indicates that the maximum ablation needs to be slightly supero-temporal. The major irregularity on the stromal surface has been completely hidden from the front surface by the epithelium, and would therefore not be included in a topography-guided ablation.

Taking Everything into Account

Arthur Cummings FRCSEd, a consultant ophthalmologist at Wellington Eye Clinic in Dublin, Ireland, notes that the advantages of a topography-guided treatment may soon be overshadowed by systems that also incorporate ray tracing. (Ray tracing is a way to use mathematics to predict how light will move as it passes through different media and strikes different surfaces. Using this technique, a computer can perform very complex analyses of a physical system such as an eye, modeling the impact of different conditions on light transmission and focus. Products currently incorporating this type of technology include Tracey Technologies' iTrace Visual Function Analyzer.)

"Topography-guided treatments regularize the cornea, but we still have to do some work to figure out how the ablation is going to affect the refraction," explains Dr. Cummings. "With ray tracing technology, you don't have to do any of that; the technology does it for you.

"When performing wavefront-optimized or wavefront-guided treatments, no matter how clever our diagnostics and compensations are, the laser thinks it's treating an eye that's 24 mm long and has a corneal curvature of 43 D," he continues. "If the treatment is topography-guided, the laser knows exactly what the cornea looks like, and that's an improvement. But it still doesn't know where the lens is sitting or the length of the eye. So we do our treatments, but occasionally we get surprises. We get surprises because using that model to plan every treatment, with its assumptions about the dimensions of the eye, doesn't make sense.

"Ray tracing technology measures the eye's wavefront, topography and biometry," he continues. "So you now have measurements along the central axis and the line of sight, all the way through the eye. The laser knows the exact location of the front and back of the lens and where the retina is. It knows, for example, that this particular eye is 28 mm long, not 24 mm. It knows where the lens is; it may be more posterior than the other models assume. Using that information, the software creates a virtual model of the eye and uses it to plan the treatment.

"Next, the software performs a vir-

tual treatment on the virtual eye," he says. "Once it has reshaped the virtual cornea, it projects an image into the virtual eye to see how well the rays are converging. If the rays all converge perfectly on the macula, that's the basic ablation profile. However, most of the time the initial treatment plan doesn't end up with the rays perfectly focused. So, the software works backwards, deducing how to adjust the treatment so the rays will all end up correctly focused. It repeats this process until the virtual outcome is perfect, and the light coming into the virtual eye is well-focused on the fovea."

Dr. Cummings says the software does one additional thing that increases the accuracy even more. "An ablation can cause epithelial and biomechanical changes," he says. "Those changes are pretty well described in the literature. So, the ray tracing algorithms include what is expected in terms of epithelial healing and biomechanical response and take that into account in the final treatment plan. This is all fine-tuning, but it's the ultimate level of fine-tuning, where you've thought of everything and you're making far fewer assumptions about the eye.

"So, I believe there is something beyond topography-guided ablation," he concludes. "Topography-guided lasers are fabulous tools, but we can still get refractive surprises. We're hoping that ray tracing will take care of those refractive surprises because it's planning the treatment using the actual measurements of the patient's eye, instead of approximations.

"Alcon is working on this technology right now," he adds. "I think it will become available within the next couple of years."

Dr. Reinstein is a consultant to Carl Zeiss Meditec. Dr. Cummings is a consultant to Alcon Laboratories and Wavelight.

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Making Allergic Conjunctivitis Treatment a Priority

Marguerite B. McDonald, MD, FACS, *and* John D. Sheppard, MD, MMSc

We make treating allergic conjunctivitis a priority by making sure our patients get BEPREVE® (bepotastine besilate ophthalmic solution) 1.5%, for severe itch due to allergic conjunctivitis, and ALREX® (loteprednol etabonate ophthalmic suspension 0.2%), for multiple signs and symptoms of seasonal allergic conjunctivitis.

Ocular allergy affects up to 20% of the US population—more than 60 million Americans.[1,2] Yet in spite of its prevalence, ocular allergy is underrecognized.[1,2] Why?

Perhaps because perennial or seasonal ocular allergies are not blinding. Despite the fact that perennial or seasonal ocular allergies are not blinding, we as ophthalmologists need to recognize allergic conjunctivitis as an important condition to diagnose and treat appropriately.

Conjunctivitis can result in symptoms that may contribute to discontinuation of contact lens wear and interference with surgical outcomes.[3-5]

BY NO MEANS BENIGN

When allergic conjunctivitis inflames the ocular surface, fluid can accumulate in the subconjunctival space. Repeated cycles of inflammation can cause chalasis, subconjunctival hemorrhages, and inhibition of the normal distribution and collection of tears.

When patients with allergic conjunctivitis rub their eyes, they can introduce microbes to the ocular surface, which can lead to other ocular complications.

IMPACT ON SURGERY

A poor quality tear film from ocular surface diseases such as allergic conjunctivitis can affect the accuracy of preoperative biometry, which in turn affects IOL power selection in cataract surgery.[6] Without repeatable, confirmable biometry in our patients, we set ourselves up for refractive surprises and postoperative complaints.

A patient with allergic conjunctivitis will reveal markedly increased tear levels of proinflammatory cytokines—inflammatory mediators that can negatively impact postsurgical healing.[5] In addition, the itch associated with allergic conjunctivitis can provoke eye rubbing, which not only perpetuates the inflammatory process but can also lead to postoperative LASIK flap dislocation.[7]

Ocular allergy is also a risk factor for regression and haze after PRK and can disqualify a patient from LASIK until symptoms resolve.[4,5] Following LASIK surgery, patients with ocular allergies are more likely to develop Sands of the Sahara, or diffuse lamellar keratitis.[8]

DIAGNOSIS

The most common ocular allergy complaints are itching and redness, followed by tearing, lid swelling, and a grey-white stringy mucous. A history of severe ocular itching, or a seasonal itching pattern, almost always indicates allergic conjunctivitis.

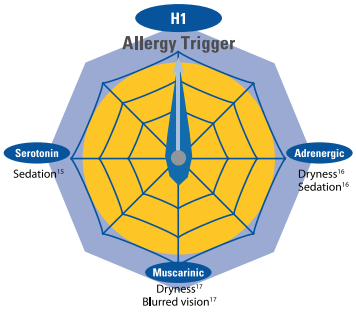
Patients can have a variety of signs, such as injection, chemosis, conjunctival chalasis, lid droop, and red, thickened lids. There is a wealth of information on examination of the everted upper tarsus: conjunctival hyperemia, papillae in the acute phase, follicles in the chronic phase, conjunctival ulcerations in

extreme cases, and conjunctival scarring in chronic cases.

RELIEF OF SEVERE OCULAR ITCH

For acute-phase problems, a selective therapeutic agent with a fast onset of action such as BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% is a good choice.

Bepotastine Does Not Have Significant Binding Affinity for Receptors that May Cause the Following Side Effects[15]



Clinical relevance of in vitro study is unknown. In the clinical safety studies, the incidence of dry eye as an adverse event was 1%.[18]

Figure 1 BEPREVE® is a selective Blocker of histamine (H1).

BEPREVE®, a selective H1 blocker (Figure 1), offers relief in minutes, and has demonstrated efficacy in severe ocular itch.[9] In two double-masked, randomized, placebo-controlled trials, 68% of BEPREVE®-treated eyes (n = 104 eyes) in patients with severe ocular itch achieved complete relief of ocular itch vs 3% of placebo treated eyes (n = 98 eyes) in minutes ($P \leq 0.001$).[10]

Marguerite B. McDonald, MD, is a Clinical Professor of Ophthalmology at NYU Langone Medical Center in New York, NY, an Adjunct Clinical Professor of Ophthalmology at Tulane University Health Sciences Center in New Orleans, and a cornea/refractive surgery/anterior segment specialist with Ophthalmic Consultants of Long Island in Lynbrook, NY. Dr. McDonald is a consultant to Bausch + Lomb; the content of this article is sponsored by Bausch + Lomb.

John D. Sheppard, MD, MMSc, is President and Managing Partner of Virginia Eye Consultants, Clinical Director of the Thomas R. Lee Ocular Pharmacology Center, and Professor of Ophthalmology, Microbiology and Molecular Biology at Eastern Virginia Medical School, and a Medical Director of the Lions Eye Bank of Eastern Virginia in Norfolk, Virginia. Dr. Sheppard is a consultant for Bausch + Lomb; the content of this article is sponsored by Bausch + Lomb.

We also appreciate the comfort BEPREVE® provides to patients. In a 6-week, double-masked, randomized, placebo-controlled trial in which 861 patients received BEPREVE® or placebo, 92% of BEPREVE®-treated patients indicated that they experienced no discomfort (grade 0) on a 0 to 3 ocular comfort scale in an analysis of >6400 assessments of both eyes.[11]

MULTISYMPTOM RELIEF

If the patient presents with more of a chronic phase, is already on an antihistamine/mast cell stabilizer, or has multiple symptoms of seasonal allergic conjunctivitis, we prescribe ALREX® (loteprednol etabonate ophthalmic suspension 0.2%).[12]

We recommend ALREX® for patients with seasonal allergic conjunctivitis because it reduced inflammation and allergic response quickly and effectively and has demonstrated efficacy in itching, burning/stinging, discomfort, foreign body sensation, tearing, and redness.

In two double-masked, placebo-controlled, six-week environmental studies conducted during pollen season (N = 268), ALREX® QID was superior to placebo QID in treating the signs and symptoms of seasonal allergic conjunctivitis. ALREX® provided reduction in bulbar conjunctival injection and itching, beginning approximately 2 hours after instillation of the first dose and throughout the first 14 days of treatment.[13,14]

In addition, in the two 42-day clinical trials, 1 out of 133 patients treated with ALREX® experienced an IOP elevation ≥ 10 mm Hg compared to 1 out of 135 patients treated with placebo.[12]

ACCESSIBILITY

Thanks to copay assistance programs from Bausch + Lomb, eligible patients can limit their copay on either their BEPREVE® or ALREX® prescriptions. Often, we can print coupons while patients are still in the office by going to Bausch.com. Ask your Bausch + Lomb Sales Representative for more information.

Sometimes a patient or pharmacist will inquire about a generic version of BEPREVE® or ALREX®. We let them know that there is no generic equivalent for either medication. Patients need to understand that as their eyecare practitioner, we are aware of the therapeutic options available to treat their condition and have chosen to prescribe BEPREVE® or ALREX® carefully.

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Please see Full Prescribing Information for BEPREVE® and Brief Summary of Prescribing Information for ALREX® on following pages.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use Alrex® (loteprednol etabonate ophthalmic suspension 0.2%) safely and effectively. See full prescribing information for Alrex.

Alrex®

loteprednol etabonate
ophthalmic suspension 0.2%

Sterile Ophthalmic Suspension

Rx only

INDICATIONS AND USAGE
ALREX Ophthalmic Suspension is indicated for the temporary relief of the signs and symptoms of seasonal allergic conjunctivitis.

CONTRAINDICATIONS
ALREX, as with other ophthalmic corticosteroids, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures. ALREX is also contraindicated in individuals with known or suspected hypersensitivity to any of the ingredients of this preparation and to other corticosteroids.

WARNINGS
Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision, and in posterior subcapsular cataract formation. Steroids should be used with caution in the presence of glaucoma.

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution.

PRECAUTIONS
General: For ophthalmic use only. The initial prescription and renewal of the medication order beyond 14 days should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

If signs and symptoms fail to improve after two days, the patient should be re-evaluated.

If this product is used for 10 days or longer, intraocular pressure should be monitored.

Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal cultures should be taken when appropriate.

Information for Patients: This product is sterile when packaged. Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the suspension. If redness or itching becomes aggravated, the patient should be advised to consult a physician.

Patients should be advised not to wear a contact lens if their eye is red. ALREX should not be used to treat contact lens related irritation. The preservative in ALREX, 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 ALREX before they insert their contact lenses.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma tk assay, or in a chromosome aberration test in human lymphocytes, or *in vivo* in the single dose mouse micronucleus assay. Treatment of male and female rats with up to 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (1500 and 750 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender.

Pregnancy: Teratogenic effects: Pregnancy Category C. Loteprednol etabonate has been shown to be embryotoxic (delayed ossification) and teratogenic (increased incidence of meningocele, abnormal left common carotid artery, and limb flexures) when administered orally to rabbits during organogenesis at a dose of 3 mg/kg/day (85 times the maximum daily clinical dose), a dose which caused no maternal toxicity. The no-observed-effect-level (NOEL) for these effects was 0.5 mg/kg/day (15 times the maximum daily clinical dose). Oral treatment of rats during organogenesis resulted in teratogenicity (absent innominate artery at ≥5 mg/kg/day doses, and cleft palate and umbilical hernia at ≥50 mg/kg/day) and embryotoxicity (increased postimplantation losses at 100 mg/kg/day and decreased fetal body weight and skeletal ossification with ≥50 mg/kg/day). Treatment of rats with 0.5 mg/kg/day (15 times the maximum clinical dose) during organogenesis did not result in any reproductive toxicity. Loteprednol etabonate was maternally toxic (significantly reduced body weight gain during treatment) when administered to pregnant rats during organogenesis at doses of ≥5 mg/kg/day.

Oral exposure of female rats to 50 mg/kg/day of loteprednol etabonate from the start of the fetal period through the end of lactation, a maternally toxic treatment regimen (significantly decreased body weight gain), gave rise to decreased growth and survival, and retarded development in the offspring during lactation; the NOEL for these effects was 5 mg/kg/day. Loteprednol etabonate had no effect on the duration of gestation or parturition when administered orally to pregnant rats at doses up to 50 mg/kg/day during the fetal period.

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

Nursing Mothers: It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemic steroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when ALREX is administered to a nursing woman.

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

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

Ocular adverse reactions occurring in 5-15% of patients treated with loteprednol etabonate ophthalmic suspension (0.2% - 0.5%) in clinical studies included abnormal vision/blurring, burning on instillation, chemosis, discharge, dry eyes, epiphora, foreign body sensation, itching, injection, and photophobia. Other ocular adverse reactions occurring in less than 5% of patients include conjunctivitis, corneal abnormalities, eyelid erythema, keratoconjunctivitis, ocular irritation/pain/discomfort, papillae, and uveitis. Some of these events were similar to the underlying ocular disease being studied.

Non-ocular adverse reactions occurred in less than 15% of patients. These include headache, rhinitis and pharyngitis.

In a summation of controlled, randomized studies of individuals treated for 28 days or longer with loteprednol etabonate, the incidence of significant elevation of intraocular pressure (≥10 mm Hg) was 2% (15/901) among patients receiving loteprednol etabonate, 7% (11/164) among patients receiving 1% prednisolone acetate and 0.5% (3/583) among patients receiving placebo. Among the smaller group of patients who were studied with ALREX, the incidence of clinically significant increases in IOP (≥10 mm Hg) was 1% (1/133) with ALREX and 1% (1/135) with placebo.

DOSAGE AND ADMINISTRATION
SHAKE VIGOROUSLY BEFORE USING.
One drop instilled into the affected eye(s) four times daily.

Revised: August 2013.

Bausch & Lomb Incorporated, Tampa, Florida 33637

Based on 9007904-9005504
US/ALX/15/0004 Issued: 02/2015

BEPREVE® (bepotastine besilate ophthalmic solution) 1.5%

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

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

----------RECENT MAJOR CHANGES----------
Contraindications (4) 06/2012

----------INDICATIONS AND USAGE----------
BEPREVE® is a histamine H1 receptor antagonist indicated for the treatment of itching associated with allergic conjunctivitis. (1)

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

----------DOSAGE FORMS AND STRENGTHS--------
Solution containing bepotastine besilate, 1.5%. (3)

----------CONTRAINDICATIONS----------
Hypersensitivity to any component of this product. (4)

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

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

To report SUSPECTED ADVERSE REACTIONS, contact Bausch & Lomb Incorporated. at 1-800-323-0000, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

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3 DOSAGE FORMS AND STRENGTHS
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*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

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

2 DOSAGE AND ADMINISTRATION
Instill one drop of BEPREVE into the affected eye(s) twice a day (BID).

3 DOSAGE FORMS AND STRENGTHS
Topical ophthalmic solution containing bepotastine besilate 1.5%.

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

5 WARNINGS AND PRECAUTIONS
5.1 Contamination of Tip and Solution
To minimize contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use.

5.2 Contact Lens Use
Patients should be advised not to wear a contact lens if their eye is red. BEPREVE should not be used to treat contact lens-related irritation.

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

5.3 Topical Ophthalmic Use Only
BEPREVE is for topical ophthalmic use only.

6 ADVERSE REACTIONS
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 the clinical trials of another drug and may not reflect the rates observed in clinical practice.

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

6.2 Post Marketing Experience
Hypersensitivity reactions have been reported rarely during the post-marketing use of BEPREVE. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a casual relationship to drug exposure. The hypersensitivity reactions include itching, body rash, and swelling of lips, tongue and/or throat.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C: Teratogenicity studies have been performed in animals. Bepotastine besilate was not found to be teratogenic in rats during organogenesis and fetal development at oral doses up to 200 mg/kg/day (representing a systemic concentration approximately 3,300 times that anticipated for topical ocular use in humans), but did show some potential for causing skeletal abnormalities at 1,000 mg/kg/day. There were no teratogenic effects seen in rabbits at oral doses up to 500 mg/kg/day given during organogenesis and fetal development (>13,000 times the dose in humans on a mg/kg basis). Evidence of infertility was seen in rats given oral bepotastine besilate 1,000 mg/kg/day; however, no evidence of infertility was observed in rats given 200 mg/kg/day (approximately 3,300 times the topical ocular use in humans). The concentration of radio-labeled bepotastine besilate was similar in fetal liver and maternal blood plasma following a single 3 mg/kg oral dose. The concentration in other fetal tissues was one-third to one-tenth the concentration in maternal blood plasma.

An increase in stillborns and decreased growth and development were observed in pups born from rats given oral doses of 1,000 mg/kg/day during perinatal and lactation periods. There were no observed effects in rats treated with 100 mg/kg/day.

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

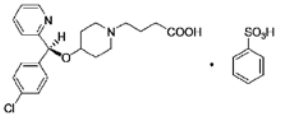
8.3 Nursing Mothers
Following a single 3 mg/kg oral dose of radiolabeled bepotastine besilate to nursing rats 11 days after delivery, the maximum concentration of radioactivity in milk was 0.40 mcg-eq/mL 1 hour after administration; at 48 hours after administration the concentration was below detection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

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

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

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

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



Bepotastine besilate is a white or pale yellowish crystalline powder. The molecular weight of bepotastine besilate is 547.06 daltons. BEPREVE® ophthalmic solution is supplied as a sterile, aqueous 1.5% solution, with a pH of 6.8.
The osmolality of BEPREVE (bepotastine besilate ophthalmic solution) 1.5% is approximately 290 mOsm/kg.
Each mL of BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% contains:
Active: Bepotastine besilate 15 mg (equivalent to 10.7 mg bepotastine)
Preservative: benzalkonium chloride 0.005%
Inactives: monobasic sodium phosphate dihydrate, sodium chloride, sodium hydroxide to adjust pH, and water for injection, USP.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Bepotastine is a topically active, direct H_1-receptor antagonist and an inhibitor of the release of histamine from mast cells.

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

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

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

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

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

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility
Long-term dietary studies in mice and rats were conducted to evaluate the carcinogenic potential of bepotastine besilate. Bepotastine besilate did not significantly induce neoplasms in mice receiving a nominal dose of up to 200 mg/kg/day for 21 months or rats receiving a nominal dose of up to 97 mg/kg/day for 24 months. These dose levels represent systemic exposures approximating 350 and 200 times that achieved with human topical ocular use. The no observable adverse effect levels for bepotastine besilate based on nominal dose levels in carcinogenicity tests were 18.7 to 19.9 mg/kg/day in mice and 9.6 to 9.8 mg/kg/day in rats (representing exposure margins of approximately 60 and 20 times the systemic exposure anticipated for topical ocular use in humans).

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

When oral bepotastine was administered to male and female rats at doses up to 1,000 mg/kg/day, there was a slight reduction in fertility index and surviving fetuses. Infertility was not seen in rats given 200 mg/kg/day oral bepotastine besilate (approximately 3,300 times the systemic concentration anticipated for topical ocular use in humans).

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING
BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% is supplied in a white low density polyethylene plastic squeeze bottle with a white controlled dropper tip and a white polypropylene cap in the following size:
5 mL (NDC 24208-629-02)
10 mL (NDC 24208-629-01)

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

17 PATIENT COUNSELING INFORMATION
17.1 Topical Ophthalmic Use Only
For topical ophthalmic administration only.

17.2 Sterility of Dropper Tip
Patients should be advised to not touch dropper tip to any surface, as this may contaminate the contents.

17.3 Concomitant Use of Contact Lenses
Patients should be advised not to wear a contact lens if their eye is red. Patients should be advised that BEPREVE should not be used to treat contact lens-related irritation.

Patients should also be advised to remove contact lenses prior to instillation of BEPREVE. The preservative in BEPREVE, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of BEPREVE.

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Preparing Your Practice For the Senior Tsunami

Christopher Kent, Senior Editor

The coming wave of elderly patients will necessitate many changes in the average ophthalmology practice.

As the baby boomer generation ages, the number of seniors coming into ophthalmology practices is swelling—and that number is projected to keep growing for years to come. The implications for ophthalmology are enormous.

Here, to help you make the best of these changing circumstances, four surgeons and a practice management expert share their insights on the ways in which these changing demographics will impact disease prevalence; patient flow; the delegation of tasks; individual patient management; and the profession as a whole. They also offer suggestions for actions you may want to take, based on which part of your career you are in today—early, middle or late.

More Seniors, Fewer Doctors

"There are 78 million baby boomers in the United States, and every day 10,000 of them are turning 65 and becoming eligible for Medicare," notes Richard L. Lindstrom, MD, founder and attending surgeon at Minnesota Eye Consultants and adjunct professor emeritus at the University of Minnesota Department of Ophthalmology. "For at least the next 30 years—as far ahead as most of us care about—we're going to see increasing numbers of patients age 65 and older. This is a critical issue for providers, but also for our government because it pays for their care, and the individual over age 65 consumes 10 times as much eye care as an individual under 65. Furthermore, this change isn't just happening in the United States; it's also happening in Europe and China and Japan. This is going to impact ophthalmology significantly."

John Pinto, president of J. Pinto & Associates, an ophthalmic practice management consulting firm, notes that this change will have impacts far beyond ophthalmology. "The oncoming wave of aging patients is affecting all of medicine and all geriatric and peri-geriatric service and product providers," he says. "It's impacting everything from adult diapers to adult care facilities, and everything in between. This is not a new phenomenon—we've been exposed to it for 10 or 15 years now, since the earliest baby boomers starting hitting their majority. However, we're nowhere near the peak impact. People typically get cataract surgery in their early 70s, for example, and it will be another 10 or 15 years before the largest number of baby boomers reach that age."

Dr. Lindstrom notes that the issues accompanying this change will be exacerbated by another shift. "As

the elderly population grows, there will be about 450 new ophthalmology residents graduating every year," he says. "At the same time, if you assume most of us have about a 35-year career, about 550 older ophthalmologists will be retiring each year. That means the number of ophthalmic providers will be declining by about 100 per year—and that calculation doesn't take into account that the current pool of ophthalmologists is top-heavy, meaning that more of us are over the age of 45 than under the age of 45. Today there's a small increase in the number of residency slots every year, but that's not going to have a meaningful impact in terms of the upcoming demographic shift."

Mr. Pinto agrees, noting that while the overall population of America is growing about 1 percent a year, the senior population is growing at about 3 percent a year. "Because seniors require about 10 times as much eye care as younger patients, we've got a 4 or 5 percent annual increase in the demand for ophthalmic care in America," he says. "Meanwhile, the growth rate in the number of ophthalmologists right now is somewhere between flat and 1 percent. This is already causing some serious labor shortages, particularly in secondary markets, leading to a sharp uptick in the number of practices that either can't find a successor doctor or are having to bid salary prices way up. For example, a decade ago a general ophthalmologist might have expected a base salary of $150,000 to $175,000. Those numbers are now in the mid $200,000s and up, and they can be even higher in secondary, rural, Midwestern markets."

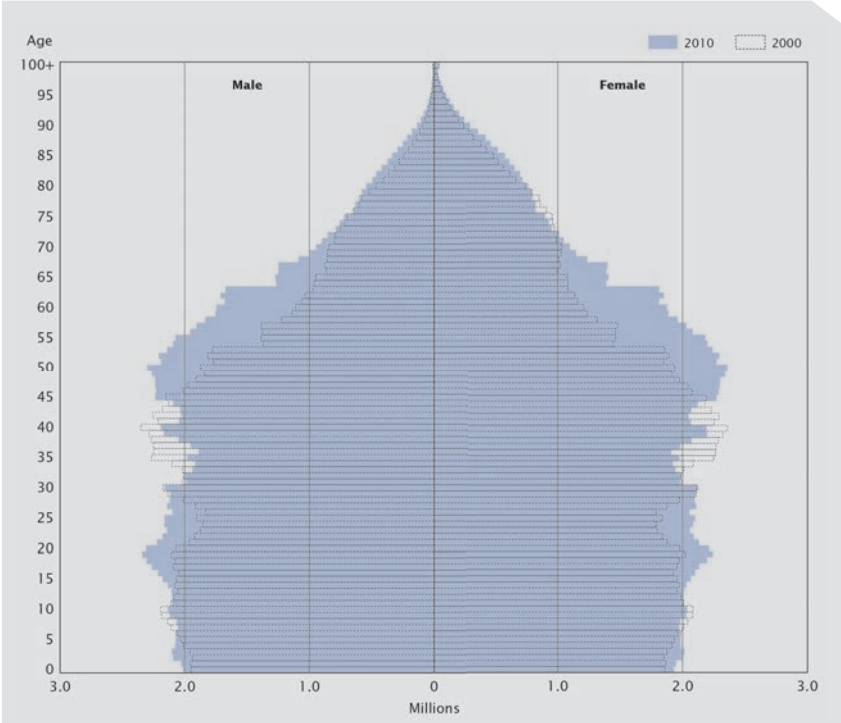
Demographics and Disease

One aspect of this shift that will clearly impact ophthalmologists is a greater need for treatment of diseases most commonly seen in the elderly. Dr. Lindstrom says both practitioners and companies are going to want to be on top of these conditions. "The number-one medical problem is cataract," he notes. "We're doing about 4 million cataract surgeries a year in the United States today, about 11 people per thousand, and that rate is growing at 3.5 percent per year. So, currently about 9,000 cataract surgeons are treating about 4 million cataracts per year. I project that in 20 years—about the middle of the career for residents graduating today—about 8,000 cataract surgeons will be treating 8 million cataracts per year. Those doctors are going to have to be even more efficient than we are today, and the federal government's triple aim of quality care, happy patients and reduced cost is going to pressure them to find some way to manage that.

"The other age-related diseases that will become increasingly important are glaucoma, ocular surface diseases such as dry eye and blepharitis, and what may be the largest group, age-related diseases of the retina," he continues. "That's because diabetes is exploding, along with an epidemic of obesity, leading to an enormous amount of diabetic retinopathy, as well as increases in dry and wet macular degeneration. These are currently quite expensive to treat, since intravitreal injections of anti-VEGF drugs have become the favorite treatment for just about all of these retinal problems."

Dr. Lindstrom believes glaucoma will move from being a medically treated disease to a surgically treated disease. "Drops will decline in importance as glaucoma surgery gets less and less invasive," he says. "Patients will opt for elective surgery as an alter-

Population by Age and Sex: 2000 and 2010



Sources: U.S. Census Bureau, Census 2000 Summary File 1 and 2010 Census Summary File 1.

The baby boomer generation (loosely represented by the bulge around age 40 in the 2000 census data and age 50 in the 2010 census data) continues to move toward the elder age bracket. Combined with gradually lengthening life expectancy, this foreshadows a dramatic increase in patients with age-related eye diseases over the next 10 to 30 years.

The Aging Optic Nerve

When managing elderly patients, it's important to be able to differentiate between disease-related changes and changes that occur naturally with aging. Thasarat S. Vajaranant, MD, associate professor of ophthalmology at the University of Illinois College of Medicine at Chicago and director of the Glaucoma Service at the Illinois Eye and Ear Infirmary, offers some insights into the differences.

"The optic nerve undergoes an aging process that results in a decreased number of retinal ganglion cells and nerve fibers," she explains. "Those changes subsequently lead to reduced visual sensitivity. Imaging with optical coherence tomography typically shows decreasing thickness of the retinal nerve fiber layer and macula with age, and visual field testing shows a corresponding decline.[1,2] Therefore, in clinical practice it's important to use age-appropriate normative data when evaluating optic nerve imaging and visual field testing results. In addition, increased cupping has been documented as a normal part of optic nerve aging. Interestingly, a previous study conducted by [Jovina L. See, MD] and colleagues[3] using the Heidelberg Retina Tomograph demonstrated that, similar to glaucoma, age-related cupping occurs preferentially in the inferotemporal region."

Dr. Vajaranant points out that changes occurring in primary open-angle glaucoma age-related optic neuropathy are similar to those observed in normal optic nerve aging. "Compared to a disease process like glaucoma, changes occur at a much slower rate in normal aging of the optic nerve," she says. "In fact, primary open-angle glaucoma is thought to represent accelerated aging of the optic nerve.[4] Practically speaking, it should take a decade for the thickness of the retinal nerve fiber to decrease by 2 to 4 µm. So if the optic nerve is losing its fibers faster than that—taking into account the variability of the imaging technology you're employing—the change is likely due to a disease process rather than normal aging." Dr. Vajaranant adds that the effects of normal aging generally do not occur suddenly. "Visual sensitivity and contrast sensitivity do decrease over time, but normal aging is a slow process, so patients usually adapt," she says. "Patients should not interpret acute visual symptoms as being part of normal aging."

Asked what advice doctors can offer patients to help slow the aging of the visual system, Dr. Vajaranant says the best advice is to maintain good general and vascular health. "The aging process involves oxidative stress, so a diet rich in antioxidants should be beneficial, at least in theory," she notes. "For example, [Anne L. Coleman, MD, PhD] and colleagues showed that foods rich in antioxidants are protective against primary open-angle glaucoma.[5] However, at present there is no evidence that a high-dose antioxidant supplement will have a beneficial effect on the health of the optic nerve."

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native to drops; it may be third-party-reimbursed or patient-pay. Once we have really safe and effective glaucoma surgeries, a lot of people will just want to have the problem fixed.

"In terms of retinal disease, we'll need to get some of the extended-release options working; having an injection every month is just not feasible in the long run," he says. "It's too expensive and too hard on the families of the patients. We're going to have to get to the point where retinal disease is treated more like glaucoma, where the patient is seen twice a year and gets some form of extended-release medication. That will be more manageable. Otherwise, we won't have enough ophthalmologists to take care of the retinal diseases."

Dr. Lindstrom points out that it will pay to be adept at treating these diseases. "If you know which problems are going to be widespread and you want to be busy, then you should be good at treating those things," he says. "If I were a retina guy, I'd stay on top of the latest treatments for diabetic retinopathy and macular degeneration. If I were a general ophthalmologist, I'd master the latest treatments for cataract, glaucoma and ocular surface disease. If I were a refractive surgeon, I'd be learning to implement the newest surgical alternatives for treating presbyopia. And if I were a company, I'd invest in finding new treatments for those diseases."

Changes in the Office

The coming gradual shift in medical focus will be accompanied by some very practical issues in the office and clinic. Perry S. Binder, MS, MD, clinical professor in the Gavin Herbert Eye Institute at the University of California, Irvine, notes that serving a much larger contingent of elderly people in a practice will necessitate changes in several areas. "Patient education may have to be adjusted to account for the fact that elderly patients may not see as well, hear as well or think as clearly as younger patients," he says. "They may have difficulty with some of our written or audiovisual educational materials. Those materials will have to

be redesigned with elderly patients in mind.

"Then there's the issue of communicating with elderly patients when they're outside the office," he continues. "Scripts for phone calls may have to be redesigned with this in mind. And by what means do you communicate with elderly patients when they're outside the office? Robocalls? Sending videos by mail or computer?

"Another reality is that an increase in the number of elderly patients may cause a major change in patient flow," he notes. "Testing will take longer. The ergonomics of your equipment may need to shift, and your staff may need to be trained to work better with older patients. And of course, there are the financial concerns; the time it takes to see these patients will increase while the reimbursement for seeing them will almost certainly decrease. Who's going to pay their bills? Which procedures will and won't be covered? Will some doctors stop seeing elderly patients because of low reimbursements? I don't know how we're going to come to grips with all of this."

Mr. Pinto notes that with the swelling number of elderly patients and decreasing reimbursements, more ophthalmologists might think about trying to decouple from Medicare and open a cash-and-carry practice that doesn't accept insurance. "In reality, this won't be practical for the vast majority of ophthalmologists," he says. "There are a few very elite ophthalmologists in selected markets who have dropped out of Medicare and are working on a pure cash-and-carry basis, but they are the exception. Sixty percent of the cash flow in ophthalmology comes from patients over 65 who are Medicare beneficiaries, so dropping out of Medicare isn't very practical.

"To put this in context," he continues, "there are about 15,000 active practicing ophthalmologists in America. I'd be surprised if more than 150—1 percent—are making a living by directly charging the patient for geriatric services such as cataract care. That number might increase a little in the future, as there are more and more patients and fewer doctors, but you're not going to see a third of ophthalmologists dropping out of Medicare."

Calling in the Cavalry

One of the inescapable realities of managing an ever-increasing number of patients will be the need to delegate many tasks to others in a practice. "Ophthalmologists 20 years from now will be very busy if they want to be," notes Dr. Lindstrom. "To manage the upcoming patient numbers they'll have to become even more efficient. That will mean lots of jobs for ophthalmic technicians and lots of opportunities for optometrists and maybe physicians' assistants. Ophthalmologists are going to be a scarce resource, and I think that will be a good thing for the field."

Dr. Binder believes that relying more on your staff is likely to become a necessity. "Dental hygienists do a lot of what the dentist used to do," he notes. "I now see a nurse practitioner for most of my routine dermatology needs—often I don't even see the dermatologist. So I think we're going to see a lot more non-medical personnel taking over the basic, mundane clinical tasks such as vision-testing, refraction, topography measurements, fundus photography and so forth, to allow us to handle more patients per unit time with efficiency. In fact, I think this is already starting to happen. Many doctors are making changes in their offices to improve efficiency through better education of patients and staff, and by modifying patient flow and delegating testing to non-doctors."

Carla J. Siegfried, MD, the Jacquelyn E. and Allan E. Kolker, MD Distinguished Professor of Ophthalmology at Washington University School of Medicine in St. Louis, agrees. "We'll have to devise team strategies to provide better care for patients," she says. "I've heard creative suggestions such as having a relatively healthy patient see a physician extender instead of the ophthalmologist once every so many visits. That could cut the physician's load by 25 percent. We'll definitely need to continue to think of new methods to manage this."

This is likely to mean that more practices will be adding optometrists to their staff—a trend that's already evident. "Our ability to provide eye care for every senior is already hitting a wall," says Mr. Pinto. "Practices are responding by adding extenders such as optometrists. I believe that a decade or so from now the typical ophthalmology practice will have one to three optometrists for every ophthalmologist."

This was not the case in the past. "When I started in practice, only about 1 percent of ophthalmologists employed an optometrist," notes Dr. Lindstrom. "Now about 50 percent do. In the future I think every practice will have to be integrated with both MDs and ODs. And because most surgery will be done in an ASC or office, doctors will be looking for ways to participate on the facility side, so to speak, in order to be efficient enough."

Dr. Binder points out that today's optometrists are facing many of the same issues. "They're going to have to handle larger numbers of patients who are living longer with more visual disorders," he says. "I think it's likely that most optometrists will be working with ophthalmologists in order to manage this new reality."

If You're Just Starting Out

Clearly this demographic shift will affect all ophthalmologists who treat seniors, but it's equally clear that the impact will be quite different depending on where you happen to be in

The Lifespan Factor

Carla J. Siegfried, MD, the Jacquelyn E. and Allan E. Kolker, MD Distinguished Professor of Ophthalmology at Washington University School of Medicine in St. Louis, points out another issue that will become more prominent as the patient population in ophthalmologists' offices continues to age: judging how long the patient you're treating may live. It's not uncommon for people to assume that a person in her 90s, for example, may not live many more years, but that assumption could be totally mistaken—especially in the upcoming years, as lifespans will likely increase. "Age-adjusted life expectancy is the subject of a great deal of scientific research," Dr. Siegfried notes. "Meanwhile, many of our treatment algorithms are guided by our ideas about the patient's potential lifespan. This can result in patients being either overtreated or undertreated, both of which can be detrimental to their long-term care.

"For example, I saw a 93-year-old glaucoma patient yesterday," she says. "We had decided we would take a small, non-invasive step and just do a laser procedure to try to control her pressure. But I told her that her disease was so far advanced that I wouldn't completely rule out further, more aggressive treatment to enhance long-term preservation of vision because there was a very good chance she could live another 10 years. She and her daughter looked at me, and then they said, 'You know, you might be right.'

"These are the kinds of important questions we deal with every day," Dr. Siegfried continues. "It's interesting that the health- and life-insurance industries devote a great deal of attention to actuarial science—determining how long people are likely to live—but we don't routinely analyze this information to provide age-appropriate care. We need to improve this aspect of our patient management.

"Of course, we don't want to suggest invasive, risky treatments for patients with a short life expectancy," she adds. "But shouldn't we provide appropriate care for those who do have a high quality of life, even if they're over 80, 90 or even 100 years of age? These are challenging questions as we look at the cost of providing this care, but we must also examine the cost of rehabilitation and long-term care. If someone has multiple falls because of poor vision due to withholding appropriate treatment, and ultimately requires skilled nursing care, that's a huge cost to society."

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your career. "You can think of an ophthalmologist's career as having three stages: the first years, the middle years and the final 10 years," says Mr. Pinto. "For the next several years, if you're in the first third of your career you'll find more jobs available at higher salaries and more patients to take care of—perhaps even more than you're comfortable dealing with. And if you're an ambitious doctor you'll have as much opportunity to provide surgical care as you'd like. This means you'll be able to climb up the learning and experience and skills curve faster than the previous generation, and you'll be more likely to find a satisfactory professional setting."

"My advice to young doctors who are just starting out and choosing a specialty," says Dr. Binder, "would be to understand how the field is going to change, what kind of patients you're going to treat in a given subspecialty and how many elderly patients you're going to see, keeping in mind that reimbursements will go down significantly over the next five to 10 years. You'll have to figure out what subspecialty within ophthalmology will make you happiest. Then I would suggest that you spend time with doctors in that subspecialty to see how they're handling these large volumes of people, such as the repeat cases that need intravitreal injections for macular degeneration and diabetics who need regular retinal treatments and follow-up exams and fluorescein angiograms. Glaucoma specialists also will be dealing with many repeat visits from elderly patients.

"Once you decide that a specialty will work for you, you need to consider whether you want to start your own practice or join a group that can handle this huge number of patients more efficiently," he continues. "I believe we're going to see more of that. I think the private practitioner is largely going to disappear, except for the carriage-trade ophthalmologists—and I think the carriage trade is going to be a very small segment of ophthalmology."

What about career options such as research and academia? Mr. Pinto believes the surplus of job openings may lead fewer young ophthalmologists to choose those options. "There will be plenty of patients to take care of," he says. "Young ophthalmologists won't feel the need to seek out an alternate career. Anybody who wants to be a busy geriatric ophthalmologist today, assuming he's in a decent market, is going to be as busy as he wants to be."

Middle to Late Career

Mr. Pinto notes that the impact of the demographic shift on ophthalmologists in the middle or later parts of their careers will be somewhat different. "If you're in the middle third of your career, roughly in your 40s and early 50s, you need to stay ahead of the curve and anticipate the need to bring on additional ophthalmologists," he says. "Anticipating this before the need becomes dire is important because the replacement cycle time isn't six or nine months the way it used to be. Depending on where you work and live, it may take a year or two—

maybe even three years—to find the next ophthalmologist to join your practice. You should also be prepared to pay more to hire a partner-track associate. The good news is that you're going to have an increasing amount of work for the new doctor to do so you won't have to carry him as long, and the higher base salary should be affordable.

"If you're in the final third of your career and you're starting to think about succession planning, the watchword is to plan as far in advance as you can, because it's getting harder to find new owner-track associates to come in and take over a practice," he continues. "There are fewer doctors and more openings, so an increasing number of doctors who are looking for a succession plan are turning to their nearby friendly competitors for a buy-out rather than going the old route of bringing in a young doctor and grooming him or her for a takeover.

"Also, when you're doing your personal financial planning, don't assume that you'll get anything more than salvage value for your equipment, or much credit for the residual value of your accounts receivable and working bank accounts. You should also expect to have little or no good-will value. Of course, this won't be true in every case, but the point is that when you're planning your retirement and making assumptions about your retirement funding, don't be too optimistic about what you're going to be able to extract from your practice.

"Understanding the nature of this shift is also very important if you own the building you practice in, because it's becoming increasingly difficult to find young doctors who are willing to come aboard, buy your practice and also take the risk of paying a hefty price for the real estate," he says. "Fortunately, your building's value will be based on the local real estate market as much as anything else, because most medical buildings can be repurposed and taken over by an accounting firm or law firm or architectural firm. Either way, it all comes down to the need for advance planning and greater effort when it's time to start pulling the trigger on these things."

Tips for Managing Seniors

In addition to an increase in the prevalence of certain diseases seen in many practices, the growing number of elderly patients will necessitate some changes in the way doctors interact with patients. Dr. Siegfried lists some things to keep in mind:

• ***The new crop of senior citizens will have different expectations.*** "They certainly will expect to remain active—even more so than current elderly patients," she says. "They won't just want to play golf, they'll want to continue driving a car and having high-quality lives."

• ***Patient perception of age may be an issue.*** "I've seen people make poor decisions in the management of their disease, against our advice, simply because they have false preconceptions about being old," says Dr. Siegfried. "They may assume that their illness is a normal part of aging, for example, and therefore should be suffered rather than treated. We need to be certain that patients understand that age and illness do not necessarily go hand in hand."

• ***Low-vision aids will become even more important.*** "With elderly patients becoming an increasingly large part of our patient population, helping patients do more with what they have will need to become a major part of the services a practice offers," she says. "Thanks to readily available devices like computers and tablets allowing people to alter font size and contrast, technology should play a big part in this."

• ***We may have to rely less on functional testing.*** "Very elderly patients often have a shorter attention

span, slower reaction times and more difficulty concentrating," notes Dr. Siegfried. "Until better visual-function tests come along, we may have to rely less on these tests with our oldest patients."

• ***Side effects of your prescriptions may have greater impact on a very elderly person.*** "Some of the medications we prescribe can have a profound effect on systemic circulation, blood pressure and mental status," notes Dr. Siegfried. "Some eye drops can affect a patient's level of energy significantly, leading to a greater risk of falling. This can certainly affect the patient's quality of life and ability to get out and interact with others.

"Medications like beta blockers, for example, can cause fatigue and dizziness and alter blood pressure," she continues. "I saw an 82-year-old patient yesterday who would take his drops and then would have to go and take a nap because he got so tired. His energy and activity dropped significantly, and he'd never had this problem until he began using the drops. I told him to stop the drops. These issues will become increasingly important with the aging of our patient population."

• ***Interaction with the patient's primary-care physician will be much more important.*** Dr. Siegfried notes that the kind of problem discussed above necessitates good communication between physicians. "We'll have to be increasingly vigilant about making sure the primary-care doctor knows about the systemic side effects of the topical medications that the patient is using, and vice versa—we'll need to be aware of the effects of any systemic drugs the patient is taking."

• ***The choice between medication and surgery involves different factors in the very elderly.*** "It's legitimate to have concerns about performing surgery on a very elderly patient," says Dr. Siegfried. "The tissues are more fragile and anesthesia risks can be more serious. On the other hand, medications come with their own potential problems; they have side effects, and the patient may have more difficulty using drops properly due to memory problems, arthritis and difficulty keeping track of multiple medications. There is no simple answer regarding what's best. You must consider each individual and determine where the greatest benefit and lowest risk lie."

Dr. Siegfried points out that if you do take a very elderly patient to surgery, you want to make sure you get the most out of it. "Some of the newer procedures sound very promising in terms of their safety profile, but they may have a lower likelihood of long-term success," she says. "With a younger patient, a lower-risk procedure may be appropriate because you can always bring the patient back into the OR; but with an elderly patient the bigger risk may be taking the patient to the OR again. So, you want to be sure you do what you need to do while you're there the first time."

• ***Be on the lookout for existing consequences of previous years of medication use (such as drops).*** "Preservatives may have altered the tissue, causing chronic inflammation and irritation," notes Dr. Siegfried. "That can definitely cause issues with wound healing and scar tissue. It's important to be prepared for this and potentially pretreat with anti-inflammatory medications."

• ***Be aware of the issue of dual sensory impairment.*** Dr. Siegfried points out that many elderly patients already have lost all or part of another sense such as hearing. "It's been shown that impairment of two senses can have an exponential effect on your functionality," she says. "Many of our elderly patients are hearing-impaired. If they start to lose their vision, the problems they are having may increase dramatically, as they are more likely to withdraw from the world."

Dr. Siegfried says this makes it important to urge family members to address other sensory problems that are not vision-related. "Sometimes I have to virtually yell at a patient in the office because he can't hear me," she says. "I'll turn to the family member and say, 'Have you thought about getting your grandfather a hearing aid?' The family member will say, 'Oh no, he doesn't want to do that.' I explain that he really does need to do that. Sometimes hearing it from a doctor will get them to take action. In fact, some practices have an audiologist on staff. Having this service available may become increasingly important as your patient population gets older."

Dr. Siegfried says this concern extends to non-auditory problems as well. "If the patient is stumbling, you might suggest getting a walking aid," she says. "A lot of people are very resistant to using a hearing aid or walker, but you may discover the patient has fallen three times in the past month. The family may say the patient is stubborn, but when she breaks her hip, she could require surgery and/or extensive rehabilitation, or perhaps be confined to a wheelchair. So you may have to strongly encourage the patient and family to take the needed steps.

"Vision loss is also more serious if a patient already has some level of dementia," she adds. "Losing vision can make people become more isolated socially, affecting how they interact and how engaged they are, causing the dementia to worsen. At the same time, I've seen a relative reversal of some aspects of dementia when we provide better vision because the individual can interact more easily with the world around him."

• ***Develop a standard protocol for involving the family when elderly patients need assistance.*** "Having the family involved is critical, especially when you're making decisions about taking the patient to

surgery," says Dr. Siegfried. "Family members can help to reinforce not only what the patient needs to do after surgery, but help the patient prepare for it mentally.

"In general, family members need to understand as much as they can about why we're doing what we're doing," she adds. "For example, in our practice we have charts that we give to both the patient and family members with written information about the patient's daily medications and the time they should be instilled. This includes a form that shows the color of the cap of each medication bottle."

• ***Older patients sometimes are more reluctant to ask for help when a problem occurs.*** Take preemptive action to avoid this. "This is partly an education issue," notes Dr. Siegfried. "Let elderly patients know it's important to contact you if they need help, and that someone is available 24/7 to answer their questions or to see them. Then, make it easy for them to call. This will be especially critical for any ophthalmologist who performs surgery."

The Future, for Better or Worse

Given the multitude of changes coming down the pike, some ophthalmologists are optimistic; others, not so much. Dr. Binder is concerned about how medicine is going to be delivered in the next five to 10 years and beyond. "I know there are some ophthalmologists who believe this population shift will be a fabulous opportunity, with so many people needing cataract surgery," he says. "But on the other hand, who's going to pay for it? How are we going to deliver the best care for these patients? Yes, we'll have new technologies, new medications, stem cells and a better understanding of genetics to help prevent a lot of the disease that we see today. There's no question that people will live longer and have better-quality lives because of those advances. But where will the money for ongoing R&D come from? Those sources are drying up. Meanwhile, it's very frustrating to not be able to prescribe Restasis, for example, when its probably the best treatment for a given patient, just because we can't get reimbursed for it."

Dr. Binder notes that the current environment is also making American surgeons the last to have access to new technologies and medical treatments. "Companies are moving overseas to get away from our tax structure," he says. "As a result, Americans are getting further and further behind the technology curve. In the past I was able to personally introduce new technologies to doctors in Japan and France and South America. Now, that's totally reversed—companies are releasing products outside the United States first. We're not getting these technologies until three to five years after the Europeans and South Americans get them. Our health care is suffering as a result, and this may not bode well in terms of managing the coming demographic shift."

Dr. Lindstrom's view is somewhat more optimistic. He notes that things have changed dramatically since he first went into practice, and those changes are likely to continue. "I'm coming to the end of my practice years," he says. "But consider what we were doing when I started. We had to hospitalize a patient for cataract surgery, which was invasive surgery, one procedure per hour. Patients spent four days in the hospital and then were fitted with a contact lens or aphakic spectacles. Today, this is outpatient surgery, 90 percent of which is done at an ambulatory surgery center. Now we do two to three cases per hour, on average, and if you look at inflation-adjusted fees, we're doing it for about 10 percent of what it cost 40 years ago.

"Looking ahead, it seems clear that things are going to continue to move in that direction," he says. "We'll prob-

ably transition from ASCs to office surgery centers; most of the surgeries will be done in, or adjacent to, a doctor's office. We'll be doing bilateral, same-day sequential cataract surgery. Instead of drops, doctors will use an injection or implant to prevent infection and inflammation. There will be fewer postoperative visits to the office, and I think many of the postoperative visits that do take place will be virtual. We'll have apps that can check your vision, refraction and visual field, take an external eye photo and fundus photo, and maybe even do optical coherence tomography. Basically, our patients will sit at home and do their own vision and refraction.

"Our ability to generate good outcomes with cataract surgery will continue to grow, and that will lead to patients having their surgery at younger and younger ages," he continues. "As the government gradually increases the age of eligibility for Medicare, those two factors will eventually lead to cataract surgery being done below the Medicare age. That will relieve the government of a large financial burden (and help to get the government out of our hair). Meanwhile, I believe the fee-for-service model that we know today will gradually disappear. There will be some form of population management; we'll be given a group of patients to take care of who are prepaid for basic eye care. At the same time, patients will have to share more of the responsibility for their eye care, leading to more of the patient-pay model. I think patients will be able to choose premium options and the like more easily than they can today. That will be a plus.

"I think the changes we're seeing today will accelerate," he concludes. "Those of us who started 30 or 40 years ago couldn't have imagined the things we're doing today, and those who are starting today can't imagine what they'll be doing in 20 years. But whatever happens, we'll have to provide very high-quality care and outcomes because we're going to continue to have very demanding patients, and they're going to be evaluating us. We'll need to ensure that they go away satisfied and, in general, the cost of intervention will have to go down. But we've managed this amazingly well over the past 30 or 40 years. We're much more efficient than we were; we have better outcomes and happier patients than we did back then. It's true that many of today's treatments don't generate as good an outcome as they should, and some are not cost-efficient. But they will become better in the future." REVIEW

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A Modest Proposal: In-Office Cataract Surgery

Walter Bethke, Managing Editor

Surgeons are trying to answer questions about safety, regulation and reimbursement.

To some surgeons, cataract surgery is a victim of its own success. The worry is that since many cataract cases can be performed in about 12 minutes or so, and still yield excellent outcomes, regulators and payors will view them as a routine procedures and devalue the surgical intensity and skill involved. Other surgeons, however, note the procedure's sophistication, speed and generally good outcomes and see them as signs that the procedure can now be done in different venues, such as the ophthalmologists' office, free of unnecessary regulations that don't really apply to the modern cataract procedure. It's against this backdrop that the Centers for Medicare & Medicaid Services has begun mulling the possibility of reimbursing surgeons for in-office cataract surgery.

In this article, ophthalmic surgeons and their professional societies share their views on, and experiences with, in-office cataract surgery.

CMS's Proposal

In a July 2015 proposal to provide special reimbursement for in-office cataract surgery, CMS mused that the time may be right for the modality, and requested comments from interested parties. Organizations such as the American Academy of Ophthalmology and the Ophthalmic Outpatient Surgery Society made sure their voices were heard, and called for more analysis.

The upshot of the CMS proposal is that cataract surgery usually uses local or topical/intracameral anesthesia, and has advanced to the point that it's not only quick but also yields very good outcomes. "We believe that it is now possible for cataract surgery to be furnished in an in-office surgical suite, especially for routine cases," the proposal states. CMS says the benefits of in-office surgery are convenience for the patient and doctor, and that, " … furnishing cataract surgery in the non-facility setting could result in lower Medicare expenditures for cataract surgery if the non-facility payment rate were lower than the sum of the [physician fee schedule] facility payment rate and the payment to either the ASC or hospital outpatient department."

After reading CMS's proposal, ophthalmic organizations began to work together to try to present a rational approach for in-office surgery to the agency. Bloomington, Minn., surgeon and president of the Outpatient Ophthalmic Surgery Society, Y. Ralph Chu, says, in effect, the devil will be in the details when it comes to CMS de-

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termining what a properly equipped in-office suite will look like. "It's not just transitioning surgery into an in-office surgery suite which, right now, is very unregulated," he says. "Cataract surgery is a success story because it is performed in a highly regulated setting. We have serious reservations about whether an office-based surgical suite can deliver current outcomes and ensure patient health and safety. The ASC environment encompasses state-of-the-art equipment, instruments, systems and protocols; as well as surgeons, anesthesia professionals, and clinical staff trained in the special needs of ophthalmic patients and capable of addressing emergent needs. There is essentially no regulation of office surgical facilities by the feds or the states."

Michael Repka, MD, medical director of government affairs for the American Academy of Ophthalmology, says the AAO also sees the need for more clarity before jumping onboard with the proposal. "How do we certify the office surgical suites?" he muses. "It's not clear how we would make sure they're safe enough for this procedure. You'd probably want to study it in some way to understand that. It's difficult for a spokesman to say 'regulation is good,' but maybe there is some level of regulation that would be appropriate in order to avoid the patient getting substandard care."

All images: Andrew Shatz, MD

Surgeons at SightTrust Eye Institute in Sunrise, Fla., built an in-office cataract surgery suite that features a five-bay post-anesthesia care unit.

Learning from Experience

For years, the discussion about the right way to perform in-office cataract surgery was academic, but now there are several ophthalmology practices actually performing in-office cataract procedures on a regular basis. It's possible that ophthalmic surgeons can use these practices' experiences as rough guides regarding the possible pros and cons of in-office surgery.

Kent Stiverson, MD, of Lakewood, Colo., is an ophthalmologist in the Kaiser Permanente Health system. Kaiser is a Medicare Advantage provider, which means the health system is capitated, and is paid a flat fee up front each month for a patient's diagnosis, no matter what treatments or exams Kaiser's physicians perform. In such an instance, since you're being paid a set amount per patient, it pays to be as efficient as possible, and Dr. Stiverson says, in his experience, in-office cataract surgery allowed Kaiser to provide good care without the large initial investment and overhead involved with a certified ASC. He and his colleagues have now performed 44,000 in-office cataract cases, which, he's quick to note, haven't resulted in even one case of endophthalmitis. What's more, he and his colleagues published an article on their outcomes from 21,501 in-office surgeries (performed between 2011 and 2014 in three offices) in the April 2016 issue of *Ophthalmology*, shedding light on how they made it work in case a surgeon were considering it for his practice.

Dr. Stiverson's study describes the surgical setup in the three office minor procedures rooms: There are two advanced cardiac life support-certified registered nurses (one circulating and one monitoring/charting) and a tech assisting. There is no anesthesiologist, and no IV lines or injections are routinely used. Only topical anesthesia, with occasional intracameral anesthesia, is administered, sometimes accompanied by oral triazolam.[1]

In terms of results, postop mean best-corrected visual acuity was a little less than 20/25. Intraoperative adverse events included capsular tears (n: 119, 0.55 percent) and vitreous loss (n: 73, 0.34 percent). Postop AEs included iritis (n: 330, 1.53 percent), corneal edema (n: 110, 0.53 percent) and retinal tear or detachment (n: 30, 0.14 percent). Repeat surgeries were performed in 0.70 percent of the eyes in the first six months postop. Dr. Stiverson says, though it's in-office surgery, it's not some dank back room. "It might conjure up the image that you'll just go to your exam room next door and start removing cataracts," he says. "We would reject that completely. Our minor procedures rooms are nicer than most people's [Medicare-certified] centers." Dr. Stiverson adds, however, that not all Kaiser's ophthalmic surgeons operate in the in-office suites. "We did have a couple of doctors who weren't comfortable

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if they didn't have an anesthesiologist with them," he says.

While Dr. Stiverson was doing Medicare cataracts in their offices, two surgeons in Florida were using their in-office suite to perform elective premium cataract surgery.

Andrew Shatz, MD, and his partner Cory Lessner, MD, at SightTrust Eye Institute in Sunrise, Fla., built their in-office suite because the square footage they had for a two-OR setup didn't meet Medicare certification for an ASC. They also wanted to shift their practice away from Medicare-reimbursed procedures and toward fee-for-service, premium cataract surgery. Their in-office suite, which they built from the ground up, consists of two ORs and a post-anesthesia care unit.

The specifications SightTrust used for their in-office OR show how the concept of in-office surgery is still in flux. While there is no governing body that certifies in-office surgical rooms, making it possible in some states to build one to the standards that a surgeon feels are proper (as Kaiser did), a practice can also pursue certification by the Accreditation Association for Ambulatory Health Care, which was the path taken by SightTrust. Certification by AAAHC has a reputation as being strict and expensive, since there are more regulations to follow and physical plant changes to implement, but some surgeons like the extra layer of protection the certification implies. "We got certification by AAAHC, and follow all the strict standards imposed by Medicare for safety reasons more than anything else," Dr. Shatz explains. "We hired a nurse administrator to oversee everything, and we bring in another RN and two anesthesiologists on surgical days. The rest of our staff is from the clinic side who are trained in surgical assistance."

Questions at Issue

When the topic of in-office surgery comes up, certain aspects of it become the focal points of criticism. Here's a look at the consensus of organized ophthalmology on these issues, as well as how they're being dealt with at existing in-office ORs.

• ***Anesthesia.*** The CMS proposal somewhat minimizes the anesthesia that patients get in most modern cataract surgery cases, implying that intravenous sedation isn't really necessary. "CMS missed an entire component of patient management which, for many elderly patients and patients in general, does include some sedation beyond the topical drops," says Dr. Repka. "I would think that, for most, it's far more comfortable to have surgery with sedation, and it's probably safer. You never know when things are going to go badly."

Dr. Stiverson says, in his experience and as shown by his study, minimal or no sedation works well. "We have no interest in igniting a debate between in-office surgery vs. ASCs, and I'd note that Kaiser also has certified ASCs," he says. "But currently we've had fewer postop issues, including fewer falls, than in the ASC because people aren't as sedated as they used to be. We actually had more hospital admissions when we were operating in a certified environment than when we went to the office environment. Now, a lot of our patients either get no sedation or a little triazolam."

Dr. Shatz agrees that cataract surgery can be done without IV sedation if patients are well-prepped, but, he adds: "I really believe non-IV sedation increases risk. You don't know how uncomfortable a patient is, and there's more sensation in the eye than one would think; even with injecting 1% lidocaine you're not deadening everything. There's a pressure sensation and light and shadows a patient doesn't understand." He says he uses IV sedation in around 95 percent of his patients.

• ***Infection control.*** In-office surgeons say certified Medicare ASCs have to abide by certain regulations that are expensive and unnecessary for performing cataract surgery effectively, such as firewalls built to last multiple hours, mandatory overhangs over exit doors, interpreters, laboratory service agreements and mountains of logbooks that need to be maintained. What these surgeons don't scrimp on is infection control. Boulder, Colo., ophthalmologist Mark Packer, who co-authored the Kaiser study, says the safeguards don't need to break the bank. "You need a clean room," he says. "This is a separate room, usually connected to the OR, that has sterilization facilities. It should have an autoclave, and a separation between the dirty side and the clean such as a wall or plastic partition. On one side are the dirty instruments with facilities to wash and sterilize them. From there, they're put on the clean side. There are also ventilation requirements in the OR and clean rooms to avoid negative pressure that could suck contaminants in."

Dr. Stiverson says Kaiser's minor procedures rooms take infection control seriously. "We don't flash sterilize anything," he says. "When I operate, I do 22 cases in half a day, and have 25 separate cataract trays. Everything gets full-cycle sterilization. Once a month, we have the ORs swabbed to check for contamination, just as they do it in a hospital or ASC. There are also positive air exchangers in the OR."

Dr. Chu says, however, that deeming certain regulations as unnecessary might be shortsighted. "I'm not sure what is unnecessary." Dr. Chu says. "The Medicare ASC conditions for coverage include rigorous standards for infection control, environment, *Life Safety* and anesthesia. There are no such detailed standards for office surgical suites in any specialty and CMS doesn't appear to be interested in developing them."

• ***Patient comorbidities.*** OOSS believes cataract patients have more

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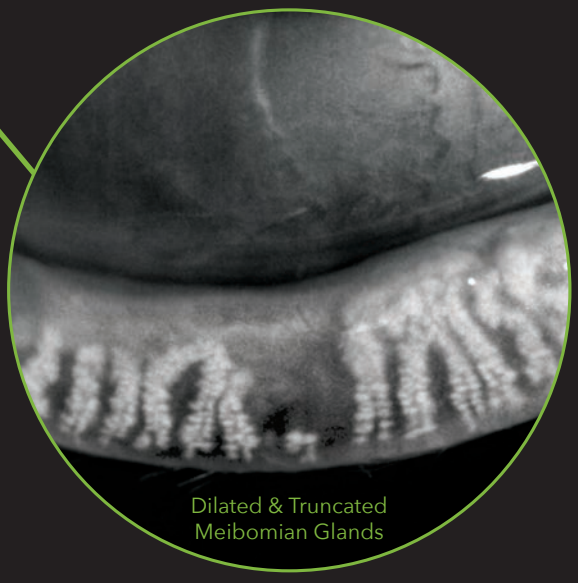

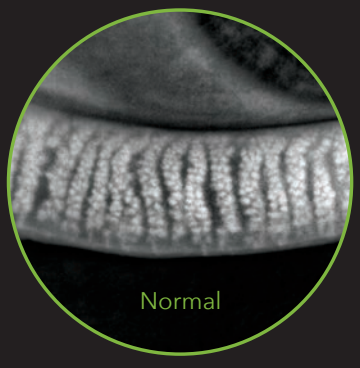

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comorbidities than CMS seems to believe, and Dr. Chu says OOSS is surveying its members on this and sharing its findings with CMS. The idea is that this has a direct impact on characterizing most cataract cases as "routine." Specifically, in a 2015 OOSS survey of 170 ophthalmic ASCs cited in OOSS's response to the CMS proposal, only 6 percent of the cataract patients presented with no comorbidities (which included hypertension, cardiovascular disease, pulmonary disease and cancer). Eighty-eight percent of the patients had two or more. The organization believes these stats should be taken into account when and if CMS determines what safeguards an in-office OR needs. Along these lines, one aspect of the Kaiser paper that stood out was that two of the in-office suites were connected to a hospital, and the third was a little less than a mile away from a hospital. "The Kaiser facilities are located in larger settings proximate to emergency care and meet institutional standards for staffing, infection control and physical plant, to name a few," Dr. Chu says. "Independent ophthalmic practices that elect to perform cataract surgery aren't presently subject to any of these requirements."

Dr. Packer says there is a spectrum of comorbidities that can accompany a cataract surgery case that presents to an ophthalmologist, and in-office centers would have to do the cases they're comfortable with. "A lot of the risk if the patient is sick with chronic obstructive pulmonary disease, diabetes or coronary artery disease actually comes from the IV sedation," he says. "The surgery itself isn't a huge impact on someone, even if he isn't in tip-top shape. But there is a spectrum, and I think everyone could draw a line at his own comfort level. For the high-risk cases, there will always be a hospital."

Surgeons say in-office cataract surgery suites, when built properly, can resemble ambulatory surgery centers.

• ***Financial issues.*** Though patient safety is foremost in everyone's mind, questions swirl regarding the economic impact of shifting procedures into the office. Dr. Packer says this shift might be worrisome to ASC owners. "In-office cataract surgery looks interesting to Medicare if an office can achieve the same safety and effectiveness as an ASC without having to pay for such things as anesthesia services, for example," says Dr. Packer. "Of the facility fee Medicare pays to an ASC for cataract surgery, which is roughly $1,000, $150 of it is for the IOL and the rest is for everything else, such as the numerous employees, firewalls, bigger parking lots, et cetera. It's very expensive. In the office, there's some overhead, but it's much less than an ASC. So Medicare is thinking if the surgery can be done safely in the office, maybe it doesn't need to pay the $1,000 facility fee anymore. The amount it will pay is the question, though.

So, if I own an ASC, all of this worries me," Dr. Packer continues. "Because now there's pressure from both sides: Physicians and patients enjoy the convenience of in-office surgery and the group paying for it is saying, 'Patients and surgeons like it and I can get it for less.' " The one consolation for ASC owners is, currently, surgeons who operate in the office only receive a surgeon fee from CMS, roughly $750—$150 of which is for the IOL—and no facility fee, so Dr. Packer says this would be a "very tough breakeven point" to just do Medicare cataracts in the office. However, if a surgeon can build a premium in-office IOL practice, in which he gets $3,000 to $5,000 per eye, the numbers work.

Dr. Repka says there's another reimbursement concern. "CMS could lower the reimbursement for in-office cataract to a point where it wouldn't be reasonable to do the service there, but surgeons could get forced to do it that way," he says. "That has to actually come down to an arcane payment policy called the indirect expense for an office vs. a certified facility. The infrastructure you need for a clinical exam in your office, for example, might be less than what you need to run an in-office surgery suite, but CMS might keep the indirect expense for both services exactly the same. It would be inappropriate if CMS were to use the same indirect expense value for both services."

Dr. Chu says OOSS recognizes that its members have a significant investment in their surgery centers, but says that's not what drives OOSS. "It's not about trying to increase the level of regulations on in-office surgery just to protect our investment," he says. "What it's about is if surgery starts happening in different environments, and the outcomes aren't the same as those in ASCs or hospitals, it gives the whole industry a black eye. My sense from the membership is that protecting how much money they've put into their surgery centers isn't the first, second or even third argument they're making about the issue. The sense I get is it's really about patient safety." REVIEW

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Dry Eye: What's New in Diagnostics & Treatment

Michelle Stephenson, Contributing Editor

Empowering technicians is the key to assessing every dry-eye patient in your practice.

Dry eye affects an estimated 25 million Americans, and tears were once the only available treatment. Today, a variety of diagnostic and treatment options are available, allowing ophthalmologists to customize treatment for patients.

"We can quickly get our patients to the best treatment regimen possible by honing our diagnostic skills with the many new point-of-service diagnostic tests available, allowing us to differentiate between the different forms of ocular surface inflammation and dry eye," says John Sheppard, MD, professor of ophthalmology, microbiology, and molecular biology at Eastern Virginia Medical School and president of Virginia Eye Consultants in Norfolk.

Robert Latkany, MD, founder of the New York Eye and Ear Infirmary's Dry Eye Clinic, agrees. "We need to not treat every patient with the same regimen. True ocular surface specialists need to think outside the box, because people have different reasons why they are dry. That's why there are various approaches to treatment. I still go with the theory that I will try certain things on patients, one or two at a time. If they work, I continue. If they don't, I stop them and move on to my next option," he adds.

All images: Karl Stonecipher, MD

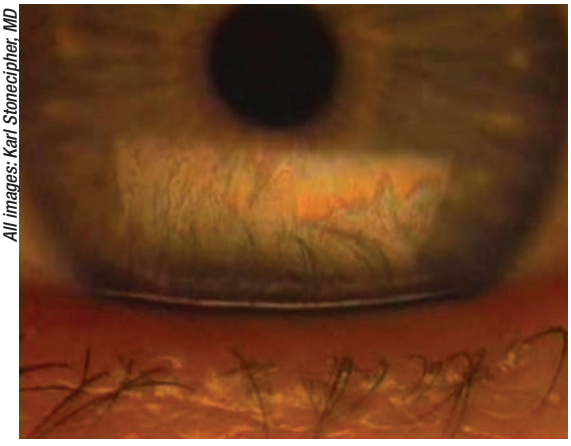

Figure 1. Evaporative dry eye can greatly influence the oils of the tear film layer secreted by the meibomian glands.

Diagnosis

There have been many advances in diagnostics in recent years. "The tear osmolarity test is one of the more commonly used point-of-care testing modalities available," Dr. Latkany says. "There are varying opinions on it because of its extreme variability in measurement, but the bottom line is that it is available, and there is a reimbursable code for it.

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

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

Potential for Cross-Sensitivity

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

Increased Bleeding Time

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

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

Keratitis and Corneal Reactions

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

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

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

Contact Lens Wear

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

ADVERSE REACTIONS

Clinical Trial Experience

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

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

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

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis and Impairment of Fertility

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

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

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

PATIENT COUNSELING INFORMATION

Slowed or Delayed Healing

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

Sterility of Dropper Tip

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

Concomitant Use of Contact Lenses

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

Concomitant Topical Ocular Therapy

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

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It is not very expensive, and it can offer some information for diagnosticians."

Because the preoperative condition of the ocular surface can have an effect on postoperative outcomes, it is helpful to know if a patient has dryness before proceeding with cataract or refractive surgery. "Having these kinds of machines would help to prevent your possibly missing an asymptomatic dry-eye patient who may not say or know that she has dry eye," Dr. Latkany says.

Rapid Pathogen Screening has the matrix metalloproteinase test, which is like a pregnancy test for detecting this inflammatory marker in the tear film. "It is nonspecific, but it can tell us if there is inflammation present in the tear film, and it can add some value in the potential diagnosis of certain ocular surface disease conditions. It is pretty simple to do, pretty inexpensive and sometimes reimbursable," Dr. Latkany notes. Another diagnostic option is LipiView (TearScience), which can help detect irregularities on the corneal surface. "These machines are especially helpful to physicians who don't know a lot about ocular surface disease," he adds.

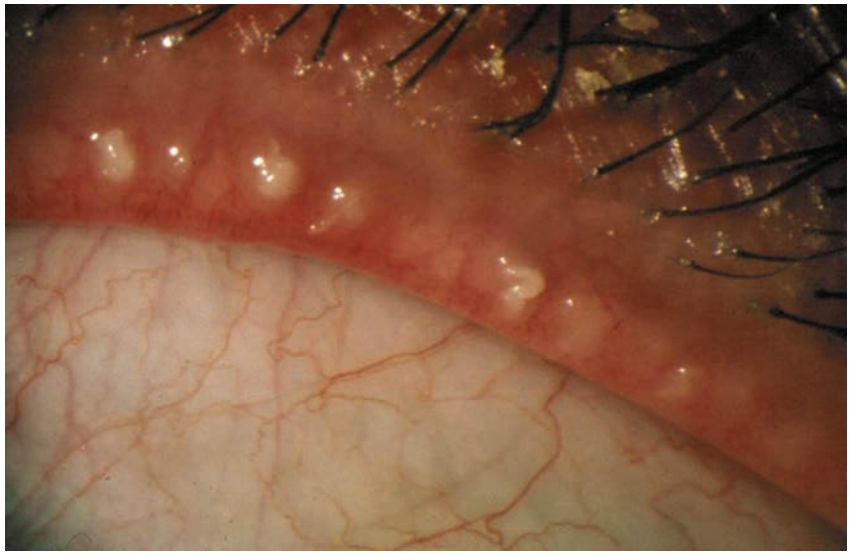

Figure 2. Evaluation of the meibomian gland orifices.

Treatment

The biggest news regarding the treatment of dry eye is the potential approval of lifitegrast (Shire), which is a small-molecule integrin antagonist that inhibits T-cell inflammation by blocking the binding of two key cellular surface proteins (LFA-1 and ICAM-1).

OPUS-2 was a multicenter, randomized, double-masked, placebo-controlled, parallel-arm study comparing lifitegrast (5% ophthalmic solution) to placebo administered twice daily for 84 days (12 weeks) in dry-eye patients with a history of active artificial tear use within 30 days prior to screening. The study included 718 patients at 31 U.S. sites and consisted of five visits over 98 days.[1]

Lifitegrast met one of the co-primary endpoints for the patient-reported symptom of improvement of dry eye compared with placebo, but it did not meet the second co-primary endpoint of the sign of inferior corneal staining. The secondary endpoints were descriptive only and were consistent with improvement in symptoms and lack of improvement in signs.

None of the patients in this study experienced serious treatment-emergent adverse events. The most commonly reported treatment-emergent adverse events associated with lifitegrast were dysgeusia (16.2 percent vs 0.3 percent for placebo), instillation site reaction (7 percent vs 1.1 percent for placebo), and reduced visual acuity (5 percent vs 6.4 percent for placebo).

"There will be a ruling from the FDA as early as July that will tell us the timetable to approval," Dr. Sheppard says. "That approval would bring the prospect of two excellent prescription medications specifically indicated and approved by the FDA for dry eye. Having two heavily marketed agents available will really increase patient awareness. There are millions of dry-eye sufferers out there who don't know they have dry eye and aren't really under anyone's care. With increased patient awareness, the hope is that these patients will actually seek out an eye doctor who will take care of that problem for them and avoid the potential morbidity that ensues from untreated or undertreated dry eye. Many times, these people are self-medicating with deleterious substances like vasoconstrictors or irritating generic eye drops that are laden with preservatives and actually do more harm than good."

He notes that there are many excellent treatment options that have become available in the past decade. Prescription medications include Restasis and topical steroids, which provide excellent induction therapy for the initiation of dry-eye treatment, he explains. "In that regard, a company named Kala is looking for a specific induction indication for its enhanced pharmacokinetic preparation of loteprednol, utilizing a unique mucus-membrane-penetrating protein vehicle. That will provide, hopefully within the next several years,

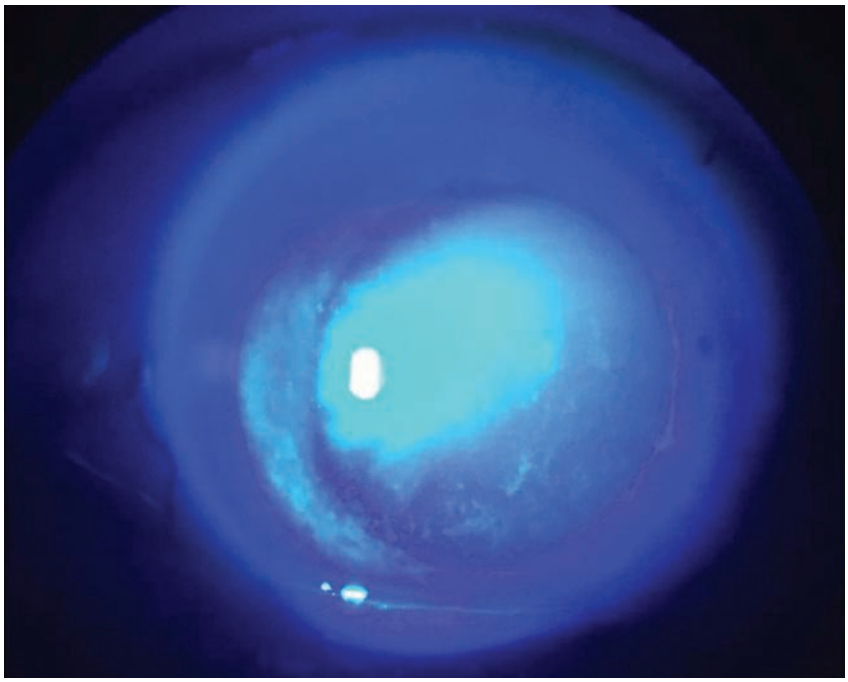

Figure 3. Corneal fluorescein staining under blue light.

the first approved medication for induction of dry-eye pharmaceutical therapy," Dr. Sheppard says.

"The treatments for blepharitis are becoming more exciting because we have the mainstays of lid scrubs, and we now have a very readily available topical hypochlorous acid," he adds. "This is available in pure form as Avenova from NovaBay and also as Hypochlor from OCuSOFT. Applying this agent to the lids reduces bacterial counts and inflammation in a very effective manner."

Also available is LipiFlow (Tear Science), which provides thermal pulsation therapy to rapidly improve the meibomian gland dysfunction that is common in up to 86 percent of dry eye patients. "We also have MiBo Thermoflo (MiBo Medical Group), which allows us to heat the meibomian glands from the exterior, and we have BlephEx (Rysurg), which allows us to debride the meibomian orifices to allow the egress of the oil. We continue to employ both oral low-dose doxycycline and topical azithromycin to not only reduce surface bacterial flora, but also to provide intrinsic anti-inflammatory and anti-MMP9 therapy," Dr. Sheppard adds.

Some other exciting products are on the horizon, as well. "One product I'm working on with R-Tech Ueno is a recombinant topical human serum albumin, which is an outstanding, and apparently very safe, protein eye drop ready for Phase IIb trials," Dr. Sheppard says. "Another exciting modality is Dextenza from Ocular Therapeutix, because their low-dose dexamethasone delivery system with a punctal plug is ideal for the dry-eye patient."

Last year, Ocular Therapeutix released topline efficacy results from a Phase II clinical trial to evaluate the safety and efficacy of Dextenza (sustained release dexamethasone) 0.4 mg, intracanalicular depot for the treatment of allergic conjunctivitis.[2] Dextenza is designed for extended drug release to the ocular surface for 30 days. The primary endpoint of treatment of ocular itching associated with allergic conjunctivitis was successfully achieved. There was a statistically significant difference in the mean scores between the Dextenza treatment group and the placebo group for ocular itching at all three time points measured on day seven post-insertion of the drug product.

Another new modality is the mimetogen secretagogue tavilermide (MIM-D3), which is now being developed by Allergan. In November, Allergan entered into an exclusive licensing agreement with Mimetogen Pharmaceuticals to develop and commercialize MIM-D3 (tavilermide), a topical formulation of a novel small-molecule TrkA agonist for the treatment of dry-eye disease.

Top-line data have been released from the second clinical study with MIM-D3,[3] and the trial demonstrated significant improvements in signs and symptoms with 1% MIM-D3 versus placebo, along with excellent safety, comfort and tolerability profiles.

The study, which included 403 patients, used Ora's Controlled Adverse Environment chamber to measure dry-eye patients' ability to withstand a stressful drying environment on the eye and patient diaries to measure the severity of dry-eye symptoms during the study. In this study, MIM-D3 was superior to placebo with regard to both central and total corneal fluorescein staining at week eight as measured by the Ora Calibra Scale. It also significantly improved common vision-related function symptoms of dry-eye disease as measured by the OSDK questionnaire. Additionally, the mean dry-eye scores for blurred vision, reading and watching TV were lower in the MIM-D3 group than in the placebo groups at week eight.

Study participants reported that MIM-D3 was comfortable and well-tolerated, and there were no unexpected or serious ocular ad-

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verse events. The most commonly reported ocular adverse events were reduced visual acuity (3 percent vs. 3 percent for placebo), instillation site pain (1 percent vs. 1.5 percent for placebo), and eye irritation (0 percent vs. 1.5 percent for placebo). All adverse ocular events were mild and transient.

"Another exciting development from Allergan is the now imminent availability of a preservative-free Restasis in a bottle because of the unique design of the filtration cap, which allows the patient to deliver repeated doses of totally preservative-free agent into the eye with a multi-dose container," Dr. Sheppard says. "That will be greatly welcomed by patients who don't like the tiny, single-dose units if they have arthritic hands and find the single-dose unit difficult to handle and squeeze. Finally, Allergan has acquired Oculeve, which introduces for the first time yet another mechanism of action for the treatment of the neurogenic component of dry eye. This device provides neural stimulation through the nasal mucous membranes to markedly increase production of tears through self-administration. I believe that Oculeve will meet an unmet need for yet another mechanism of action that was previously totally unaddressed. Hovione Scientia is developing a topical formulation of minocycline, overcoming legendary solubility and pharmacokinetic challenges for the dry-eye and meibomitis patient."

He adds that ophthalmologists are increasingly using ProKera amniotic membranes from BioTissue to rapidly accelerate the healing of severe dry eye with an in-office procedure to apply the suture-free amniotic membrane. "For the most severe dry-eye patients, the PROSE (Prosthetic Ocular Surface Environment) contact lens, which is available in a dozen facilities around the country, can be custom-made for a very broad area that traps the tears and lubricates the eye, improves comfort and improves oxygenation and protection of the ocular surface," he explains.

Empowering Staff

Because so many patients have dry eye, it can be a daunting task to screen everyone. Karl Stonecipher, MD, empowers his technicians to screen for dry eye in the waiting room. "When patients walk in, there is a sign that says 'Do you have dry eye?' If they go to the effort to fill out the form, my technicians will use lissamine green or some other stain. If the screening is positive, it looks like the patient is dry, and she has staining, the next step may be tear osmolarity or InflammaDry (Rapid Pathogen Screening) or other options," says Dr. Stonecipher, who is in private practice in Greensboro, N.C.

Technicians in his practice administer tests and questionnaires. "I really like the OSDI, because it is an app. I or one of the technicians can hand it to the patient while I'm doing EMR," says Dr. Stonecipher. "The patient takes the test, and then it says mild, moderate, severe or normal. Then, the technician is empowered to go ahead and stain the patient. I like to diagnose the patient with a simple questionnaire while he is in the office waiting room before he is even seen by a technician. Then, the patient doesn't have to see me and then go back to a technician to get repeat or additional testing. Basically, patients can be diagnosed and stained, and by the time they come to me, all I have to do is look at them and tell them their grade of dry eye. Next, I implement a treatment based on those diagnostics. For meibomian gland disease, I have enabled my technicians to be able to look at the eyelid margins and initiate appropriate diagnostics, such as LipiView."

Dr. Stonecipher has developed a diagnostic and treatment center that is available to all doctors in the community. They can send patients over to get diagnostics done, and patients can get treatment. "I am all about teaching doctors how to diagnose dry-eye disease," he says. "Once they can diagnose it, they need to be able to determine whether it is an aqueous-deficient dry eye, a meibomian gland disease or mixed mechanism, and then determine appropriate treatment. More and more people are taking the time and the effort to treat dry-eye disease, as opposed to referring the patient to a dry-eye specialist. It is economically profitable now, however far along the path you want to take it. By putting together a neutral diagnostic and treatment center, the doctors are referring their patients to these centers and then they get their patients back. It is the perfect co-management model."

He empowers patients to learn more about their specific type of dry-eye disease, and he empowers technicians to learn as well, because he is unable to have these conversations with all of his patients. "I love talking to my patients, but, with the schedules I face today, that time is limited. If a lot of the education process has taken place before a patient comes to me, then we can focus on the patient," he says. REVIEW

Dr. Latkany has no financial interest in any of the products mentioned. Dr. Sheppard is a consultant for Alcon, Allergan, BioTissue, Kala, NovaBay, Rutech, Shire and TearScience. Dr. Stonecipher is a consultant for Alcon, Allergan and Shire.

1. Tauber J, Karpecki P, Latkany R, et al. Lifitegrast ophthalmic solution 5.0% versus placebo for treatment of dry eye disease: Results of the Randomized Phase III OPUS-2 study. Ophthalmology 2015;122(12):2423-2431.
2. http://investors.ocutx.com/phoenix.zhtml?c=253650&p=irol-newsArticle&id=2100517.
3. http://www.firstwordpharma.com/node/1234316#axzz3FCBLSLlh

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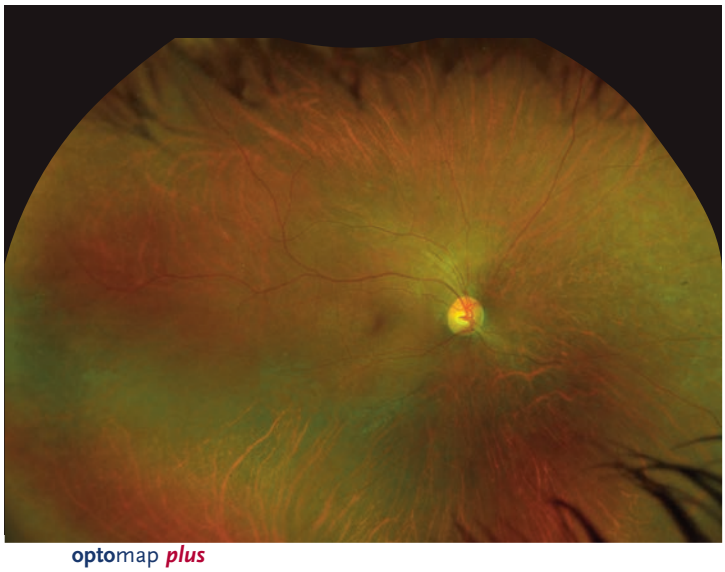

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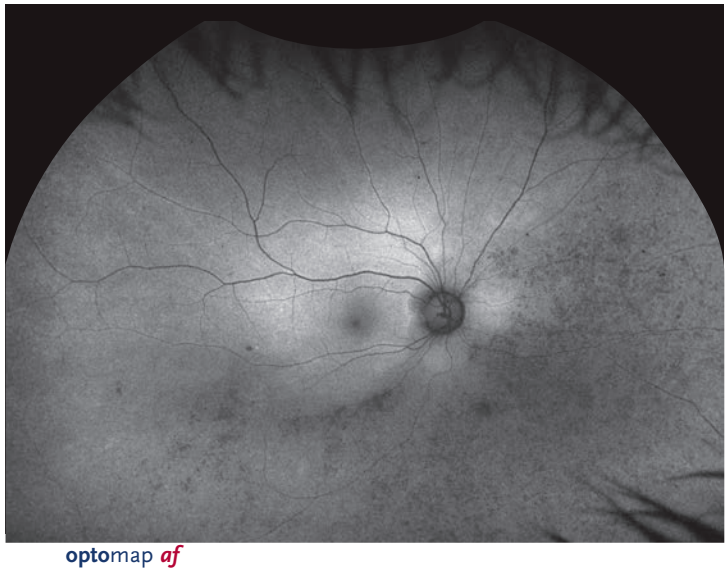

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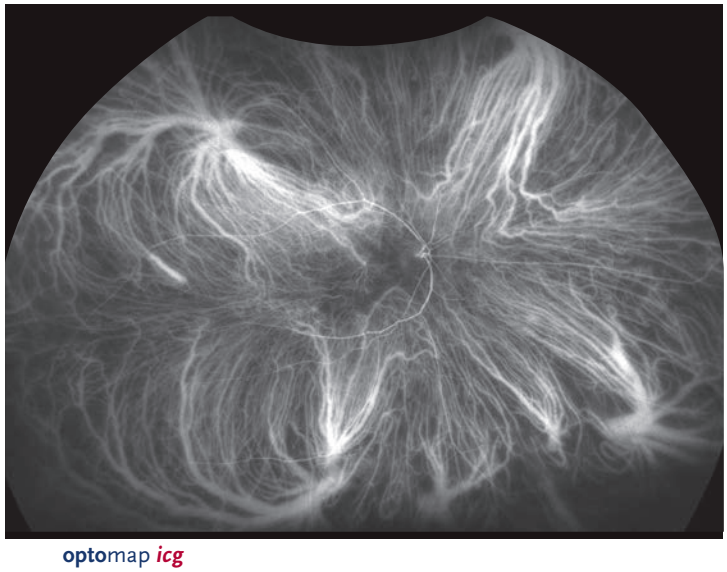

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V-Slice: A New, Easy Way To Tackle Soft Lenses

Peter Daniel, MD, Kristen Jijelava, MD, Hongvan Le, MD, Katherine Orman, MD, and Jordan Stanley, MD, Birmingham, Ala.

This approach to dealing with soft nuclei relies neither on rotation nor cracking, and needs no specialized instrumentation.

Soft cataracts seem like they should be easy to remove. After all, the epitome of difficulty is rumored to be their opposite—the "rock hard" lenses. Of course, every beginning surgeon soon learns the truth: that, actually, these cases can be quite challenging. And in fact, the softer the cataract, the less effective and the less applicable are the standard strategies for nuclear disassembly.[1]

To be specific, at our teaching program, the residents begin with the typical tactics for phacoemulsification. These include the divide-and-conquer, stop-and-chop, and the various pure chopping methods, along with a litany of ancillary manipulations including tricks for rotating the lens.

The problem is that many of these maneuvers don't work particularly well against soft nuclei. Their amorphous, semi-solid bodies lack rigid cleavage planes, so they don't chop or crack. Instruments placed to spin them, instead, may pass harmlessly through without exerting any torque. And so, because our usual tactics aren't effective, removing these cataracts can be a surprisingly frustrating and difficult ordeal.

Recently, however, we stumbled upon a new way of tackling these cases that is safe, simple, and—in our hands—successful. It relies on neither nuclear cracking nor rotation and can be performed without any specialized or expensive equipment. We call the tactic the V-slice.

The operation begins per usual: following the paracentesis, the anterior chamber is filled with preservative free lidocaine and an ophthalmic viscosurgical device. The main wound is created with a 2.2-mm keratome, through which a normal diameter (5.5- to 6-mm) capsulorhexis is fashioned. A blunt tipped chopping instrument (we prefer the Goldberg Nucleus Manipulator [Ambler Surgical, Rhein Medical]) is brought through the main wound, over the nuclear face, underneath the anterior capsule, and around the lens equator at the 7-o'clock position *(See Figure 1)*. Then, the chopper is slowly passed through the lens at approximately one-half to two-thirds depth, aiming for the 12-o'clock position, stopping immediately if any resistance is encountered. Thereafter, the chopper is moved to the 5-o'clock position and this process is repeated. The effect is to produce a central pie-shaped segment bounded laterally by two independent crescentic pieces. Gentle hydrodelineation followed by hydrodissection is then performed. (Alternatively, one can simply hydrodissect and eliminate the

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hydrodelineation step.). Next, OVD is injected into the sliced grooves to further define the pieces and to push the posterior capsule back. The phaco hand- piece can then be introduced through the main wound and a second instrument through the paracentesis (we like the Connor Wand [Ambler Surgical, Rhein Medical]). Typically, the central, pie-shaped piece is the easiest to remove first, since it is usually totally separated from its surroundings and floating at the level of the capsulorhexis. After this, the two remaining crescentic pieces can be removed in similar fashion. Thereafter the operation concludes per routine: The irrigation/aspiration handpiece is used to complete cortical cleanup, the capsular bag is filled with OVD, the lens injected, the OVD removed, and the eye brought to a physiologic pressure with the wounds checked for leaks.

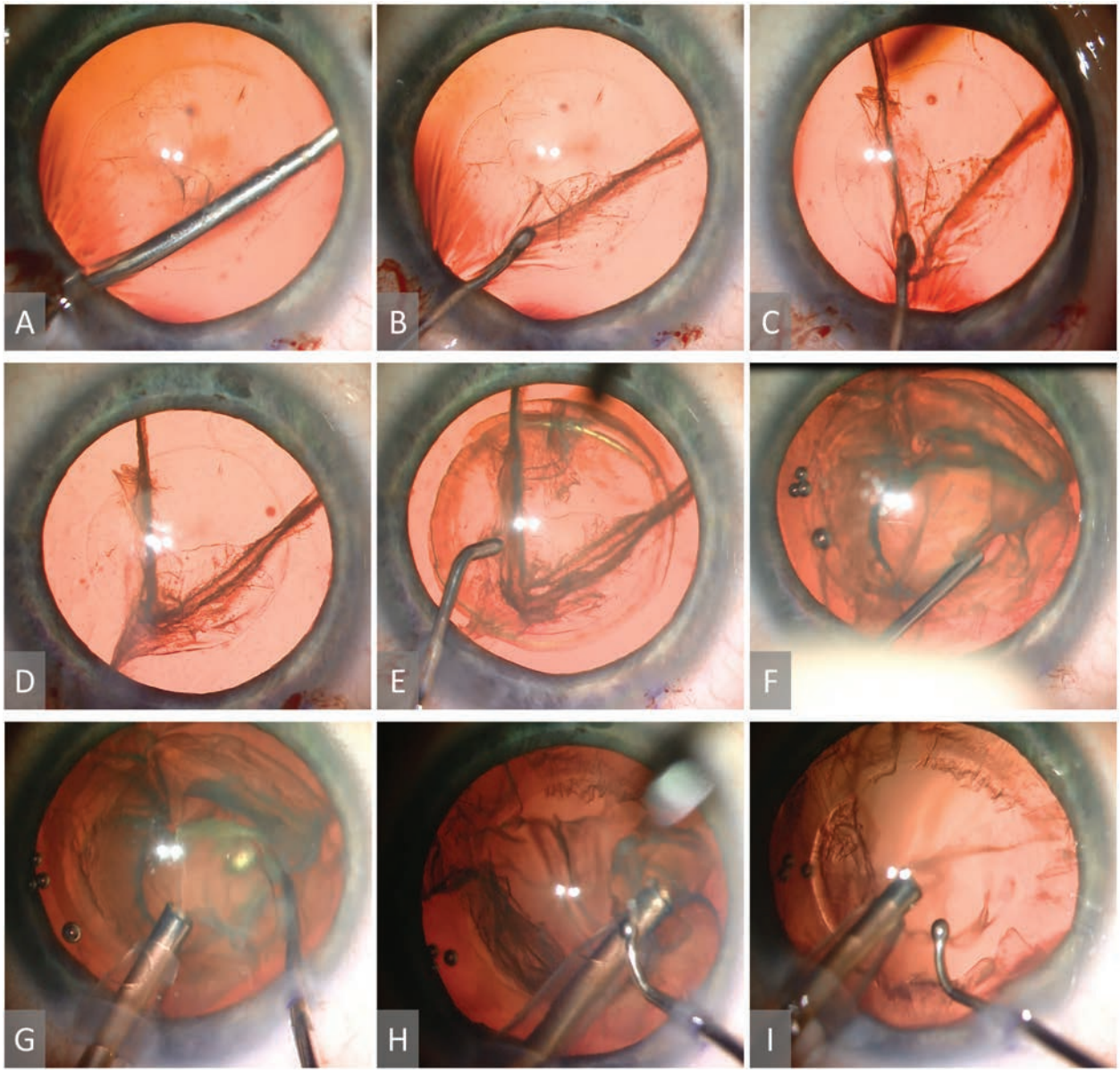

Figure 1. After the capsulorhexis is completed, a blunt tipped instrument is slipped beneath the anterior capsule at the 7-o'clock position and around the lens equator (A). It is then gently passed through the nucleus at approximately 50-percent depth towards the 12-o'clock position (B). This procedure is then repeated, slicing from 5 to 12-o'clock, to produce a central pie-shaped portion and two lateral crescentic pieces (C,D). Gentle hydrodelineation and hydrodissection are then performed (E), and viscoelastic is injected into the grooves between the three segments (F). The phaco handpiece is inserted into the main wound and the central pie-shaped piece is removed (G), after which, the two remaining pieces are gently aspirated by turning the bevel of the phaco tip in their direction (H) until all nuclear material is removed (I).

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INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

- 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), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR) in Patients with DME.

CONTRAINDICATIONS

- 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.

WARNINGS AND PRECAUTIONS

- 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 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 from baseline to week 52 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; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 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.

ADVERSE REACTIONS

- 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.

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

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BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

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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), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR) in Patients with 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 Diabetic Retinopathy (DR) in Patients with DME. 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 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.

2.6 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.

2.7 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 from baseline to week 52 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; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 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%
Ocular hyperemia	4%	8%
Corneal epithelium defect	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) from baseline to week 52 and from baseline to week 100.

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

Adverse Reactions	Baseline to Week 52		Baseline to Week 100	
	EYLEA (N=578)	Control (N=287)	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

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

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 24-100 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: March 2015
Initial U.S. Approval: 2011

Regeneron U.S. Patents 7,070,959; 7,303,746; 7,303,747; 7,306,799; 7,374,757; 7,374,758; 7,531,173; 7,608,261; 7,972,598; 8,029,791; 8,092,803; 8,647,842; and other pending patents. LEA-0721

At our program, the advantages of this technique are: Rotation of the nucleus is not essential; it permits easy and reliable segmentation of the lens before hydrodissection when visualization is optimized; it doesn't rely on "cracking" to achieve this segmentation; lens division may proceed "one-handed" (which may be especially helpful for beginning surgeons, who may find a bimanual chopping procedure more challenging); it mobilizes the lens within the capsular bag without depending on nuclear rotation (or requiring hydrodissection, which may be advantageous in eyes with posterior polar cataracts); and finally, these steps can be performed without the need for specialized instruments.

Over the years, this has become our primary strategy for soft cataract removal in our resident clinics. To our knowledge, no complications stemming from this technique have occurred, which is perhaps a testament to its inherent safety, considering that many of our surgeons are only just learning the basics of cataract surgery.

The primary downside of the V-slice is that it may be useful only in very soft cataracts, since the maneuver may place undue stress on the lens zonules if a dense nucleus is encountered. Careful patient selection is therefore required. But, so far, we have been encouraged by our results with this approach and we would like to invite other interested surgeons to give it a try. REVIEW

The authors are ophthalmology residents at the University of Alabama, Birmingham, Callahan Eye Hospital, Birmingham, Ala. *They acknowledge the assistance of Jeffrey Yee, MS, MD; and Jack Parker, MD.*

Contact Dr. Parker at jack.parker@gmail.com.

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CMV Retinitis: Reduced Incidence, Still a Threat

Cytomegalovirus retinitis is a sight-threatening infection caused by a member of the human herpesviridae family.

Ian Y. L. Yeung, MD, Kenneth M. Downes, MD, Emmett Cunningham, MD, PhD, MPH, and H. Nida Sen, MD, MHS

Cytomegalovirus retinitis is a sight-threatening disease caused by CMV, a DNA virus from the human herpesviridae (HHV) family.[4-6] Epidemiology of CMVR differs due to global variation of CMV seroprevalence. Forty to 60 percent of American, Australian and European populations are CMV seropositive.[9-11] Adult CMV seropositivity rates are higher in Africa and Asia, where they approach 100 percent.[9-14]

CMVR has been associated with the human immunodeficiency virus infection since the 1980s.[16] CMVR occurs in 15 to 40 percent of acquired immune deficiency syndrome patients.[5] The advent of highly active antiretroviral therapy (HAART) in the 1990s has reduced the incidence of CMVR by 90 percent in the United States.[9,17] HAART has reduced the rate of CMVR-associated rhegmatogenous retinal detachments by 60 percent.[5]

CMVR typically occurs when CD4+ T-cell counts fall below 50 cells/µl, and rarely occurs at counts above 100 cells/µl.[2,9] Immune recovery uveitis refers to intraocular inflammation that occurs in HIV-positive patients with prior, inactive CMVR, in whom the CD4+ counts rise above 100 cells/µl. IRU occurs in up to 63 percent of patients with prior CMVR.[18]

Uveitic manifestations of IRU include vitritis; vitreomacular traction; cystoid macular edema; epiretinal membrane; papillitis; neovascularization; proliferative vitreoretinopathy; and RRD.[17,18] The vitritis and CME of IRU can be treated with periocular or intravitreal triamcinolone, but with caution, so as to avoid recurrence.[2] Systemic CMV manifestations include encephalitis; esophagitis; colitis; pneumonitis; hepatitis; leukopenia; and arthralgia. Systemic CMV disease occurs in about 25 percent of patients with CMVR.[5]

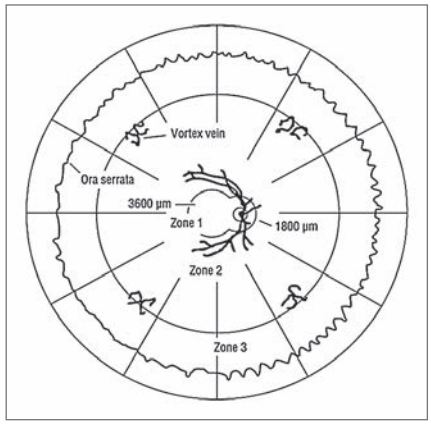


Figure 1. Retinal Zones. One disc diameter is approximately 1,800 µm.[1-3]

CMVR can also occur in non-HIV patients, but is much less common. In a recent comprehensive review of 178 HIV-negative patients with CMVR, factors that contributed to relative immunosuppression included age over 60 years (33.1 percent); leukemia (19.7 percent); systemic autoimmune disease (19.1 percent); organ transplantation (15.2 percent); lymphoma (7.9 percent); diabetes mellitus (6.1 percent); and multiple myeloma (1.7 percent).[19] CMVR has been described in nine patients with Good syndrome.[19,20] Among 105 HIV-negative CMVR patients on immunosuppressives, CMVR was found in patients on corticosteroids (65.7 percent); cyclophosphamide (31.4 percent); azathioprine (16.2 percent); methotrexate (14.3 percent); cyclosporine (12.4 percent); tacrolimus (10.5 percent); mycophenolate (7.6 percent); and fludarabine (6.7 percent).[19] CMVR can also occur following periocular or intraocu-

ADD SIMBRINZA® Suspension to a PGA for Even Lower IOP[1]*

INDICATIONS AND USAGE

SIMBRINZA® (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2% is a fixed combination indicated in the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

Dosage and Administration

The recommended dose is one drop of SIMBRINZA® Suspension in the affected eye(s) three times daily. Shake well before use. SIMBRINZA® Suspension may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

IMPORTANT SAFETY INFORMATION

Contraindications

SIMBRINZA® Suspension is contraindicated in patients who are hypersensitive to any component of this product and neonates and infants under the age of 2 years.

Warnings and Precautions

Sulfonamide Hypersensitivity Reactions—Brinzolamide is a sulfonamide, and although administered topically, is absorbed systemically. Sulfonamide attributable adverse reactions may occur. Fatalities have occurred due to severe reactions to sulfonamides. Sensitization may recur when a sulfonamide is readministered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation.

Corneal Endothelium—There is an increased potential for developing corneal edema in patients with low endothelial cell counts.

Severe Hepatic or Renal Impairment (CrCl <30 mL/min)—SIMBRINZA® Suspension has not been specifically studied in these patients and is not recommended.

Contact Lens Wear—The preservative in SIMBRINZA® Suspension, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of SIMBRINZA® Suspension but may be reinserted 15 minutes after instillation.

Severe Cardiovascular Disease—Brimonidine tartrate, a component of SIMBRINZA® Suspension, had a less than 5% mean decrease in blood pressure 2 hours after dosing in clinical studies; caution should be exercised in treating patients with severe cardiovascular disease.

Adverse Reactions

SIMBRINZA® Suspension

In two clinical trials of 3 months' duration with SIMBRINZA® Suspension, the most frequent reactions associated with its use occurring in approximately 3-5% of patients in descending order of incidence included: blurred vision, eye irritation, dysgeusia (bad taste), dry mouth, and eye allergy. Adverse reaction rates with SIMBRINZA® Suspension were comparable to those of the individual components. Treatment discontinuation, mainly due to adverse reactions, was reported in 11% of SIMBRINZA® Suspension patients.

Prescribe SIMBRINZA® Suspension as adjunctive therapy to a PGA for appropriate patients

SIMBRINZA® Suspension should be taken at least five (5) minutes apart from other topical ophthalmic drugs

Learn more at myalcon.com/simbrinza

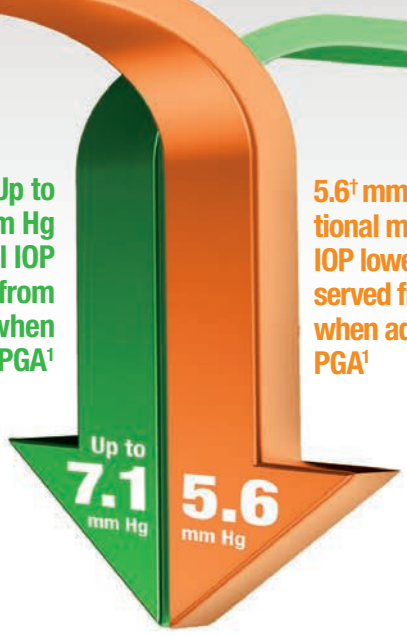
For additional information about SIMBRINZA® Suspension, please see Brief Summary of full Prescribing Information on adjacent page.

Reference: 1. Data on file, 2014.

Alcon
a Novartis company

Up to 7.1 mm Hg additional IOP reduction from baseline when added to a PGA[1]

5.6† mm Hg additional mean diurnal IOP lowering observed from baseline when added to a PGA[1]



		IOP Time Points (mm Hg)[1‡]			
Treatment Arm		8 AM	10 AM	3 PM	5 PM
PGA + SIMBRINZA® Suspension (N=83)	Baseline[§]	24.5	22.9	21.7	21.6
	Week 6	19.4	15.8	17.2	15.6
PGA + Vehicle (N=92)	Baseline[§]	24.3	22.6	21.3	21.2
	Week 6	21.5	20.3	20.0	20.1

‡Least squares means at each Week 6 time point. Treatment differences (mm Hg) and *P*-values at Week 6 time points between treatment groups were: -2.14, *P*=0.0002; -4.56, *P*<0.0001; -2.84, *P*<0.0001; -4.42, *P*<0.0001.
§Baseline (PGA Monotherapy).

		Mean Diurnal IOP (mm Hg)[‖]
Treatment Arm		
PGA + SIMBRINZA® Suspension (N=83)	Baseline[¶]	22.7
	Week 6	17.1
PGA + Vehicle (N=92)	Baseline[¶]	22.4
	Week 6	20.5

‖Treatment difference (mm Hg) and *P*-value at Week 6 was -3.4, *P*<0.0001.
¶Baseline (PGA Monotherapy).

Study Design: A prospective, randomized, multicenter, double-blind, parallel-group study of 189 patients with open-angle glaucoma and/or ocular hypertension receiving treatment with a PGA. PGA treatment consisted of either travoprost, latanoprost, or bimatoprost. Patients in the study were randomized to adjunctive treatment with SIMBRINZA® Suspension (N=88) or vehicle (N=94). The primary efficacy endpoint was mean diurnal IOP (IOP averaged over all daily time points) at Week 6 between treatment groups. Key secondary endpoints included IOP at Week 6 for each daily time point (8 AM, 10 AM, 3 PM, and 5 PM) and mean diurnal IOP change from baseline to Week 6 between treatment groups.[1]

*PGA study-group treatment consisted of either travoprost, latanoprost, or bimatoprost.
†Treatment difference (mm Hg) and *P*-value at Week 6 was -3.7, *P*<0.0001.

SIMBRINZA®
(brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2%

BRIEF SUMMARY OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE

SIMBRINZA® (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2% is a fixed combination of a carbonic anhydrase inhibitor and an alpha 2 adrenergic receptor agonist indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

DOSAGE AND ADMINISTRATION

The recommended dose is one drop of SIMBRINZA® Suspension in the affected eye(s) three times daily. Shake well before use. SIMBRINZA® Suspension may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

DOSAGE FORMS AND STRENGTHS

Suspension containing 10 mg/mL brinzolamide and 2 mg/mL brimonidine tartrate.

CONTRAINDICATIONS

Hypersensitivity - SIMBRINZA® Suspension is contraindicated in patients who are hypersensitive to any component of this product.

Neonates and Infants (under the age of 2 years) - SIMBRINZA® Suspension is contraindicated in neonates and infants (under the age of 2 years*) see Use in Specific Populations*

WARNINGS AND PRECAUTIONS

Sulfonamide Hypersensitivity Reactions - SIMBRINZA® Suspension contains brinzolamide, a sulfonamide, and although administered topically is absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulfonamides may occur with topical administration of SIMBRINZA® Suspension. Fatalities have occurred due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Sensitization may recur when a sulfonamide is re-administered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation *[see Patient Counseling Information]*

Corneal Endothelium - Carbonic anhydrase activity has been observed in both the cytoplasm and around the plasma membranes of the corneal endothelium. There is an increased potential for developing corneal edema in patients with low endothelial cell counts. Caution should be used when prescribing SIMBRINZA® Suspension to this group of patients.

Severe Renal Impairment - SIMBRINZA® Suspension has not been specifically studied in patients with severe renal impairment (CrCl < 30 mL/min). Since brinzolamide and its metabolite are excreted predominantly by the kidney, SIMBRINZA® Suspension is not recommended in such patients.

Acute Angle-Closure Glaucoma - The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. SIMBRINZA® Suspension has not been studied in patients with acute angle-closure glaucoma.

Contact Lens Wear - The preservative in SIMBRINZA® Suspension, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of SIMBRINZA® Suspension but may be reinserted 15 minutes after instillation *[see Patient Counseling Information]*.

Severe Cardiovascular Disease - Brimonidine tartrate, a component of SIMBRINZA® Suspension, has a less than 5% mean decrease in blood pressure 2 hours after dosing in clinical studies; caution should be exercised in treating patients with severe cardiovascular disease.

Severe Hepatic Impairment - Because brimonidine tartrate, a component of SIMBRINZA® Suspension, has not been studied in patients with hepatic impairment, caution should be exercised in such patients.

Potentiation of Vascular Insufficiency - Brimonidine tartrate, a component of SIMBRINZA® Suspension, may potentiate syndromes associated with vascular insufficiency. SIMBRINZA® Suspension should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans.

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 have been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface *[see Patient Counseling Information]*.

ADVERSE REACTIONS

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

SIMBRINZA® Suspension - In two clinical trials of 3 months duration 435 patients were treated with SIMBRINZA® Suspension, and 915 were treated with the two individual components. The most frequently reported adverse reactions in patients treated with SIMBRINZA® Suspension occurring in approximately 3 to 5% of patients in descending order of incidence were blurred vision, eye irritation, dysgeusia (bad taste), dry mouth, and eye allergy. Rates of adverse reactions reported with the individual components were comparable. Treatment discontinuation, mainly due to adverse reactions, was reported in 11% of SIMBRINZA® Suspension patients.

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

Brinzolamide 1% - In clinical studies of brinzolamide ophthalmic suspension 1%, the most frequently reported adverse reactions reported in 5 to 10% of patients were blurred vision and bitter, sour or unusual taste. Adverse reactions occurring in 1 to 5% of patients were blepharitis, dermatitis, dry eye, foreign body sensation, headache, hyperemia, ocular discharge, ocular discomfort, ocular keratitis, ocular pain, ocular pruritus and rhinitis.

The following adverse reactions were reported at an incidence below 1%: allergic reactions, alopecia, chest pain, conjunctivitis, diarrhea, diplopia, dizziness, dry mouth, dyspnea, dyspepsia, eye fatigue, hypertonia, keratoconjunctivitis, keratopathy, kidney pain, lid margin crusting or sticky sensation, nausea, pharyngitis, tearing and urticaria.

Brimonidine Tartrate 0.2% - In clinical studies of brimonidine tartrate 0.2%, adverse reactions occurring in approximately 10 to 30% of the subjects, in descending order of incidence, included oral dryness, ocular hyperemia, burning and stinging, headache, blurring, foreign body sensation, fatigue/drowsiness, conjunctival follicles, ocular allergic reactions, and ocular pruritus.

Reactions occurring in approximately 3 to 9% of the subjects, in descending order included corneal staining/erosion, photophobia, eyelid erythema, ocular ache/pain, ocular dryness, tearing, upper respiratory symptoms, eyelid edema, conjunctival edema, dizziness, blepharitis, ocular irritation, gastrointestinal symptoms, asthenia, conjunctival blanching, abnormal vision and muscular pain.

The following adverse reactions were reported in less than 3% of the patients: lid crusting, conjunctival hemorrhage, abnormal taste, insomnia, conjunctival discharge, depression, hypertension, anxiety, palpitations/arrhythmias, nasal dryness and syncope.

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

Apnea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in infants receiving brimonidine tartrate ophthalmic solutions *[see Contraindications]*.

DRUG INTERACTIONS

Oral Carbonic Anhydrase Inhibitors - There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and brinzolamide ophthalmic suspension 1%, a component of SIMBRINZA® Suspension. The concomitant administration of SIMBRINZA® Suspension and oral carbonic anhydrase inhibitors is not recommended.

High-Dose Salicylate Therapy - Carbonic anhydrase inhibitors may produce acid-base and electrolyte alterations. These alterations were not reported in the clinical trials with brinzolamide ophthalmic suspension 1%. However, in patients treated with oral carbonic anhydrase inhibitors, rare instances of acid-base alterations have occurred with high-dose salicylate therapy. Therefore, the potential for such drug interactions should be considered in patients receiving SIMBRINZA® Suspension.

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

Antihypertensives/Cardiac Glycosides - Because brimonidine tartrate, a component of SIMBRINZA® Suspension, may reduce blood pressure, caution in using drugs such as antihypertensives and/or cardiac glycosides with SIMBRINZA® Suspension is advised.

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 SIMBRINZA® Suspension in humans can lead to resulting interference with the IOP lowering effect. Caution is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

Monoamine Oxidase Inhibitors - Monoamine oxidase (MAO) inhibitors may theoretically interfere with the metabolism of brimonidine tartrate 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:* Developmental toxicity studies with brinzolamide in rabbits at oral doses of 1, 3, and 6 mg/kg/day (20, 60, and 120 times the recommended human ophthalmic dose) produced maternal toxicity at 6 mg/kg/day and a significant increase in the number of fetal variations, such as accessory skull bones, which was only slightly higher than the historic value at 1 and 6 mg/kg. In rats, statistically decreased body weights of fetuses from dams receiving oral doses of 18 mg/kg/day (180 times the recommended human ophthalmic dose) during gestation were proportional to the reduced maternal weight gain, with no statistically significant effects on organ or tissue development. Increases in unossified sternebrae, reduced ossification of the skull, and unossified hyoid that occurred at 6 and 18 mg/kg were not statistically significant. No treatment-related malformations were seen. Following oral administration of ^{14}C-brinzolamide to pregnant rats, radioactivity was found to cross the placenta and was present in the fetal tissues and blood.

Developmental toxicity studies performed in rats with oral doses of 0.66 mg brimonidine base/kg revealed no evidence of harm to the fetus. Dosing at this level resulted in a plasma drug concentration approximately 100 times higher than that seen in humans at the recommended human ophthalmic dose. In animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent.

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

Nursing Mothers - In a study of brinzolamide in lactating rats, decreases in body weight gain in offspring at an oral dose of 15 mg/kg/day (150 times the recommended human ophthalmic dose) were observed during lactation. No other effects were observed. However, following oral administration of ^{14}C-brinzolamide to lactating rats, radioactivity was found in milk at concentrations below those in the blood and plasma. In animal studies, brimonidine was excreted in breast milk.

It is not known whether brinzolamide and brimonidine tartrate are excreted in human milk following topical ocular administration. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from SIMBRINZA® (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2%, 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 - The individual component, brinzolamide, has been studied in pediatric glaucoma patients 4 weeks to 5 years of age. The individual component, brimonidine tartrate, has been studied in pediatric patients 2 to 7 years old. Somnolence (50-83%) and decreased alertness was seen in patients 2 to 6 years old. SIMBRINZA® Suspension is contraindicated in children under the age of 2 years *[see Contraindications]*.

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

OVERDOSAGE

Although no human data are available, electrolyte imbalance, development of an acidotic state, and possible nervous system effects may occur following an oral overdose of brinzolamide. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored.

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

PATIENT COUNSELING INFORMATION

Sulfonamide Reactions - Advise patients that if serious or unusual ocular or systemic reactions or signs of hypersensitivity occur, they should discontinue the use of the product and consult their physician.

Temporary Blurred Vision - Vision may be temporarily blurred following dosing with SIMBRINZA® Suspension. Care should be exercised in operating machinery or driving a motor vehicle.

Effect on Ability to Drive and Use Machinery - As with other drugs in this class, SIMBRINZA® Suspension may cause fatigue and/or drowsiness in some patients. Caution patients who engage in hazardous activities of the potential for a decrease in mental alertness.

Avoiding Contamination of the Product - Instruct patients that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions *[see Warnings and Precautions]*. Always replace the cap after using. If solution changes color or becomes cloudy, do not use. Do not use the product after the expiration date marked on the bottle.

Intercurrent Ocular Conditions - Advise patients that if they have ocular surgery or develop an intercurrent ocular condition (e.g., trauma or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container.

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

Contact Lens Wear - The preservative in SIMBRINZA® Suspension, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of SIMBRINZA® Suspension, but may be reinserted 15 minutes after instillation.

U.S. Patent No:
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lar corticosteroid injection.[4,13,19-22] IRU can also occur in HIV-negative patients with prior CMVR, but appears to be less common, having been described in 5 to 10 percent of such eyes.[19]

Many patients with CMVR are asymptomatic, as the retinitis often begins in the peripheral retina. Screening for CMVR is indicated for all HIV-positive patients with a CD4+ count less than 100 cells/µl.[2,5]

Classical CMVR is a slowly progressive necrotizing retinitis that may affect the posterior pole and periphery, and may be unilateral or bilateral. White intraretinal infiltrates are often seen along the vascular arcades and are associated with necrotic areas and retinal hemorrhages. CMVR progression leads to retinal atrophy. Anterior segment inflammation with or without keratic precipitates is often present. Optic atrophy is a common late manifestation.[2,5]

CMVR can be classified into indolent or fulminant CMVR. Indolent CMVR consists of granular retinal opacification with visible choroidal details with no hemorrhage and no vascular sheathing. Fulminant (edematous) CMVR consists of dense confluent retinal opacification of necrotizing retinitis and hemorrhages with no atrophic areas.[3]

CMVR assessment should include grading of the area of retina involvement into three zones *(See Figure 1)*. Zone 1 is the area 3,000 µm from the fovea and 1,500 µm from the optic disc. Zone 2 is from Zone 1 to the vortex veins. Zone 3 is the remaining retina up to the ora serrata.[1,23] In HIV-positive patients, the majority of CMVR is peripheral (i.e., Zone 1-sparing; 61 to 71 percent of eyes) with only a minority involving Zone 1 (i.e., 29 to 39 percent of eyes).[17,24] CMVR assessment should also include estimation of the percentage of the total retinal surface area affected by the CMVR (e.g., <10 percent, 10 to 24 percent, 25 to 50 percent, >50 percent) since this has implications regarding the risk of retinal detachment.[24]

Table 1. Differential Diagnoses of Cytomegalovirus Retinitis

Infective causes	Non-infective causes
Acute retinal necrosis (ARN)	Behçet's disease
Progressive (outer) retinal necrosis (PORN)	Primary vitreoretinal lymphoma (PVRL)
Herpes simplex virus retinitis	
Toxoplasmosis	
Candida infection	
Syphilis	
Subacute sclerosing panencephalitis (SSPE)	

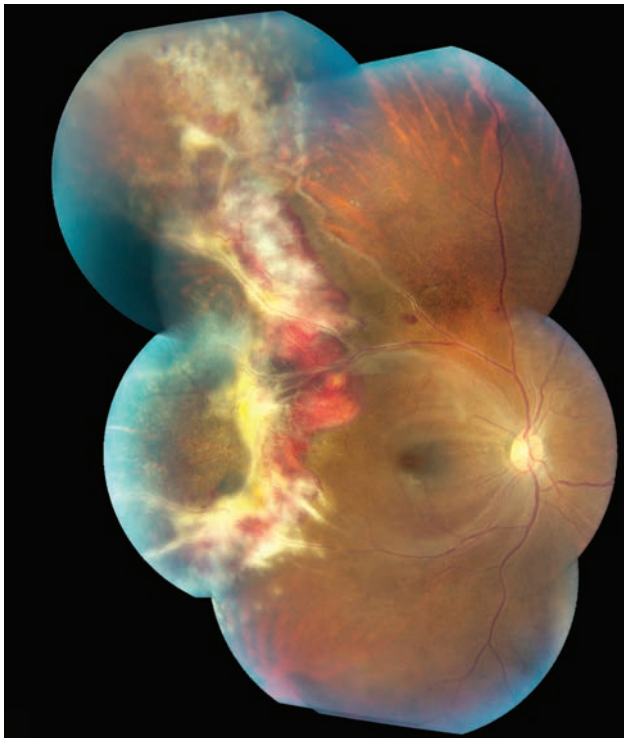

Figure 2: Color fundus photograph of the right eye of an HIV-positive 35-year-old female. The hemorrhage and vascular sheathing suggests fulminant CMVR. Encroachment of the CMVR into the superotemporal macular area suggests Zone 1 involvement. The border opacification at 9 o'clock matches the standard peripheral photograph of severe (4+) border opacification; this is active retinitis. The CMVR involves approximately 25 percent of the retina surface of the right eye. This patient died of AIDS soon after this photograph was taken.

CMV is a neurotropic virus that infects neural tissue and retina. It progresses in two ways: First, CMV enters the eye hematogenously, and so early perivascular involvement is common. Second, once in, eye lesions tend to extend via involvement of contiguous retina. To judge whether an area of CMVR is progressing or reactivating, it is important, therefore, to focus on the borders.[2,5]

CMVR borders can be graded based on photographs. Mild (1+) is where the CMVR border is faint and does not obscure the choroid. Moderate (2+) is where the CMVR border consists of isolated areas of denser retinal whitening which partially obscures the choroid. Marked (3+) is confluent retinal whitening, partially obscuring the choroid. Severe (4+) is where the border opacification is so dense that the choroid cannot be seen, indicating ac-

Table 2. Systemic Antivirals

Drug	Route	Dosage & Timing	Side Effects (by %) and Comments
Valganciclovir	Peroral	900 mg b.i.d. for three weeks (induction); 900 mg daily (maintenance)	Diarrhea (38%), nausea (23), neutropenia (10), anemia (12), thrombocytopenia (2)
Ganciclovir	Intravenous	5 mg/kg q12h for two to three weeks (induction); 5 mg/kg/day (maintenance)	Granulocytopenia (33), neurologic dysfunction, abnormal liver function, thrombocytopenia.
Foscarnet	Intravenous	90 mg/kg b.i.d. for two to three weeks (induction); 90 mg/kg daily (maintenance)	Nephrotoxicity, neutropenia, anemia, hypocalcemia, Mg2+, PO4- abnormalities. Consider saline loading.
Cidofovir	Intravenous	5 mg/kg once a week for two to three weeks (induction); 3 to 5 mg/kg alternate weeks (maintenance)	Iritis (50), ocular hypotony. Probenecid and IV hydration reduces nephrotoxicity.

tive retinitis.[3,7] Screening has revealed that 42.9 percent of CMVR eyes have 1+ opacification; 28.6 percent have 2+ opacification; 4.7 percent have 3+ opacification; and 23.8 percent have 4+ opacification.[24] Figures 2 and 3 show color and fundus autofluorescence montages of active CMVR in an HIV-positive patient.

Differential Diagnosis

The differential diagnoses for CMVR is shown in Table 1.[5] Most of these conditions can be differentiated from CMVR clinically, but retinitides mediated by HHV family members (e.g., CMV, herpes simplex virus and varicella zoster virus) may be more difficult to distinguish clinically.[5,6]

An aqueous tap for polymerase chain reaction-based testing can distinguish between CMV, HSV and VZV infection. An anterior chamber tap typically provides 50 to 150 µl of fluid. A vitreous tap provides 300 µl of fluid. Among 178 HIV-negative CMVR eyes, 71.8 percent had their diagnosis of CMVR confirmed by PCR.[19] PCR for toxoplasmosis could also be requested if there is a concern.[25] It should be noted that the sensitivity of PCR-based testing falls if the sample is obtained following the initiation of anti-viral therapy.[4]

Serial fundus photography and wide-angle fluorescein angiography can be helpful in the management of patients with CMVR. Wide-angle imaging, in particular, can demonstrate peripheral ischemia, which may require pan-retinal photocoagulation.[26] In HIV-negative CMVR patients, an occlusive vasculopathy was reported in 47 of 199 eyes—or nearly one in four cases.[19]

RRD occurs in about 20 to 30 percent of HIV-infected CMVR patients, and occurs most often in areas of prior retinal necrosis.[2,5,27] The risk of RRD increases as the amount of peripheral retina affected by the CMVR increases.[2] For post-CMVR RRD, a retina reattachment rate of 86 percent can be achieved with a 360 degree encircling band, vitrectomy, endolaser and silicone oil injection.[5,28]

Table 3. Local Antivirals

Drug	Route	Dosage & Timing	Comments
Ganciclovir	Intravitreal	2 mg twice a week (induction*); 2 mg weekly (maintenance)[15, 30]	5 mg weekly, high-dose possible.[31]
Foscarnet	Intravitreal	2.4 mg, one to two times a week (induction); 2.4 mg weekly (maintenance)[32]	Costly.[32]
Cidofovir	Intravitreal	20 µg every five to six weeks[32]	Long-acting. Give oral probenecid 2 g two hours before injection, and 1 g two hours and eight hours after injection. Hypotony and iritis risks are lower with a 10-µg dose.
Fomivirsen	Intravitreal	Two doses 330 µg (0.05 ml), two weeks apart (induction); 330 µg monthly (maintenance)	No longer available in the United States. Reports of peripheral retinal toxicity and inflammation.
Ganciclovir (Vitrasert)	Sustained-release implant	1 µg per hour for eight months	No longer available.[5, 29]

* Intravitreal ganciclovir (2 mg/0.1 ml) is given twice a week until the cytomegalovirus retinitis lesions are stable (i.e., no further progression). Weekly intravitreal ganciclovir is given as maintenance until granular atrophy has occurred.

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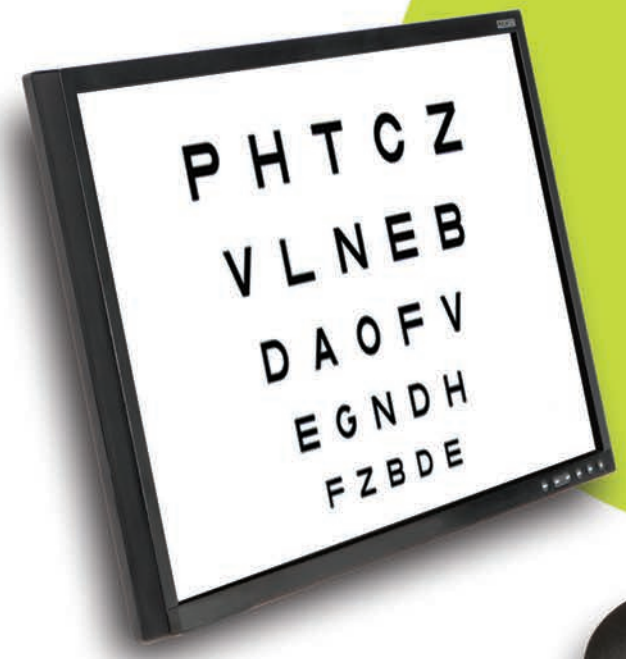

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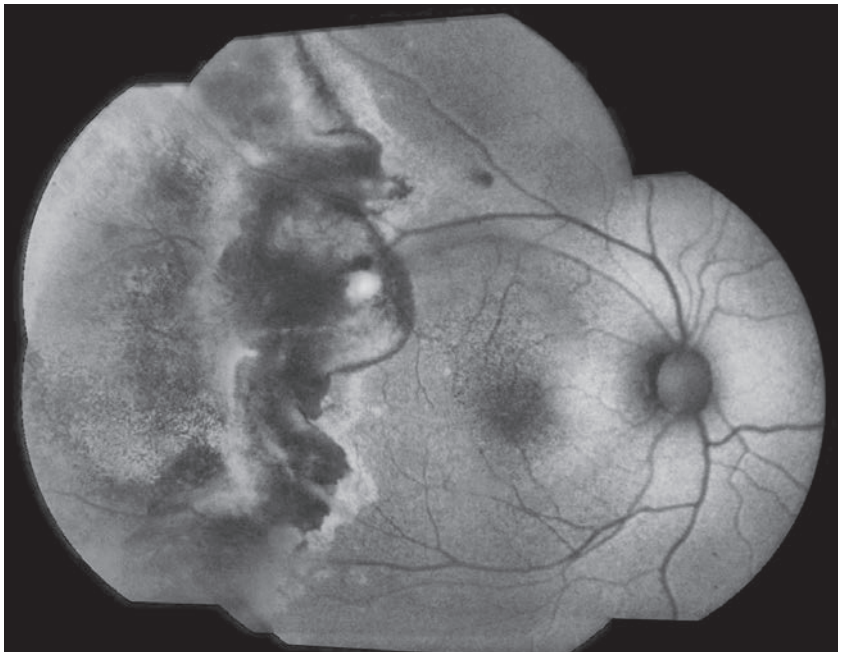

Figure 3. Fundus autofluorescence photograph of the same patient from figure 2. Intense, confluent hyperautofluorescence temporal to the macula corresponds to the advancing, active edge of retinitis. Mottled hyper- and hypoautofluorescence peripheral to the area of active retinitis corresponds to a large area of previously infected, but not necrotic, atrophic retina.[8]

Treatment of CMVR

Treatment options for CMVR vary. Systemic options are shown in Table 2. Local options are shown in Table 3.[2,5,29]

The gold standard for the treatment of CMVR, in both HIV-positive and HIV-negative patients, is systemic antiviral therapy.[15,17] Systemic therapy is generally preferred both because it reduces overall morbidity and because it generally works, with nearly three-quarters of patients achieving a post-treatment vision of 20/40 or better.[17] First-line treatment for both HIV-positive and HIV-negative patients with CMVR includes either intravenous ganciclovir or oral valganciclovir.[5,15]

If an HIV-positive patient's CD4+ count cannot be elevated with HAART, systemic antiviral therapy may need to become lifelong. This typically requires placement of a permanent indwelling venous catheter. If the CD4+ count can be kept above 100 cells/µl for three to six months, anti-CMV treatment typically can be stopped. Oral valganciclovir is as effective as IV ganciclovir, and allows patients to be maintained without long-term intravenous access.[5]

CMV resistance to ganciclovir can occur with long-term antiviral therapy.[5,25] When ganciclovir resistance does occur, treatment options include the use of systemic foscarnet, or use of adjunctive high-dose intravitreal antiviral foscarnet or ganciclovir.[31,33] Combination intravenous ganciclovir/foscarnet or oral valganciclovir plus intravenous foscarnet is more effective than monotherapy in resistant CMVR.[5] While a 2-mg intravitreal injection of ganciclovir maintains therapeutic vitreous levels for up to seven days,[34,15] use of intravitreal injections alone has been associated with worse visual acuity outcomes—at least in HIV-positive patients.[2,35]

As many CMVR patients are initially asymptomatic, screening for CMVR is recommended. CMVR progresses approximately 250 µm per week.[2,37] Currently no laboratory marker exists that predicts the occurrence of CMVR.[5] Clinical examination by a fellowship-trained retina specialist diagnosed CMVR in 15.5 percent of HIV-positive patients with CD4+ counts <100 cells/µl (i.e., 16 out of 103 patients). Fundus photography mediated telescreening is less successful, with a lower pick-up rate of 5.8 percent (i.e., six out of 103 patients). Use of ultra-widefield retinal imaging may improve the success rate of telescreening.[24]

In conclusion, CMVR is a sight-threatening infection caused by a member of the HHV family.[5,6,9] Both HIV and CMVR are more common in the developing world.[9-11,38] The gold-standard in CMVR therapy is systemic antiviral medication (e.g., valganciclovir).[17] But due to cost, CMVR is still treated by intravitreal antivirals alone (e.g., ganciclovir) in many settings.[13,31,32,36] REVIEW

Dr. Yeung is a uveitis and ocular immunology fellow at the National Eye Institute, Bethesda, Md. Dr. Downes is a cornea fellow at The Casey Eye Institute, Oregon Health Science University, Portland, Ore. Dr. Sen is the director of the uveitis and ocular immunology fellowship program at the NEI and has a joint appointment as a clinical professor in the Department of Ophthalmology at George Washington University, Washington, D.C. Dr. Cunningham is the director of the Uveitis Service at California Pacific Medical Center, San Francisco; an adjunct clinical professor of ophthalmology at Stanford University School of Medicine; a research associate at the Francis I. Proctor Foundation, UCSF School of Medicine, San Francisco; and a partner in the West Coast Retina Medical Group, San Francisco.

Correspondence should be directed to Dr. Sen at senh@nei.nih.gov. *This work was supported by the NEI Intramural Research Program.*

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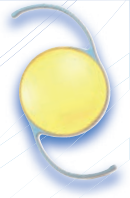

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The Form and Function Of Meibomian Glands

A discussion of gland mechanisms, how they can go awry and what you can do to nurse them back to health.

Mark B. Abelson, MD, CM, FRCSC, FARVO, George Ousler, Aron Shapiro and David Rimmer, Andover, Mass.

Meibomian glands are essential pieces of the homeostatic machinery that keep the ocular surface clean, healthy and well-lubricated. Dysfunction of these glands is a common disorder, with a widespread prevalence of 39 to 50 percent of the population that increases with age.[1,2] It's characterized by alterations in gland morphology and location, as well as a waning in quality and quantity of gland secretion. The etiology of meibomian gland dysfunction is unknown and may be due to any one of a variety of conditions, including bacterial infection, hormonal imbalance, autoimmune disease, inflammation, conditions inducing premature cell death or external mechanical factors. This month's column, the second half of our discussion of eyelid health, focuses on the anatomy and physiology of sebaceous and meibomian glands, the pathophysiology and classification of MGD, diagnostic tools and current and emerging treatment options.

The Anatomy

Both upper and lower eyelashes are coupled to two types of secretory glands: the sebaceous glands of Zeis and the apocrine (sweat) glands of Moll. Secretions from these glands protect the eyelid surface, while the glands of Meibum, positioned between the lashes and the bulbar conjunctiva, exude a fat and oil mixture onto the ocular surface. There are approximately 20 to 30 meibomian glands on the lower lid and 40 to 50 on the upper lid. Healthy glands are easily visualized by illumination of either lid, and appear as grape-like clusters attached to a central stalk. This structure is composed of acinar cells connected to a central duct that opens onto the mucocutaneous junction at the lid margin.[3] Lipid secretions containing dozens of oils and waxes are constantly synthesized and secreted, pushing meibum slowly toward the marginal orifice. In addition to this basal exudation, contraction of the Riolan's muscle coupled with normal blinking causes the meibum to be expressed and spread over the ocular surface. Essential lipids in the tear film reduce evaporation, seal the lid margins during sleep and help maintain the near-perfect optical surface required for visual acuity.[3]

Pathophysiology

Transillumination of the lid margin reveals anatomical differences between normal and MGD patients. Normal individuals show the grape-like clusters of acini that form long meibomian glands, while MGD patients may have congenitally absent or atrophied glands and gland dropout, as well as enlargement or laxity of the glands, particularly with aging.[3] Inflammation may or may not be present and patients may exhibit dry-eye symptoms, chalazia and hordeola.

There is no global consensus on the classification and diagnosis of MGD. The MGD Workshop distinguished meibomian gland disease, a term that encompasses secretory dysfunction as well as congenital or neoplastic conditions, from meibomian gland dysfunction, defined as including only hypo- or hypersecretory conditions.[4] For our purposes, we focus on the latter definition, as it includes other proposed categories including hormonal, bacterial and contact lens-associated MGD.[5-7] Other proposed grading systems, such as anterior and posterior, hypersecretory and hypose-

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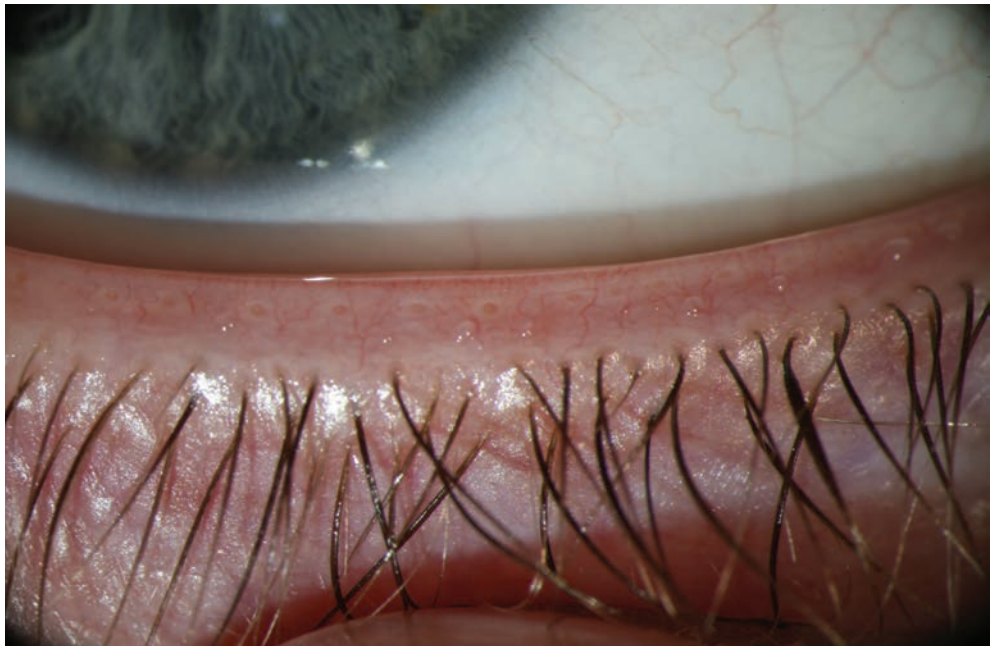
cretory, and non-obvious and obstructive provide little practical information on disease etiology and are of little clinical use. When developing a grading system, particularly one designed to assess new therapies, the system should be sensitive and precise enough to detect small but clinically relevant changes in outcome variables.



A patient with healthy meibomian gland function. In the normal patient, note how the meibomian gland ducts are visible, clear and properly aligned.

One of the first steps in translational research is moving from an understanding of the pathophysiology behind diseases such as MGD to a well-constructed clinical trial in which the therapeutic impact of a compound can be evaluated. To this end, researchers at Ora have developed the Lid Margin Disease Digital Image Grading System. This validated, standardized set of scales comprises a structurally based classification system that allows clinicians and researchers to reproducibly measure anatomic and functional components of the lid margin and surrounding structures including the meibomian glands, skin, palpebral conjunctiva, mucocutaneous junction, tear meniscus, lashes and follicles, as well as the degree of inflammation of each. In several clinical trials,[8] the grading system has been used to quantify lid margin redness (temporal, medial and nasal regions); palpebral conjunctival redness; lid edge shape; keratinization; lash folliculitis; lash loss; debris; mucocutaneous junction placement; meibomian gland morphology and MG secretion. *(Shapiro A, et al. IOVS 2008;49:ARVO E-abstract 84; Blackie CA, et al. IOVS 2008;49:ARVO E-abstract 86)* Assessment of secretion includes the number of glands, gland geometry, alignment, height and peri-gland redness, as well as meibum quality, viscosity and color. All assessments were based upon a 0 to 3 visual analog scale. By using scales such as this to assess all aspects of lid health, clinicians can more easily recognize underlying pathophysiology and will be in a position to best know how to treat the underlying dysfunction.

Danish ophthalmologist Mogens Norn was the first to suggest that the Marx line represents the border between the tear film and the skin and corresponds to the mucocutaneous junction.[9] As a marker of the tear-film boundary, researcher Masahiko Yamaguchi, MD, and his colleagues at Japan's Ehime University hypothesized that a more anterior location of the Marx line might be correlated with MGD.[10] They found a strong correlation between the position of the line, meibomian gland dropout and abnormal gland secretion.

The Marx line runs parallel to and away from the meibomian orifices along the conjunctival border in normal, younger subjects, while it becomes irregular and moves closer (anteriorly) to the orifices with aging. We don't yet know whether the development of MGD precedes or is caused by displacement of the Marx line with aging. It seems, though, that meibomian gland dropout and anterior line displacement are related.[11]

Obstructive MGD might involve hyperkeratinization of the central duct, with excess keratin causing adherence of sloughed epithelial cells, blockage of the gland, cystic dilation and gland atrophy.[11] Alternatively, age-related increases in cellular debris in the central duct may lead to obstruction.[12] It's also possible that stress induced by contact lens wear or ocular surface drying can alter the stem cell proliferation and gene expression necessary for normal acinar function.[11,13,14] Furthermore, with aging, there appears to be a decline in meibocyte differentiation and lipid synthesis, which can lead to meibomian gland dysfunction, gland atrophy, gland dropout and altered lipid synthesis. These studies suggest that hyperkeratinization may not play as great a role as previously thought in

either the migration of the Marx line or in age-related MGD. If hyperkeratinization were the primary driver of MGD, then the position of the mucocutaneous junction would be expected to move posteriorly toward the gland orifice and not away from it.[11] More definitive studies will be needed clarify and extend these observations.

Complicating Matters …

Lid health can be compromised and complicated by various conditions that can all ultimately exacerbate MGD. Seborrheic dermatitis, bacterial infections, dry eye and obstructions can all lead to a dysfunctional lid, lid margin and, consequently, tear film. However, like the proverbial chicken or the egg, often in these lid-related diseases it's difficult to discern which pathology came first.

When MGD is suspected, it's important to do a global assessment of the patient's health, since non-ocular disorders such as rosacea are often associated with MGD. Similarly, the red, scaly patches of seborrheic dermatitis can be telling. This chronic inflammatory skin condition is found in areas with a dense distribution of sebaceous glands, and is more common during periods of increased sebum production.[15]

The bacteriological origin of sebaceous gland pathology also leads us to consider a bacterial origin of MGD. In lid skin, antimicrobial lipids are stored in epidermal granules and dispersed into the intercellular spaces of the epithelium, where they release antibacterial sapenic and lauric acids. These fatty acids act in synergy with tear lactoferrin and lysozyme. Many organisms are susceptible to these acids, such as *S. aureus*, *S. pyogenes* and *S. epidermidis*. A deficiency in the quality or quantity of meibomian secretions can compromise this innate defense mechanism, putting the lid margin at greater risk for microbial invasion and the development of MGD.[6] Altered flora on the lids of patients with MGD may be an indication for the use of antimicrobial agents.

A number of ocular conditions are related to meibomian gland obstruction. Chalazia can cause abnormally thick meibomian gland secretions and increase the risk of meibomian gland obstruction. Foreign body giant cells are present in chalazia, yet they aren't thought to be related to an infectious process. By contrast, a hordeolum may be present and is usually caused by infection. Most hordeola are external and result from obstruction and infection of an eyelash follicle and the adjacent glands of Zeis or Moll. An internal hordeolum, which is very rare, results from infection of a meibomian gland.

Dry Eye and MGD Therapies

The relationship between MGD and dry-eye disease is truly tenuous and may be viewed as overlapping circles in a Venn diagram. There's a temptation to presume that MGD causes dry eye due to abnormal meibum secretion, leading to tear film instability and increased evaporation. However, it also may be true that evaporative dry eye precedes the development of MGD. Chronic lowering of the tear-film meniscus causes the delicate mucocutaneous shoreline to dry up, and hyperkeratosis, chronic inflammation, metaplasia and obstruction of the meibomian orifices can ensue. In this scenario, the development of MGD is a self-propelling process.

With the realization that the meibomian gland is a modified sebaceous gland, it follows that hormonal effects on gland function are likely to be significant.[16] Sebaceous glands are relatively inactive until the teenage years, at which point they increase in size and secrete larger quantities of sebum. Sebum levels stay relatively constant until about 80 years of age in males and until menopause in females. Both the increase in gland activity accompanying puberty and the decrease observed later in life are attributed to changes in androgen production.

Also, the impact of hormone levels on meibomian glands are readily observed in male patients undergoing anti-androgen therapy for prostate disease. These men have increased rose bengal and fluorescein staining; abnormal meibum; decreased glyceride, wax ester and cholesterol ester concentrations; and an increased free cholesterol content.[7] We now believe that acinar cells respond to androgens by activating expression of a host of genes, some of which encode enzymes involved in synthesis and secretion of meibum components.[13]

Managing lid-margin disease ultimately relies on the patient-doctor relationship. Evaluation should include a history of medication use, as a number of commonly used drugs can impact meibomian gland function in these patients.

If there are no overt signs of rosacea, dermatitis, hordeolum or chalazia, many clinical tools are available to evaluate MGD. Traditional examinations include slit-lamp biomicroscopy of the gland orifices, the Schirmer's test, tear meniscus height measurement, fluorescein staining, meibographic assessment of gland structure by transillumination, and subjective questionnaires. More sophisticated assessments available to researchers include fluorophotometry; lipid analysis using mass spectroscopy or thin-layer chromatography;[17-19] Ora's Lid Imaging System;[20] and the LipiView Ocular Surface Interferometer (TearScience, Morrisville, N.C.).[21]

Traditional treatments for MGD patients involve the use of warm compresses, lid scrubs, lid massage and

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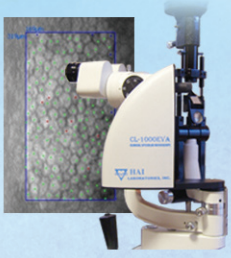

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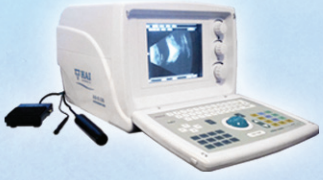

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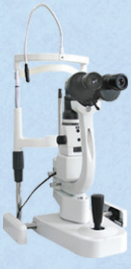

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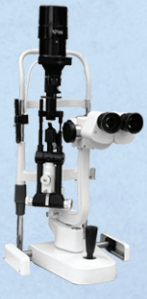

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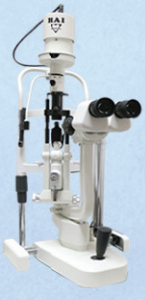

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gland expression with a cotton-tipped applicator. Although there is no one medication that works best for all patients, compounds that contain steroids seem to be the most effective in treating severe cases. One such therapy in development that was tested using Ora's anatomically based scales is NCX 4251 (Nicox, SA, Sophia Antipolis, France), a novel formulation of fluticasone propionate that utilizes an applicator for topical delivery to the eyelid margin.

Topical tetracyclines such as doxycycline have proven beneficial due to antibacterial and anti-inflammatory effects. In a study conducted by Ora using the Controlled Adverse Environment model, which exacerbates the signs and symptoms of dry eye with a desiccating environment, ALTY-0501 (Alacrity Biosciences, Laguna Hills, Calif.), a formulation of doxycycline, protected MGD patients against environmentally induced keratitis, as shown by significant reductions in fluorescein staining scores compared to controls. *(Shapiro A, et al. IOVS 2008;49:ARVO E-abstract 84)*

A combination of agents may be required for inflammatory conditions in which superficial bacterial ocular infection exists. In a study sponsored by Alcon, TobraDex ST (tobramycin/dexamethasone, Alcon, Ft. Worth, Texas), which is a multiple-dose antibiotic and steroid combination, was shown to be faster than Azasite (azithromycin, Inspire Pharmaceuticals) in controlling the signs and symptoms of lid-margin disease.[8] LipiFlow (TearScience), a novel thermal pulsation system that applies heat and pressure to the eyelid tissue, has been shown to be effective in expressing meibomian glands.[22]

Meibomian gland intraductal probing in the form of the Maskin Meibomian Gland Intraductal Probe (Rhein Medical, St. Petersburg, Fla.) is a procedure that physically removes material obstructing the gland ducts using a 1- or 2-mm probe. Probing is indicated in patients who complain of lid tenderness or who have symptoms such as burning and stinging and manual lid compression produces little to no sebum.

Although no one medication works best for all patients, compounds containing steroids seem to be most effective in severe cases of MGD.

Meibomian gland secretion plays a crucial role in ocular surface health. Lipids secreted by meibomian glands have an essential role in reducing evaporation from the ocular surface, lowering the surface tension of tears, preventing tear spillover and preventing damage to the skin of the lid margin. Diagnostic accuracy—putting a name to the diagnosis—is the first step in a successful therapeutic strategy. No matter what name we give them, though, related tear-film disorders including blepharitis, meibomian gland dysfunction and meibomitis all have the potential to impact the health of the ocular surface. REVIEW

Dr. Abelson is a clinical professor of ophthalmology at Harvard Medical School. Mr. Ousler and Mr. Shapiro are vice-presidents at Ora Inc. Mr. Rimmer is a medical writer at Ora. Comments or questions may be sent to MarkAbelsonMD@gmail.com

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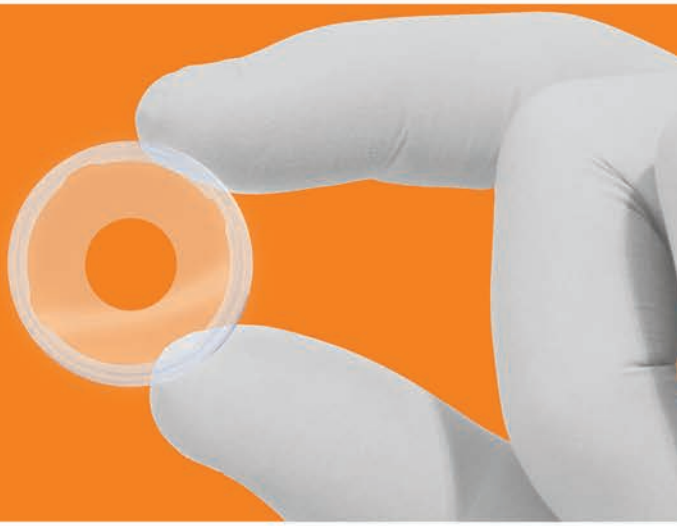

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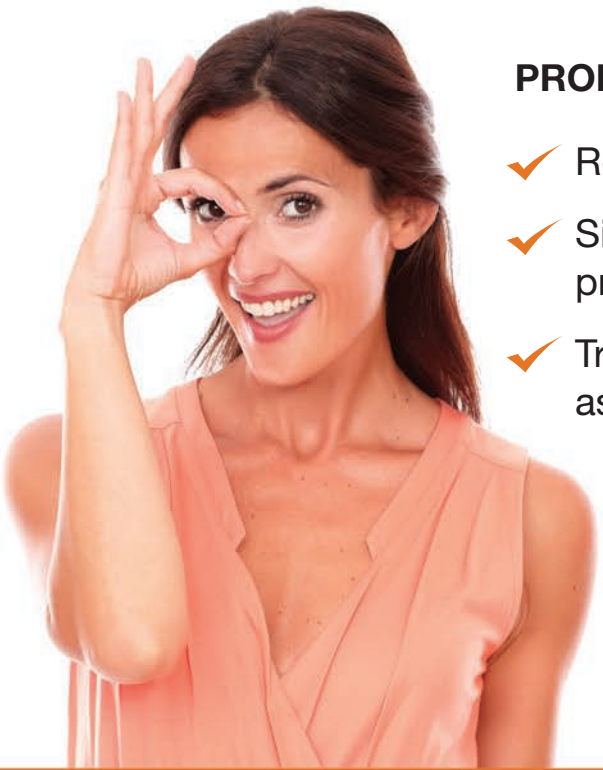

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Congenital Hereditary Endothelial Dystrophy

CHED is a rare corneal disorder. Treatment decisions depend on severity and are driven by a careful, observant clinical exam.

Danielle Trief, MD, David C. Ritterband, MD, John Seedor, MD, and Emily Waisbren, MD, New York City

Congenital hereditary endothelial dystrophy is a rare corneal dystrophy characterized by bilateral diffuse clouding of both corneas from infancy. CHED was first described in 1960 by Edward Maumenee, MD, who reported a series of cases of varying corneal clouding that was congenital and principally stationary.[1] The corneal clouding in CHED ranges from a mild haze to a ground glass, milky appearance. This clouding can lead to amblyopia. Patients present with a thickened cornea, with pachymetry readings two to three times normal, and a thickened Descemet's membrane.[2]

The incidence of congenital corneal opacities, including congenital glaucoma, is six per 100,000. CHED makes up a small minority.[3] Although the incidence of CHED is quite low, it is more common in places with higher consanguinity. In reviews from the Middle East and India, a diagnosis of CHED accounted for 21 percent of all pediatric keratoplasties.[4,5]

The corneal clouding and thickening seen in CHED is a result of a paucity of endothelial cells. In the healthy cornea, the endothelium exists as a monolayer of polygonal cells, which serves as a fluid "pump" to keep the stroma dehydrated and maintain corneal clarity. A healthy corneal endothelium in children and young adults is around 3,500 cells/mm^2.[6] These cells work by a Na/K ATPase ion pump to remove water from the stroma and deposit it in the aqueous humor. Fluid can disrupt the highly organized lamellar collagen matrix and lead to a loss of corneal clarity. In CHED (and other endothelial dystrophies like Fuchs' dystrophy), a loss of endothelial cells results in a buildup of fluid in the corneal stroma (edema). Electron microscopy studies have revealed severely reduced and atrophic endothelial cells in CHED patients.[7]

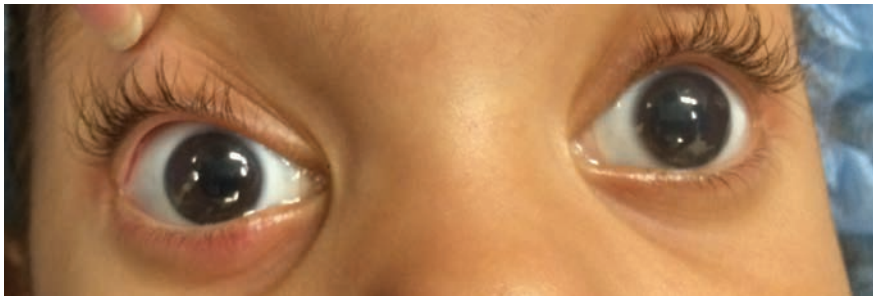

Figure 1. A 3-year-old female with congenital hereditary endothelial dystrophy. The right eye is 1.5 months post-DSAEK without endothelial stripping. There is increased corneal clarity. The left eye has not been operated on yet. There is a mild but diffuse corneal clouding, which in this picture can best be appreciated over the pupil.

Until recently, CHED had been classified into two variants: 1) an autosomal dominant variant that presents after 1 year of age and is progressive (CHED1); and 2) an autosomal recessive variant that presents at birth and is stationary (CHED2). Patients with CHED1 are described as being born with clear corneas and develop clouding over the first few years of life. They complain of epiphora and photophobia, but

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do not have nystagmus. By contrast, CHED2 patients are described as having corneal clouding from birth with accompanying nystagmus. They do not complain of epiphora or photophobia. The corneal clouding in CHED2 is generally more advanced than in CHED1, and corresponds to a worse visual acuity. Recent genetic studies have mapped CHED1 to an area on chromosome 20 that overlaps with posterior polymorphous corneal dystrophy (PPCD).[8] Additionally, a review of reported cases of CHED1 found considerable overlap in clinical, histopathologic and electron microscopic examinations between CHED1 and PPCD.[9] Clinically, patients with both conditions have been described as having small flakes, spots and irregular white areas throughout the stroma. A review of histopathologic and electron microscopy studies of previously diagnosed CHED1 patients reveals multiple abnormal endothelial layers and microvilli, which can also classically be seen with PPCD.[10,11] Recently, the international classification of corneal dystrophies (IC3D) has been revised to eliminate CHED1 from classification, stating that, "There is no convincing published evidence to support the existence of AD CHED as a distinct entity."[12] The autosomal recessive CHED (CHED2) is now renamed CHED.

Clinical Findings

In addition to corneal clouding and thickened pachymetry, patients with CHED may have an irregular or roughened appearance of their epithelium, suggestive of edema. This can be better delineated by the instillation of fluorescein. The clouding in CHED is diffuse (limbus to limbus) and relatively uniform. While the cornea can be quite cloudy, even milky, the iris is usually visible. This is in contrast to other etiologies of congenital corneal clouding like Peter's anomaly or a limbal dermoid, which can vary in size/location and often obscure underlying iris. Aside from the corneal abnormalities, the structure of the eye in CHED patients is usually normal.

It is important to differentiate congenital glaucoma from CHED, as both conditions can produce corneal clouding from infancy. Additionally, CHED patients often have relatively high intraocular pressure secondary to thick pachymetry.[13] Clinicians should look carefully for signs of glaucoma including increased corneal diameter, increased cup-to-disc ratio, Haab's striae and buphthalmos. However, there are several reports of concomitant CHED and glaucoma.[14,15] Some authors consider both CHED and congenital glaucoma neurocristopathies.[16,17] CHED may be secondary to a failure of regression of primordial endothelium during the development of the anterior chamber and congenital glaucoma may result from a sheet of primordial endothelium that fails to fenestrate appropriately within the angle, causing an abnormal insertion of the iris. To diagnose either condition, a careful exam is paramount, which can be difficult in young children. If necessary, an exam under anesthesia should be scheduled. Pre-intubation IOP, refraction, corneal diameter, axial length and gonioscopy should be documented.

Clinicians should also inquire about hearing loss, as several patients with CHED have been found to have Harboyan syndrome, also called corneal dystrophy and perceptive deafness. These patients have progressive post-lingual sensorineural hearing loss. The hearing loss typically becomes clinically apparent by 10 to 25 years old. Deficits start in the 20 to 25 dB range (mild to moderate) and occur at higher frequencies.[18] More than 50 percent of cases have been associated with parental consanguinity.

Genetics

CHED has been mapped to chromosome 20 loci 20p13. The gene codes solute carrier family 4, sodium borate transporter member 11 (SLC4A11).[8] Eranga Vithana and

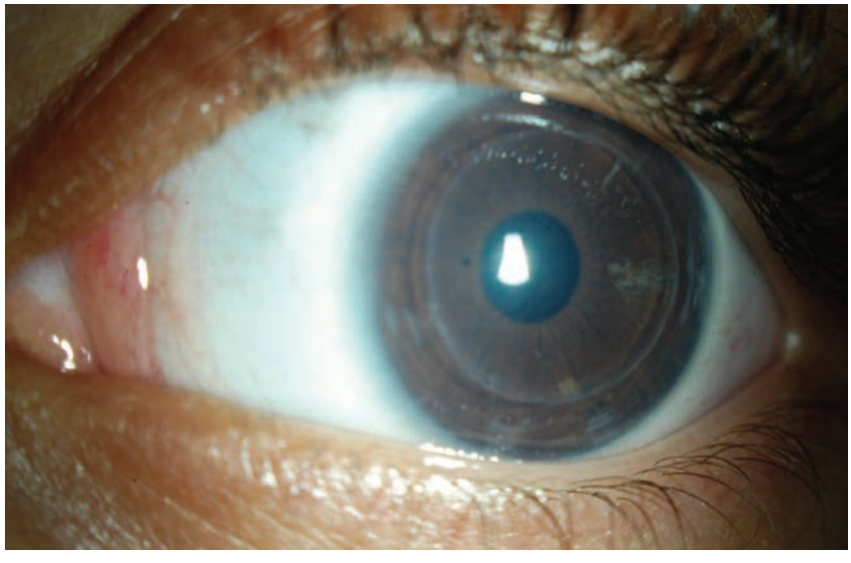

Figure 2. A 3-year-old female with CHED, three months after DSAEK without endothelial stripping of the left eye. Her corneal clarity is significantly improved and her visual acuity improved from 20/250 to 20/80.

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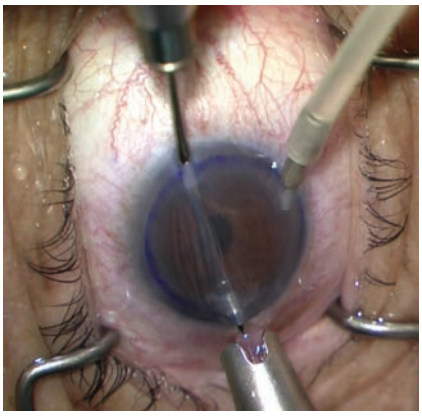

Figure 3. Performing a DSAEK with a Busin glide, anterior chamber maintainer and a miotic pupil.

colleagues studied 10 families with CHED and found seven different mutations in the SLC4A11 gene.[19] The gene encodes a sodium borate transporter. Transfection of an immortalized cell line with mutant SLC4A11 cDNAS resulted in little to no expression of transporter protein on the cell surface. The majority of pedigrees with CHED who have been screened demonstrate coding region mutations in the SLC4A11 gene.[9] It is thought that the intracellular boron concentration plays a key role in the growth and terminal differentiation of neural crest cells. Therefore, loss of function of this transporter may result in abnormal corneal endothelial synthesis and differentiation.

Patients with Harboyan syndrome also have mutations in the SLC4A11 gene. The gene is expressed in the cochlea of adult mice and thought to play a role in the homeostasis of cochlear fluid and endolymph secretion.[18] This may explain the concomitant corneal edema and hearing loss seen in patients with Harboyan syndrome.

Management

CHED patients have varying visual acuities depending on the degree of corneal clouding. A decision must be made whether to intervene or observe. If intervention is desired, surgery is required. The pathophysiology is a result of inadequate endothelium, and treatment therefore requires replacing the endothelium. This can be accomplished by either a full-thickness transplant (penetrating keratoplasty) or a partial-thickness transplant surgery, where only the endothelium is replaced (Descemet's stripping endothelial keratoplasty). In all cases, patients should be carefully followed and amblyopia should be treated.

Penetrating Keratoplasty

PK in children can be challenging for a number of reasons: Children have higher rates of graft rejection than adults. Surgery is challenging because of lower scleral rigidity, increased fibrin reaction and positive vitreous pressure. Children may be difficult to examine and suture adjustments may necessitate multiple exams under anesthesia, all the while taking into account changing refractions and managing amblyopia.[5]

A multicenter retrospective study for PK in CHED by Debra A. Schaumberg, MPH, and colleagues found a first graft survival rate of 71 percent.[20] Half of the children improved one or more Snellen lines, but only 40 percent ultimately achieved visual acuity of 20/200 or better.[21] A second series from India found a 75 percent graft survival rate at four years for presumed AR CHED patients. Ali A. Al Rajhi, MD, and colleagues compared "early onset CHED," formerly CHED2, to "delayed onset CHED," formerly CHED1 but now considered part of the PPCD spectrum. They found better acuities and graft survival in the delayed onset group.[22] Similarly, series where patients received grafts at later ages report improved visual acuity and graft survival.[23,24] However, this relative success may be a function of the fact that these patients have more mild disease/PPCD.

DSEK

Given the fact that CHED is primarily a disorder of the corneal endothelium and Descemet's membrane, a DSEK is another good surgical option. Compared to PK, DSEK offers the advantage of faster visual recovery, a relatively closed system during surgery and fewer corneal sutures, producing less corneal astigmatism and necessitating less postoperative suture adjustment/removal. One challenge of DSEK in CHED is Descemet's scoring and removing the corneal endothelium. Visibility is often compromised due to corneal clouding, and the endothelium has been found to be more adherent than in other cases of endothelial dysfunction, like Fuchs' dystrophy.[25] A second challenge is the fact that CHED patients are often phakic and, therefore, causing a cataract is a significant risk during surgery. In adults, Janet Y.M. Tsui, MD, and colleagues found that the presence of an air bubble caused a premature cataract in 40 percent of phakic eyes.[26] In a study at L.V. Prasad Eye Institute, Jatin N. Ashar, MD, and colleagues did a paired comparison, where patients with CHED underwent PK in one eye and DSEK in the contralateral eye.[27] At one year, they found that all grafts were clear. In the DSEK group, the astigmatism was significantly lower and had faster stabilization of refraction. By contrast, grafts appeared overall clearer in the PK group, although final visual acuity was equivalent. Several case series have reported improved visual acuity and corneal clarity with a relatively short visual recovery in patients undergoing DSEK for CHED.[28,29]

Specific Considerations

Given the difficulty of Des-

cemet's stripping in the setting of reduced corneal clarity and adherent endothelium, several authors have completed DSEK in CHED without stripping and without removing the host endothelium. Massimo Busin, MD, and colleagues did not strip Descemet's in patients less than 1 year old at the time of surgery because Descemet's could not be identified. In all patients, the donor tissue ultimately attached and the cornea cleared completely by one week after surgery, although in four of the six eyes, re-bubbling was necessary.[29] Jatin N. Ashar, MD, and colleagues compared patients with CHED where Descemet's was not stripped (nDSEK) to those where it was stripped (DSEK), and found comparable final visual acuities between the two groups.[30] One of the three patients with nDSEK needed to be re-bubbled compared to 0 with DSEK. Based on these findings, DSEK without stripping is a viable option for patients where there is poor visibility, who are very young and/or Descemet's is difficult to identify and remove.

Several techniques have been described to minimize lens trauma in phakic pediatric DSEK patients. Mahmoodreza Panahi-Bazaz, MD, and colleagues describe a suture pull-through method, to minimize anterior chamber manipulation when visibility is poor.[31] Additionally, topical pilocarpine was used to induce miosis. Dr. Busin and colleagues advocate moving the incision superiorly so that the pull- through method can be done over the superior iris, which protects the underlying crystalline lens.[29]

Prognosis

Final visual outcomes in patients with CHED vary and depend on the degree of corneal clouding, the level of amblyopia and whether or not there was a successful surgical intervention. Compared to other etiologies of congenital corneal clouding, CHED patients tend to have better surgical outcomes.[5] This is likely due to the fact that, in most circumstances, CHED patients have an otherwise healthy eye. The recent advent of DSEK offers a much less invasive alternative to PK surgery. Clinicians should screen carefully for concomitant conditions like glaucoma and hearing loss. Patients and family should be counseled on the necessity of long-term follow-up and should understand the genetic nature of this disease. REVIEW

Dr. Trief is an assistant professor of ophthalmology at the Edward S. Harkness Eye Institute, Columbia University Medical Center. Dr. Ritterband is a clinical professor of ophthalmology at the Icahn School of Medicine of Mt. Sinai, and the assistant director of the cornea service at the New York Eye and Ear Infirmary of Mt. Sinai. Dr. Seedor is a clinical professor of ophthalmology at the Icahn School of Medicine, and system director of cornea and external disease at NYEEI of Mt. Sinai. Dr. Waisbren is an assistant professor of ophthalmology at Icahn. Also contributing to the article were Luna Xu, MD, and Yijie Lin, MD, MBA, ophthalmology residents at NYEEI of Mt. Sinai.

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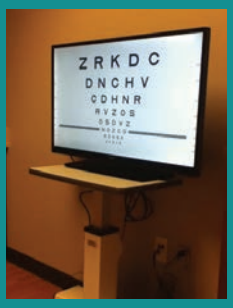

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Managing Pediatric Patients With Glaucoma

Managing young patients with this disease presents a number of challenges, in terms of both diagnosis and treatment.

Sharon Freedman MD, Durham, N.C.

Childhood glaucoma is distinct from adult glaucoma in several ways. For one thing, it's relatively rare. Also, even more than in adults, it encompasses a rather broad group of disorders sharing a common feature: elevated eye pressure and the resultant damage. If a child has primary glaucoma, the main problem is an outflow dysfunction, but a child can also have secondary glaucoma as a result of trauma, inflammation or bleeding in the eye, or as the result of an ocular malformation. Childhood glaucoma can also be associated with a variety of systemic syndromes and disorders.

Here, I'll review some of the basic steps an ophthalmologist who is not a specialist in pediatric glaucoma can take to identify and manage a child who presents with possible signs of glaucoma. I'll also share some of the latest thinking on how the different types of childhood glaucoma can be most effectively categorized and addressed.

Diagnosing the Problem

When you want to make a judgment about whether a child has glaucoma, you should follow these steps:

• ***Assess the child's overall appearance and behavior.*** The first thing to do is step back and take a look at the child. Is there anything abnormal in the child's appearance? Does the child seem to have a problem, or be entirely well?

• ***Check the child's history.*** Has the child had a past problem with his eyes? If the child has had a cataract removed, that child is automatically at risk for getting glaucoma. The child might have been injured, which could trigger glaucoma. The child might have a form of childhood inflammation in the eye called juvenile idiopathic arthritis or uveitis, in which case joints could be involved as well.

• ***Look closely at the eyes.*** If the child looks well overall, then focus on the eyes. Clues that glaucoma may be present include:

— *Enlarged eyes.* Early in life our eyes are still expandable and stretchy. As a result, elevated intraocular pressure from early onset of a condition such as primary congenital glaucoma can cause one or both eyes or corneas to become larger. *(See example, facing page.)* So, if a child's cornea is larger than you would expect at that age, that should make you suspicious of the possibility of glaucoma. (You can estimate the cornea's width by holding a ruler or a card with a ruler printed on it up to the eye.)

Ironically, these kids are often thought to have beautiful eyes, and they get compliments everywhere their parents take them. It may take some time for everybody to realize that the large eyes are the result of a disease.

— *Hazy corneas.* The haze could be the result of corneal edema or breaks in Descemet's membrane caused by elevated pressure (Haab striae).

— *Behavior indicating light sensitivity.* Corneal changes in childhood glaucoma with onset in infancy can produce photophobia, so a very young child with primary congenital glaucoma will often be squinting, tearing or squeezing the eyelids to avoid bright light.

— *Asymmetry between the eyes.* If the glaucoma is affecting one eye more than the other, the affected eye may be larger or have more haze on the cornea. Generally, it's the bilateral,

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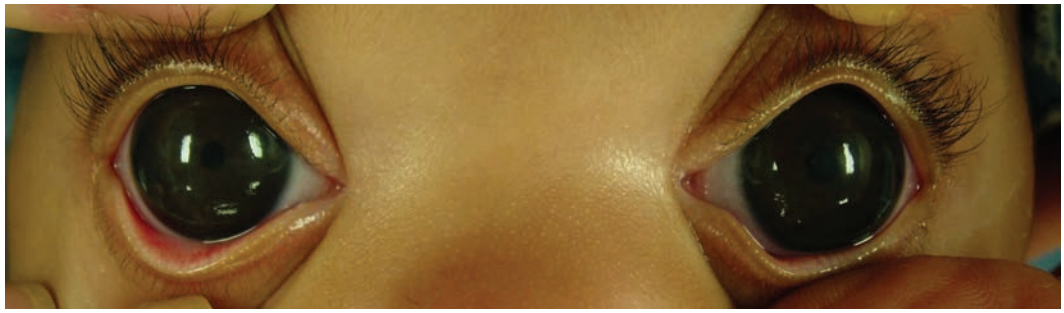
symmetrical cases that get missed because both eyes look the same. If one eye starts getting bigger than the other, the parent, pediatrician or an eye-care provider will usually notice.



This 4-month-old child presented with large, hazy corneas and was diagnosed with primary congenital glaucoma. The photograph was taken during examination under anesthesia, just prior to angle surgery that successfully reduced the elevated intraocular pressure and controlled the glaucoma.

— *Abnormal iris.* The iris may be abnormal in Axenfeld-Rieger syndrome or in aniridia, where most of the iris is missing.

— *Shaking eyes.* Nystagmus in a young child is often a sign of poor vision and possible glaucoma.

• ***Try to assess vision.*** The most effective way to do this depends on the age of the child. An older child may be able to read the Snellen chart. If the child is younger, you may have to see if the child can fixate on a toy or an interesting object such as a face, and follow it. Myopia can sometimes result from the elevated pressure associated with glaucoma, since high pressure can stretch the eye; the stretching increases the eye's axial length, making the child myopic in one or both eyes. (Most healthy children are actually hyperopic when they are very young.)

• ***Try to assess intraocular pressure.*** This can often be accomplished with the instruments you would use in adults, but you may need to use them in modified form. For example, we often attempt to check the pressure in the clinic with an iCare rebound tonometer, which can be done without an anesthetic.

One important note: Try to keep the child happy. A common mistake is to do something such as holding the child down to check the intraocular pressure. If the child is crying or doing a valsalva maneuver the pressure is going to be artificially elevated. So if the child is crying, the reading you get won't mean much.

• ***Try to assess the condition of the optic nerve.*** Abnormal cupping can also be a sign of glaucoma. Most healthy children don't have a lot of cupping, especially when they're very young; they usually have a good rim, and good symmetry in the appearance of the optic nerve in both eyes. Of course, looking at the optic nerve may not be easy in some children, unless you're an experienced pediatric ophthalmologist or pediatric glaucoma specialist.

It's worth noting that some surgeons might expect us to put a child under anesthesia in order to conduct an exam. Certainly there are things you need to put a child to sleep for, but most pediatric glaucoma specialists won't use anesthesia unless we're already pretty sure that something is seriously wrong with the child. Furthermore, in that situation we wouldn't be simply collecting data or doing gonioscopy, we'd be deciding what we need to do to address the problem: how severe it is; what type of problem is it; and what surgery would be most appropriate to treat the child, if surgery is indeed needed.

When to Use Meds

Pediatric glaucoma specialists often use medications to manage glaucoma in children, but many types of glaucoma in young children are primarily surgical diseases. In those cases, we only use medications as either a temporizing measure before we do surgery or as an adjunct to surgery postoperatively. For example, primary congenital glaucoma is a surgical disease; we do either a goniotomy or a trabeculotomy to open the drainage angle. Often, we don't need any medicine long-term if the surgery works well enough.

On the other hand, some types of childhood glaucoma can be treated using medication as the first-line therapy. In those cases, surgery would be used only if the medications aren't adequate to keep the pressure under control, pretty much as you would do with an adult. However, medications have to be used very judiciously in children; some children can be injured by giving them medication that isn't appropriate. I recently saw a 10-week-old baby who was given both brimonidine 0.15% and timolol 0.5%; it put the baby in the hospital with bradycardia and lethargy. The beta-blocker was too strong for a baby, and the alpha-2 agonist brimonidine is absolutely contraindicated in babies. So medications can be used to treat some types of childhood glaucoma, but they must be used with care.

Defining Pediatric Glaucomas

Once a diagnosis is made, deciding



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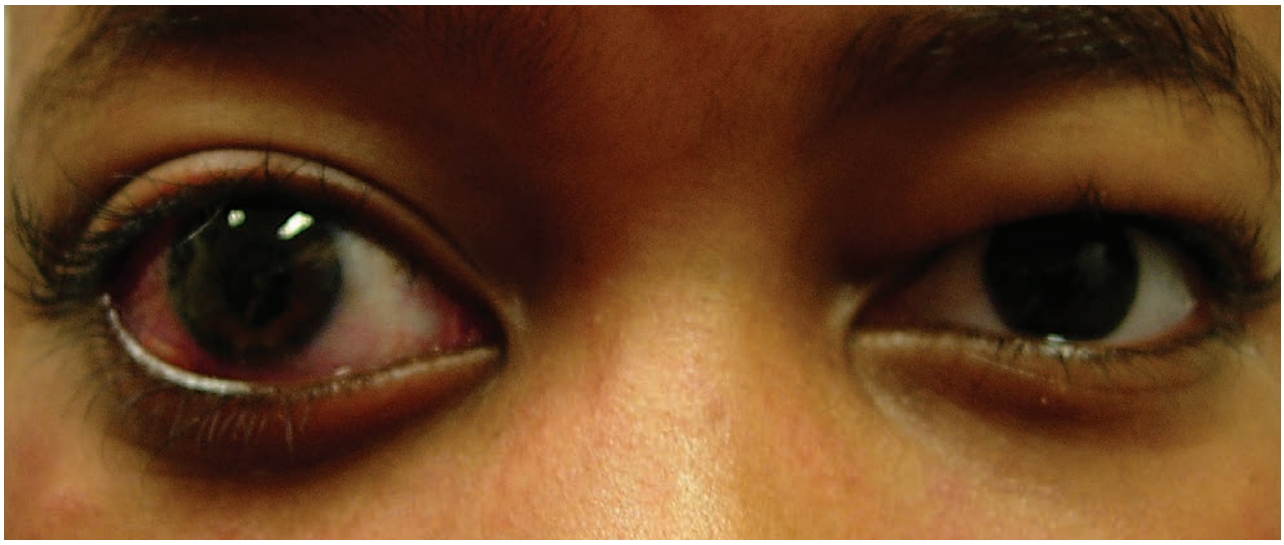

This child was born with a port wine mark on the right side of his face involving his upper eyelid. He developed seizures and was noted to have an enlarged and often pink right eye. Glaucoma was diagnosed when he was 18 months old, and required medications as well as glaucoma drainage implant surgery to control. The left eye is unaffected and is normal.

how to proceed can be a challenge. The numerous types and sources of glaucoma found in children have contributed to a lack of agreement about how best to manage some of the variations. The different disorders falling under the umbrella of "childhood glaucoma" have a variety of severities and prognoses—from mild to moderate to severe, in terms of the glaucoma itself and the impairment of the child's vision—and each child's response to therapy can be very different.

Because all of these diseases are relatively uncommon, the literature is sparse and sometimes confusing. If I'm treating one of the glaucomas that responds very well to treatment X, and you're treating a much more difficult subgroup of patients that doesn't respond so well to treatment X, what do we make of that? These circumstances have made it difficult to come up with any sort of optimal strategy for managing pediatric glaucoma, so the same type of childhood glaucoma may be treated very differently in different parts of the world.

My colleagues and I have attempted to reduce some of the confusion and improve diagnosis, treatment and outcomes by coming up with standardized guidelines for how to treat some types of childhood glaucoma. Allen Beck, MD, and I were both involved as pediatric glaucoma specialists in the Infant Aphakia Treatment Study, a randomized, controlled trial comparing the efficacy of implanting an intraocular lens vs. aphakia in babies with a unilateral cataract. One of the dreaded complications of removing a cataract from a baby's eye is glaucoma, so we and the study's lead investigator, Scott Lambert, MD, realized that we needed a consistent, specific definition of glaucoma and glaucoma suspect in these babies. (It may be very obvious if a child has full-blown glaucoma, but determining when or if a child is developing glaucoma can be very difficult.)

Once we developed clear criteria for that, we decided to use those definitions as a basis for a much larger project. The Childhood Glaucoma Research Network, a volunteer group of experts in pediatric glaucoma from all over the world, took on the task of agreeing upon a definition of childhood glaucoma and a consensus classification system of the types of childhood glaucoma, building upon much work that has already been done by many dedicated leaders in the field over many decades.

As a group we have agreed upon a classification system that divides childhood glaucoma into primary and secondary types, with congenital glaucoma being the most common primary glaucoma. Among the secondary glaucomas, some are associated with eye problems such as aniridia; others are associated with systemic problems such as Marfan syndrome and Lowe syndrome. Secondary glaucomas include those acquired as a result of another process in the eye such as trauma or inflammation, and one that's unique to children: the glaucoma that can occur after removal of a childhood (usually congenital) cataract. The resulting classification system has been published.[1] Having a common language is allowing clinicians and researchers around the world to compare results and move forward coherently.

The Four Most Common Types

If you're a comprehensive ophthalmologist, it's important to remember that glaucoma in children is a group of diseases. In particular, you should recognize four categories of childhood glaucoma.

First, the most common primary glaucoma in children—meaning glaucoma that's not caused by another problem—is primary congenital glaucoma. If you see a baby who is otherwise well but has a big eye, a teary eye or a cloudy eye, a diagnosis of primary congenital glaucoma will be correct most of the time. This is a surgically treated disease, and you need to get that child to a glaucoma specialist.

The second most common kind of childhood glaucoma is glaucoma that occurs following cataract removal. If a baby or young child has had a cataract removed, that child's eye is at lifelong risk of glaucoma. The median age of onset is 5 years old, but some children will get much older before a problem develops. These individuals may even go off to college, by which time everybody thinks any risk of glaucoma has passed. They are done with amblyopia, they've had a lens implant or they're wearing a contact lens; but then suddenly they present to a comprehensive ophthalmologist with glaucoma in that eye.

This is a secondary glaucoma, a type that would be treated first with medications. A comprehensive ophthalmologist could certainly begin the treatment in this situation, especially in the case of a child who is old enough to be able to sit at the slit lamp, get her pressure checked and get her optic nerve photographed.

The third kind of childhood glaucoma a comprehensive ophthalmologist should be aware of is any glaucoma caused by a separate problem—for example, an eye that has undergone trauma or has inflammation uveitis. These eyes are definitely at risk for glaucoma, so if you are the primary care provider you should be alert for any signs of glaucoma developing in a child who fits this description. These eyes would be treated first with medication, provided the angle configuration was open. (Angle closure requires surgical intervention.)

If you're not used to working with children, you should team up with someone who takes care of a lot of kids with this type of problem.

Finally, there's an unusual type of primary glaucoma called juvenile open-angle glaucoma; this is very similar to the kind of open-angle glaucoma that the elderly get—the kind a comprehensive ophthalmologist treats all the time. This type of pediatric glaucoma typically shows up in a school-age or early teenage child. Notably, this may be a child who comes in to get eyeglasses because of myopia. In fact, when you're dealing with children, you should treat every myopia patient as a possible glaucoma suspect. If you routinely check the pressure and look at the nerve when a child comes in with myopia, you won't miss one of these cases.

Most Important: Take Action

The good news for the comprehensive ophthalmologist is this: If you simply use common sense, most of the time you'll see lots of clues that something is not right with a child who has glaucoma. The most important thing is to recognize that the child you're seeing has a problem and not let it go past. I've seen really bad cases where a child has a cloudy, teary eye, and the pediatrician has been calling it a blocked tear duct. Or the child is thought to be shy because light sensitivity makes the child not want to look up at anybody. Sometimes it isn't until the child develops nystagmus that the glaucoma is diagnosed.

If you're a comprehensive ophthalmologist and you suspect glaucoma in a child, don't hesitate to contact someone who has more expertise. In some areas where there is no pediatric glaucoma specialist, that might mean working with an adult glaucoma specialist. In other areas, a pediatric ophthalmologist can be the first line of defense. The pediatric ophthalmologist may then, in turn, pass the patient along to an adult glaucoma specialist if certain types of surgery are needed which are not in the armamentarium of the pediatric ophthalmologist.

If you're a glaucoma specialist and you strongly suspect a child of having glaucoma, it's OK to attempt to address the problem. However, if you're not used to working with children, you should team up with someone who takes care of a lot of kids with this type of problem. It's an unusual enough condition that there are tricks and tips an average glaucoma specialist may not be familiar with—things the average comprehensive ophthalmologist certainly won't be familiar with. REVIEW

Dr. Freedman is a professor of ophthalmology and pediatrics and chief of the Pediatric Ophthalmology and Strabismus Service at Duke Eye Center in Durham, N.C.

1. Beck AD, Chang TCP, Freedman SF. Definition, classification, differential diagnosis. In: Weinreb RN, et al., eds. Childhood Glaucoma: Consensus Series 9. Amsterdam: Kugler; 2013:3-10.

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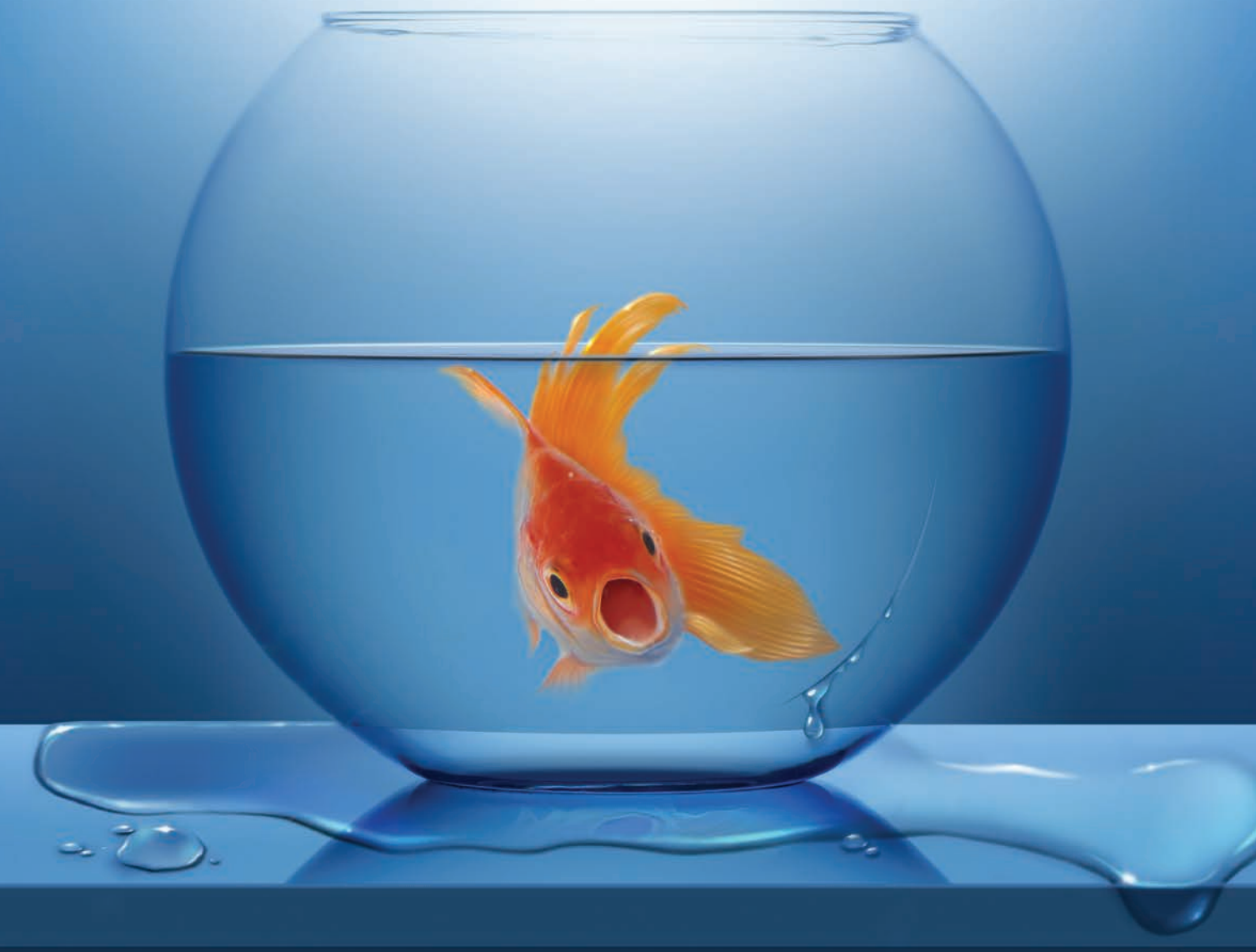

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The Keys to Better Femto Flaps

The proper laser settings and technique will make for a smoother femtosecond LASIK case.

Walter Bethke, Managing Editor

Some refractive surgeons have mastered femtosecond flapmaking to the point where it's almost automatic. Though being able to automatically create a flap is admirable, skills that become automatic can sometimes lull one into a false sense of security that can lead to problems. Here, refractive experts describe what they remain mindful of when creating flaps in order to ensure a problem-free LASIK case.

Docking the Laser

Surgeons say there are steps you can take to avoid stumbling out of the gate when you start the procedure.

Inadequate suction while trying to dock the laser on the patient's eye can scuttle a case. Vancouver, Wash., surgeon Brian Will says, in his experience, there are three patient-related reasons for this to occur. "The first is related to the patient's presentation or actions that affect the quality of suction," he says. "For instance, in a patient with high astigmatism, such as 4 to 6 D, the entire globe is kind of elliptical, not just the cornea. So, you're trying to put a device on the football-shaped eye that was actually designed to be used on a spherical shape. You're more prone to get a vacuum break in that situation, even with a silicone skirt on your device.

"The second reason," Dr. Will continues, "is if you've got really tight lids or a small fissure. This will make it difficult to get full apposition of the vacuum ring on the globe. This type of eye is more prone to getting a vacuum break because it's more challenging to get the skirt seated on the globe itself. The third patient-related reason is excessive lid squeezing, or instances when the eye tends to roll superiorly due to Bell's phenomenon. These can torque the vacuum ring once it's on the eye, and can cause a break in vacuum, as opposed to a patient who is well-fixated and not stressing or straining against the vacuum ring."

Dr. Will says a second group of causes stems from improper technique. "A vacuum break can result from having some lashes under the silicone vacuum-ring skirt," Dr. Will says. "Even a broken-off lash under there can cause it. So, make sure the ocular surface environment is clean. A break can also happen if there's a fold of the silicone skirt itself, or if it's a small eye or tight lid that doesn't give much room for the skirt to spread out into the fornices. A possible cause that was more common years ago than now is that there's something wrong with the vacuum ring: The ring is either defective, such as an instance in which the silicone skirt isn't perfect, or there's a poor seal where the syringe meets the silicone. There can be a potential leak there."

To deal with a suction break, Dr. Will says to first look for obvious problems. "Take out the failed ring and assess the situation," he says. "Note how chemotic the conjunctiva is, and look around the lids and fornices for debris such as lashes. Have the patient blink to possibly clear debris. If need be, instill another drop of anesthetic if the patient is having some discomfort and squeezing a lot." Dr. Will says it's also important that the patient understands to be relaxed so as not to move during flap creation. Vance Thompson, MD, a surgeon from Sioux Falls, S.D., says this idea of preop patient communication about intraoperative movement is an important point. "The most common cause of suction

This article has no commercial sponsorship.

loss is a slow drift," Dr. Thompson avers. "It's up to us to prepare the patient with pre-docking instructions. I tell him the best thing to do is hold still, but I define what that means: not just keeping the eye and head still, but also not moving the arms or legs or talking. We don't do small talk because it creates movement."

Dr. Will says, in many cases, the problem may be mechanical. "Most of the time, I'll assume the vacuum ring is defective and just replace it," he says. There's not much downside to doing that, because the company will give you a new ring for free. However, never change the applanation cone if the suction break occurred during dissection."

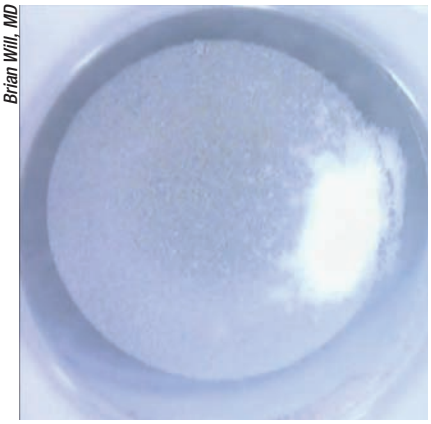
Dr. Will provides these other tips:

- if it's a large flap, try shortening the diameter to shave seconds off the case to help ensure you can complete your treatment before another break occurs;
- use an open-wire lid speculum to control the lids better and to stretch redundant conjunctiva—which can result in a suction break—back in the fornices;
- in the absence of a speculum, go around the perimeter of the eye with your finger, retracting the lid and pulling it away from the edge of the vacuum ring; and
- put a little downward pressure onto the globe with the vacuum ring throughout the entire applanation.

Intraoperative Complications

Surgeons say you can take steps to prevent or manage other events that occur during the LASIK case, as well.

- ***Opaque bubble layer.*** The photodisruption of the femto can result in bubbles that block subsequent laser pulses or interfere with the pupil tracker. Salt Lake City surgeon Majid Moshirfar, who is a professor of ophthalmology at the Moran Eye Center, says OBL can often be prevented with the proper steps. "Using less energy, using a smaller spot separation, maintaining the laser regularly and avoiding too much suction can help prevent OBL," he explains. "If you end up with OBL, it's recommended that you wait three to 10 minutes, examine the patient either in the supine position or at the slit lamp and then attempt to lift the flap and continue with the treatment. The other recommendation: If the bubble layer is paracentral and you don't think it's going to impact the central 4 to 6 mm of the ablation zone, just lift the flap and continue."


Brian Will, MD

Less energy, a smaller spot separation, regular laser maintenance and soft docking can help avoid an opaque bubble layer.

- ***Vertical gas breakthrough.*** This is when the photodisruption causes an upward-directed break in the corneal layers. "It's analogous to the buttonholes we used to see with mechanical microkeratomes," explains Dr. Moshirfar. "But with them, they were quite central, while vertical gas breakthrough is usually peripheral and somewhat paracentral. I've never seen it in the center of a flap. Most of the time, vertical gas breakthrough happens due to some abnormality in the corneal density such as a scar or a subepithelial opacity due to contact lens use that caused subepithelial haze. If the gas breakthrough is very paracentral—not involving the central 6 mm—and it's small, you can lift the flap, do the treatment and lay it back down. Many will place a bandage contact lens after such a treatment to ensure the vertical gas breakthrough doesn't result in ingrowth in that area. However, if it's larger than 0.5 mm x 0.5 mm, even if it's paracentral, I recommend not lifting the flap and postponing the procedure. Maybe later you can consider creating a much thicker flap with a different device, possibly a microkeratome, or performing a PRK."
- ***Corneal scar.*** A scar can cause problems with the femtosecond laser, but many cases are salvageable, surgeons say. "Since a scar, especially one from a previous foreign body removal, involves the loss of tissue, you could easily cause a stromal hole as you're creating the flap," says Dr. Thompson. "Then, as you use your LASIK spatula to dissect the plane, the tip can get into that hole and tear the flap. If we're operating on someone with a scar, we try to go to a 130-µm flap, as opposed to our usual 110 µm. In the case of a subtle scar from contact lens use, we'll note how much loss of tissue there is, and it's not unusual that we can do these at 130-µm flap thickness. If it's another type, such as from an injury, we probably aren't going to do it. Note that, if the patient has a scar from Salzmann's or early pterygium, the changes in the corneal stroma are often more pronounced than the scar looks. The collagen in such cases is often disorganized, and the femto will go through it irregularly and result in an irregular flap." Dr. Will says, since scars are often composed of disorganized collagen, the slit lamp can be misleading. "It's helpful to assess the scar's density by also viewing it with a pen light," he says. "Use your own two eyes, because there's often a disconnect between the scar's density at the slit lamp and its density in natural light. The latter will be much more predictive of how much trouble you'll have with flap creation." REVIEW

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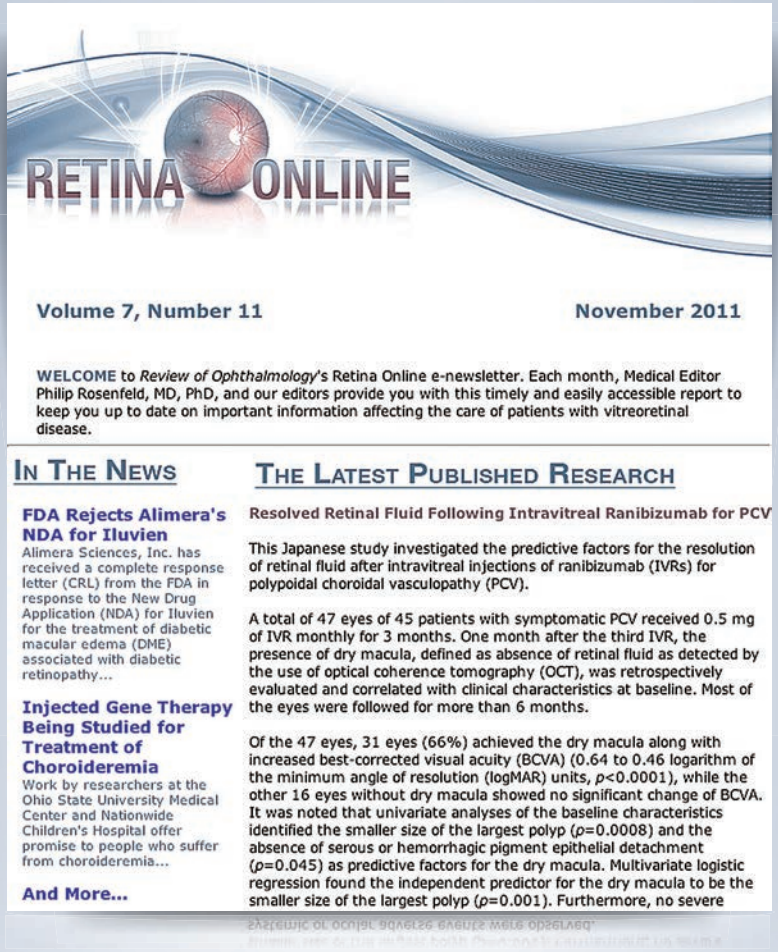

RETINA ONLINE

Volume 7, Number 11 November 2011

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

IN THE NEWS

FDA Rejects Alimera's NDA for Iluvien
Alimera Sciences, Inc. has received a complete response letter (CRL) from the FDA in response to the New Drug Application (NDA) for Iluvien for the treatment of diabetic macular edema (DME) associated with diabetic retinopathy...

Injected Gene Therapy Being Studied for Treatment of Choroideremia
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Resolved Retinal Fluid Following Intravitreal Ranibizumab for PCV

This Japanese study investigated the predictive factors for the resolution of retinal fluid after intravitreal injections of ranibizumab (IVRs) for polypoidal choroidal vasculopathy (PCV).

A total of 47 eyes of 45 patients with symptomatic PCV received 0.5 mg of IVR monthly for 3 months. One month after the third IVR, the presence of dry macula, defined as absence of retinal fluid as detected by the use of optical coherence tomography (OCT), was retrospectively evaluated and correlated with clinical characteristics at baseline. Most of the eyes were followed for more than 6 months.

Of the 47 eyes, 31 eyes (66%) achieved the dry macula along with increased best-corrected visual acuity (BCVA) (0.64 to 0.46 logarithm of the minimum angle of resolution (logMAR) units, $p<0.0001$), while the other 16 eyes without dry macula showed no significant change of BCVA. It was noted that univariate analyses of the baseline characteristics identified the smaller size of the largest polyp ($p=0.0008$) and the absence of serous or hemorrhagic pigment epithelial detachment ($p=0.045$) as predictive factors for the dry macula. Multivariate logistic regression found the independent predictor for the dry macula to be the smaller size of the largest polyp ($p=0.001$). Furthermore, no severe

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African Ancestry, Higher IOP in Latinos

A population-based genetic association study of 3,541 patients recruited from the Los Angeles Latino Eye Study has shown that African ancestry and its interaction with hypertension is associated with higher intraocular pressure in Latinos.

Study participants were genotyped, and simple and multiple linear regression, as well as quantile regression, analyses were performed to investigate the relationship between genetic ancestry and IOP.

African ancestry was significantly associated with higher IOP in Latinos in a simple linear regression analysis (p=0.002). After adjusting for age, gender, body mass index, systolic blood pressure, central corneal thickness and type 2 diabetes, the association remained significant (p=0.0005). The main association was modified by a significant interaction between African ancestry and hypertension (p=0.037), with hypertensive individuals experiencing a greater increase in IOP with increasing African ancestry.

Ophthalmology 2016;123:102-108.
Nannini D, Torres M, Chen Y, Taylor K, et al.

Some Clinical Judgment Leeway in ROP Treatment

Researchers at a host of U.S. centers report a study they say has important clinical implications in the management of retinopathy of prematurity.

The group generated a database of 1,444 eyes prospectively from all babies screened for ROP at six major ROP centers whose parents provided informed consent. The retrospective study reviewed all patients treated for ROP milder than type 1, with the main outcome being indications for treatment.

A total of 137 eyes of 70 infants were treated for ROP. Of the 137, 13 (9.5 percent) were treated despite a clinical diagnosis milder than type 1 ROP. Indications for treatment included active ROP with the fellow eye being treated for type 1 ROP (two eyes, 15.4 percent); concerning structural changes (nine eyes, 69.2 percent), including tangential traction with temporal vessel straightening concerning for macular dragging (eight eyes, 61.5 percent) and thick stage 3 membranes with anteroposterior traction concerning for progression to stage 4 ROP (three eyes, 23.1 percent); persistent ROP at an advanced postmenstrual age (four eyes, 30.8 percent); and/or vitreous hemorrhage (three eyes, 23.1 percent).

Experts in this study occasionally recommended treatment in eyes with disease less than type 1 ROP. The study highlights the role of individual clinical judgment in situations not covered by evidence-based treatment guidelines, the authors concluded.

Am J Ophthalmol 2016;163:1-10.
Gupta M, Chan R, Anzures R, Ostmo S, et al.

Glaucoma Rx Coverage Before And After Medicare Part D

A new study indicates that Medicare Part D enrolled most beneficiaries with glaucoma who previously lacked prescription drug coverage, but suggests that coverage gains lag among the near-poor. While the data evaluated changes in coverage among cohorts of beneficiaries and not from longitudinal follow-up of patients, targeted efforts to improve prescription drug coverage among vulnerable beneficiaries would likely improve access to prescribed ocular hypotensive medications.

To determine changes in prescription drug coverage and out-of-pocket spending after the implementation of Medicare Part D across income strata, and to identify characteristics of beneficiaries associated with prescription status, researchers designed a longitudinal observational study using the Medicare Current Beneficiary Survey (pooled 2004, 2005, 2007 and 2008 data). Participants were non-institutionalized Medicare beneficiaries who filled at least one glaucoma prescription during the survey years.

Survey respondents included more than 11,000 participants in each of the survey years. The sample included 19,045 glaucoma prescriptions, and 2,519 Medicare beneficiaries who filled at least one glaucoma prescription during the study years. Overall, 574 (22.8 percent) beneficiaries reported living below the poverty level, and 795 (31.6

(continued on page 97)

This article has no commercial sponsorship.

Sun Pharma Gains Approval for BromSite

Sun Pharmaceutical Industries announced that one of its wholly owned subsidiaries has received approval from the Food and Drug Administration for its New Drug Application related to BromSite (bromfenac ophthalmic solution) 0.075% for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery. BromSite is the first non-steroidal anti-inflammatory drug approved by the FDA to prevent pain and treat inflammation in the eye for patients undergoing cataract surgery; other NSAIDs in this class are currently indicated for the treatment of inflammation and reduction of pain.

BromSite, developed by InSite Vision, is the first bromfenac ophthalmic solution formulated in DuraSite, a polymer-based formulation that can be used to improve solubility, absorption, bioavailability and residence time as compared to conventional topical therapies. Sun Pharma acquired InSite Vision in November 2015 and is likely to commercialize BromSite through its newly formed, U.S.-based division, Sun Ophthalmics, in the second half of 2016. Sun Ophthalmics aims to provide eye-care practitioners products that enhance their practice patterns and treatment options and to deliver those products through its unique, concierge-level approach to customer care, the company says.

In two multicenter, randomized, placebo-controlled Phase III studies, a significantly higher proportion of BromSite-treated patients were pain-free at day one post-surgery (77 percent and 82 percent) compared to patients treated with vehicle control (48 percent and 62 percent) ($p<0.001$). Additionally, a significantly higher proportion of subjects administered BromSite were inflammation-free at day 15 post-cataract surgery (57 percent and 38 percent), compared to a vehicle control group (19 percent and 22 percent, $p<0.001$ and $p=0.035$).

For information, visit sunpharma.com.

Triggerfish Comes to Market

Sensimed AG announced the FDA marketing clearance of its first-of-kind product, the Sensimed Triggerfish. The Sensimed Triggerfish is a sensor-embedded contact lens-based system that Sensimed developed to improve the management of glaucoma.

Combining a fully integrated sensor and telemetry, it provides a wireless automated recording of continuous ocular dimensional changes over the course of 24 hours. This measurement parameter, while closely correlated with intraocular pressure, is a unique measure in itself, the company says. A recent study published in *Ophthalmology* linked this unique continuous volumetric eye measurement to glaucoma disease progression and concluded that the Sensimed Triggerfish "may be useful in detecting eyes at higher risk of glaucoma progression while receiving treatment."[1]

The FDA reviewed the Sensimed Triggerfish application through the *de novo* process used for first-of-a-kind technologies that are not substantially equivalent to an already marketed device. The Sensimed Triggerfish was classified in the newly created category entitled Diurnal Pattern Recorder System, defined as a non-implantable, prescription device incorporating a telemetric sensor to detect changes in ocular dimension for monitoring diurnal patterns of intraocular pressure fluctuations.

The device has been approved with the following indication:

The Sensimed Triggerfish is a prescription device indicated to detect the peak patterns of variation in intraocular pressure over a maximum period of 24 hours to identify the window of time to measure intraocular pressure by conventional clinical methods. The Sensimed Triggerfish is indicated for patients 22 years of age and older.

The company's goal for the upcoming months is not to immediately launch the product but rather to work closely with the glaucoma community to design and execute a major post-approval study to confirm the use of the Sensimed Triggerfish signal to predict the course of progres-

This article has no commercial sponsorship.

sion of the disease. The overall aim is to build additional clinical utility for the device and establish ocular volume change patterns as a significant stand-alone reference biomarker for use in the management and treatment of glaucoma, the company said. For information, visit sensimed.ch

1. De Moraes C. G. et al. Visual Field Change and 24-Hour IOP-Related Profile with a Contact Lens Sensor in Treated Glaucoma Patients. Ophthalmology, in press.

SVOne: Automated, Self-Guided Objective Refraction

Smart Vision Labs, a maker of mobile autorefractors and other diagnostics, announced two additions to its product offerings. The SVOne Enterprise is the world's first fully automated, self-guided objective refraction technology, combining the power of mobile computation, precision optics and connectivity.

The SVOne Pro is an upgraded version of the company's core technology with an increased range of power and several features that improve usability and accuracy. Results from the voice-guided refraction examination are automatically uploaded to a secure, HIPAA-compliant cloud platform. Ideal for use in retail locations, pharmacies, hospitals, workplaces, schools and other remote settings, the SVOne Enterprise provides eye-care providers a powerful patient engagement and remote patient monitoring tool. The SVOne Pro has the same core technology as the original SVOne autorefractor, but with increased range of power and improved usability. The new device features a new open view channel so the operator can see patients' eyes when aligning the SVOne Pro. When the pupil is detected, the SVOne Pro auto-triggers to automatically acquire wavefront data through its software. The measurement parameters of both the SVOne Enterprise and SVOne Pro have been increased to cover the vision needs of 99 percent of the population: The sphere range is -14 to +14 D, and the cylinder range is -7 to +7 D. The SVOne Enterprise and SVOne Pro are powerful enough to use in any clinical setting while portable enough to be an ideal tool in any non-clinical setting. The FDA Class 1 exempt devices weigh less than a pound each and the price point makes it accessible to the average clinician. The smartphone-based aberrometer has been shown to measure refractive error comparable with subjective refraction and an office-based autorefractor under both cycloplegic and non-cycloplegic conditions in visually normal young adults, the company reports. For information, visit smartvisionlabs.com.

PanoCam Wide-field Imaging for Newborn Infants

Visunex Medical Systems announced the FDA clearance of its PanoCam Pro Wide-field Imaging System for the imaging of all newborn infants.

PanoCam Pro is a wireless imaging system that fills an unmet need in the imaging of all newborn babies that may help detect external, anterior and posterior segment vision disorders that may have long-term effects on the vision of millions of children around the world each year.

Early research done in Asia, Brazil and the United States suggests that one in 70 children born may have some form of vision disorder, the company says.

Newborn vision screening is already a clinically valued and established method for evaluating retinopathy of prematurity and retinoblastoma, which are life-threatening and can lead to newborn vision loss. The PanoCam Pro allows for complete visualization of the surface and sub-surface retinal pathologies unlike any other device on the market.

Newborn eye testing is most commonly performed when a child enters kindergarten at the age of 5 or 6 years. The company says that many clinicians believe the vision screening of newborns with the PanoCam Pro may help shed additional light on the significance of disorders such as retinal hemorrhages, which may be a precursor to amblyopia. Other vision disorders may be detected, and if detected early, can give caregivers the opportunity to intervene and provide the treatment to thwart vision loss and improve care pathways and newborn vision into adulthood.

Darius M. Moshfeghi, MD, director of pediatric vitreoretinal surgery and ophthalmologic telemedicine at Stanford University, said, "The advent of technology that helps assess the structures and function of the retina, combined with software solutions that elevate patient care, is a huge step forward." Dr. Moshfeghi runs SUNDROP, the Stanford University Network for the Diagnosis of Retinopathy of Prematurity, the largest network looking at the care of premature infants who may be at the greatest risk of newborn vision disorders. For more information, visit visunexmedical.com. REVIEW

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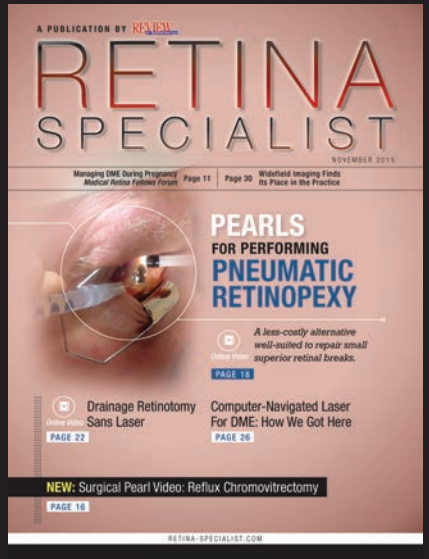

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An infant is referred for nystagmus of both eyes. The initial evaluation suggests bilateral aniridia.

Tim Arlow, MD, PhD, Jenina Capasso, MS, and Alex Levin, MD

Presentation

A 7-month-old boy was referred for nystagmus of both eyes. His parents reported the nystagmus started at 1 month of age. On initial evaluation he was found to have bilateral aniridia.

Medical History

The patient was the product of a normal pregnancy and uncomplicated repeat cesarean section. Birth weight was 5 pounds. Family history was unremarkable—there were no other family members with aniridia. He had one sibling, a healthy 2-year-old brother.

Examination

His extraocular motility was full without strabismus, and he was able to fix and follow with no preference for fixation with either eye. He demonstrated horizontal moderate frequency and moderate amplitude symmetric bilateral nystagmus with a null point in primary position. There was no anomalous head positioning.

Examination under anesthesia disclosed that he had deep and quiet anterior chambers and clear corneas without pannus or Haab striae. Corneal diameters were 10.75 mm OD and 10.5 mm OS. Corneal thickness was 650 µm and 641 µm respectively. Tonopen pressure was 13 mmHg OD and 12 mmHg OS. There was bilateral, almost complete aniridia with rudimentary iris stumps inferiorly, temporally and nasally *(See Figure 1)*. Gonioscopy revealed a somewhat dysgenic trabecular meshwork that had multiple iris processes extending over the angle *(See Figure 2)*.

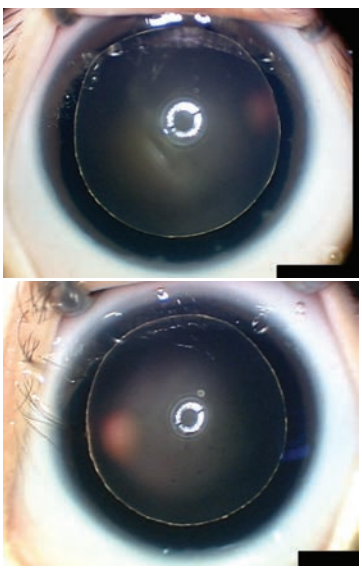

Figure 1. Right (top) and left eyes, demonstrating near total absence of iris tissue.

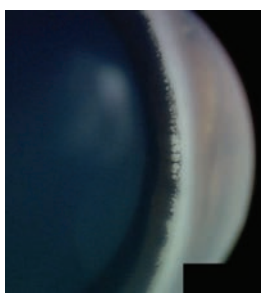

Figure 2. Iris processes spanning a dysgenic trabecular meshwork.

Each eye was found to have a 1.5-mm anterior subcapsular cataract. Retinoscopy revealed a cycloplegic refraction of +3.50 +0.75 x 090 OD and +3.50 + 0.50 x 090 OS. A-scan ultrasound by immersion disclosed appropriate-sized globes for age with axial length of 19.77 mm OD and 19.81 mm OS.

Funduscopic evaluation disclosed normal optic nerves with moderate macular hypoplasia in each eye with anomalous vessels in the maculas *(See Figure 3)*.

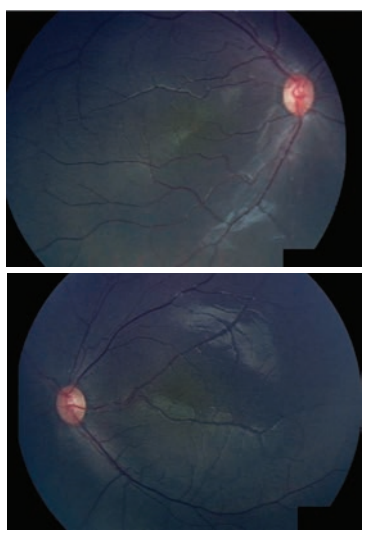

Figure 3. Foveal hypoplasia with anomalous vessels present in the right (top) and left eyes.

What is your differential diagnosis? What further workup would you pursue? Please turn to p. 96

Diagnosis, Workup and Treatment

The patient underwent ultrasound of the kidneys, which did not identify any irregularity or mass.

Genetic analysis was initiated and revealed a normal male karyotype. Reflex testing to chromosomal microarray analysis did not identify submicroscopic dosage abnormalities. This ruled out a contiguous gene deletion in chr11p13, encompassing the Wilms tumor 1 gene (WT1) and PAX6 that would result in WAGR syndrome (Wilms tumor, Aniridia, Genitourinary abnormalities, and Retardation of growth and development). PAX6 gene sequencing identified a point mutation at nucleotide position 718, substituting a thymine for cytosine. This resulted in a nonsense mutation creating a premature stop codon and a truncated form of the protein. Further testing using exon level deletion/duplication analysis did not identify any intragenic deletions in the PAX6 gene or nearby WT1 (associated with Wilms tumor), DCDC1 or ELP4 genes (PAX6 enhancer genes).

Discussion

Aniridia is a panocular disorder affecting the cornea, angle, lens and retina, among other ocular structures. The term aniridia is a misnomer, as it is rare for the iris to be completely absent. Aniridia is reported to have an incidence from 1:40,000-100,000.[1,2] PAX6 gene mutations are implicated in almost all cases of congenital aniridia, however other loci have been reported.[3] Two-thirds of aniridia cases are familial, while one-third are sporadic.[1] Typically, hereditary aniridia is inherited in an autosomal dominant pattern and not associated with increased risk of Wilms tumor. Sporadic aniridia is more likely associated with 11p13 deletions involving PAX6 and the nearby WT1 locus resulting in WAGR syndrome, which necessitates urgent screening for early detection of renal malignancy.

Visual acuity with aniridia can range from mild impairment to legal blindness; however, the majority of patients with aniridia have visual acuities worse than 20/200 in adulthood.[1] The decreased visual acuity is due to numerous mechanisms including keratopathy, cataract, glaucoma, nystagmus and macular hypoplasia.

Keratopathy occurs in 20 percent to 50 percent of aniridia cases[1] and usually presents within the first decade of life. It is thought to be due in part to limbal stem cell deficiency and results in a vascularized, non-healing corneal surface, which is predisposed to recurrent erosions and ulcerations. Symptoms include decreased vision, dry-eye symptoms and photophobia.[4] Management includes lubrication, autologous serum drops and amniotic membrane grafts.[4] Artificial cornea keratoprostheses may have a role in selected cases due to the high rate of corneal graft failure.[2]

Patients with aniridia also require lifelong screening for glaucoma, which typically develops in childhood but also has an increased incidence in adulthood. Approximately 50 percent of patients develop glaucoma.[5] Glaucoma may be due to trabecular dysgenesis, a progressive turning up of the iris stump over the trabecular meshwork or congenital aplasia of Schlemm's canal. Medical management of aniridic glaucoma has demonstrated success rates as high as 40 percent.[2] Nonetheless, many require surgery for this difficult-to-control form of glaucoma.

Cataract is also frequent in aniridia with a prevalence between 50 percent and 85 percent.[6] Similar to our patient, these are initially noticed as lens abnormalities in infancy before developing into visually significant cataracts.[1]

Our patient presented with pendular horizontal nystagmus, which occurs in 81 to 95 percent of patients with aniridia.[1] This nystagmus is thought to be secondary to macular hypoplasia, which has been documented to occur in approximately 75 percent of patients.[1] Optic nerve hypoplasia is also found in approximately 10 percent of cases.[2,8]

Looking forward, STAR, the study of Ataluren in patients with aniridia is a Phase ll clinical trial that is currently recruiting patients with nonsense mutations in PAX6. Ataluren (formerly PTC124, PTC Therapeutics) promotes "read through," which causes ribosomes to be more likely to continue translating protein through premature stop codons. Ataluren Phase ll clinical trials were found to be successful for cystic fibrosis due to nonsense mutations.[9] In an aniridia mouse model with nonsense mutation in PAX6, Ataluren not only prevented disease progression but also reversed corneal, lens and retinal defects and restored electrical and behavioral responses of the retina postnatally.[10,11] STAR is hoping to enroll 36 patients over the age of 2 and with confirmed nonsense mutation in PAX6 for treatment with Ataluren. STAR aims to be completed by 2018, and may offer new options in the treatment of aniridia.

Aniridia is a panocular condition that affects multiple tissues in the eye. Patients have decreased visual potential due to numerous mechanisms between keratopathy, cataract, glaucoma and macular hypoplasia.

Aniridia is typically due to mutations in PAX6. Sporadic cases may be due to deletions involving PAX6 and the nearby WT1 locus thus predisposing to Wilms tumor. REVIEW

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(continued from page 89)

percent) had incomes consistent with near-poor status. The implementation of Medicare Part D resulted in increased rates of prescription drug coverage across all economic strata, with reductions in beneficiaries without coverage from 22.8 percent to 4 percent among poor beneficiaries, 29.1 percent to 7.3 percent among near-poor beneficiaries and 19.9 percent to 3.7 percent among higher-income beneficiaries. Despite these gains, near-poor status remained a risk factor for lack of prescription drug coverage after Medicare Part D implementation (p=0.04). No differences were identified in adjusted out-of-pocket drug costs between the near-poor and those with higher income, although out-of-pocket costs were 37 percent (p<0.001) lower among the poor relative to those with higher income.

JAMA Ophthalmol 2016;134:2:212-220.
Blumberg D, Prager A, Leibmann J.

T-CAT Safe and Effective

Topography-guided custom ablation treatment (T-CAT) can achieve predictable refractive outcomes and reduce visual symptoms with stable results through 12 months, say U.S. researchers. (The researchers and the T-CAT study group were supported by or consultants to Alcon.)

The prospective, observational, nonrandomized, unmasked study enrolled 212 patients (249 eyes) at nine clinical sites. Patients were 18 to 65 years old with myopia or myopic astigmatism with a manifest refraction spherical equivalent (MRSE) up to -9 D and astigmatism of 6 D or less. Patients with previous refractive surgery or abnormal topography were excluded. Corneal topographies were obtained using the Allegro Topolyzer, and laser treatment was delivered with the Allegretto Wave Eye-Q excimer laser system. Visual outcomes were evaluated postoperatively at seven time points over 12 months.

The T-CAT procedure significantly reduced the MRSE and cylinder, with stability of outcomes evident from three to 12 months after surgery. Compared with the preoperative corrected distance visual acuity, the postoperative uncorrected distance VA improved by one line or more in 30 percent of eyes and the postoperative UDVA was at least as good as the preoperative CDVA in 90 percent of eyes. Most visual symptoms improved after T-CAT. No significant treatment-related adverse events or loss of vision occurred.

J Cataract Refract Surg 2016,42:11-18.
Stulting RD, Fant BS, T-CAT Study Group.

LCT and AMT Compared

Citing a dearth of studies comparing different surgical procedures for the treatment of corneal thinning, Brazilian researchers assessed lamellar corneal transplantation (considered efficient, but subject to allograft rejection, opacification or high astigmatism) versus amniotic membrane transplantation (considered a good alternative, but not as resistant as LCT and the tissue can be reabsorbed after surgery). The prospective, randomized, interventional and comparative study included consecutive patients with corneal thinning over six months. Subjects were examined before transplant surgery and then at six intervals over six months after surgery; ultrasound biomicroscopy was performed before and at 30, 90 and 180 days after surgery to assess corneal thinning.

Herpes simplex infection was the main cause of corneal thinning (nine eyes); followed by surgery (cataract, glaucoma, five cases); and a single case each of rheumatoid arthritis, chemical burn, perforating trauma, previous band keratopathy treatment, and Stevens-Johnson syndrome. Although all patients showed significant increase in final thickness in the area of thinning, it was higher in those subjected to LCT at 180 days postoperatively. Regardless of the surgical technique, all patients showed epithelialization. Patients undergoing AMT showed an 89 percent decrease in neovascularization. Final corrected distance visual acuity was better in patients subjected to AMT.

LCT proved to be the best option for treating corneal thinning, the authors say. AMT represents an alternative that allows good visual recovery but does not restore corneal thickness as efficiently as LCT.

Cornea 2016;35:438-44.
de Farias C, Allemann N, Gomes JÁ.

REVIEW

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INDICATION FOR USE. The iStent® Trabecular Micro-Bypass Stent (Models GTS100R and GTS100L) is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate open-angle glaucoma currently treated with ocular hypotensive medication. **CONTRAINDICATIONS.** The iStent® is contraindicated in eyes with primary or secondary angle closure glaucoma, including neovascular glaucoma, as well as in patients with retrobulbar tumor, thyroid eye disease, Sturge-Weber Syndrome or any other type of condition that may cause elevated episcleral venous pressure. **WARNINGS.** Gonioscopy should be performed prior to surgery to exclude PAS, rubeosis, and other angle abnormalities or conditions that would prohibit adequate visualization of the angle that could lead to improper placement of the stent and pose a hazard. The iStent® is MR-Conditional meaning that the device is safe for use in a specified MR environment under specified conditions, please see label for details. **PRECAUTIONS.** The surgeon should monitor the patient postoperatively for proper maintenance of intraocular pressure. The safety and effectiveness of the iStent® has not been established as an alternative to the primary treatment of glaucoma with medications, in children, in eyes with significant prior trauma, chronic inflammation, or an abnormal anterior segment, in pseudophakic patients with glaucoma, in patients with pseudoexfoliative glaucoma, pigmentary, and uveitic glaucoma, in patients with unmedicated IOP less than 22 mmHg or greater than 36 mmHg after "washout" of medications, or in patients with prior glaucoma surgery of any type including argon laser trabeculoplasty, for implantation of more than a single stent, after complications during cataract surgery, and when implantation has been without concomitant cataract surgery with IOL implantation for visually significant cataract. **ADVERSE EVENTS.** The most common post-operative adverse events reported in the randomized pivotal trial included early post-operative corneal edema (8%), BCVA loss of ≥ 1 line at or after the 3 month visit (7%), posterior capsular opacification (6%), stent obstruction (4%) early post-operative anterior chamber cells (3%), and early post-operative corneal abrasion (3%). Please refer to Directions for Use for additional adverse event information. **CAUTION:** Federal law restricts this device to sale by, or on the order of, a physician. Please reference the Directions for Use labeling for a complete list of contraindications, warnings, precautions, and adverse events.

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

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

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